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MD Research News

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Drug treatment

N Engl J Med. 2015 Feb 18. [Epub ahead of print]

Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema.

The Diabetic Retinopathy Clinical Research Network.

Background: The relative efficacy and safety of intravitreous aflibercept, bevacizumab, and ranibizumab in the treatment of diabetic macular edema are unknown.

Methods: At 89 clinical sites, we randomly assigned 660 adults (mean age, 61±10 years) with diabetic macular edema involving the macular center to receive intravitreous aflibercept at a dose of 2.0 mg (224 participants), bevacizumab at a dose of 1.25 mg (218 participants), or ranibizumab at a dose of 0.3 mg (218 participants). The study drugs were administered as often as every 4 weeks, according to a protocol-specified algorithm. The primary outcome was the mean change in visual acuity at 1 year.

Results: From baseline to 1 year, the mean visual-acuity letter score (range, 0 to 100, with higher scores indicating better visual acuity; a score of 85 is approximately 20/20) improved by 13.3 with aflibercept, by 9.7 with bevacizumab, and by 11.2 with ranibizumab. Although the improvement was greater with aflibercept than with the other two drugs (P<0.001 for aflibercept vs. bevacizumab and P=0.03 for aflibercept vs. ranibizumab), it was not clinically meaningful, because the difference was driven by the eyes with worse visual acuity at baseline (P<0.001 for interaction). When the initial visual-acuity letter score was 78 to 69 (equivalent to approximately 20/32 to 20/40) (51% of participants), the mean improvement was 8.0 with aflibercept, 7.5 with bevacizumab, and 8.3 with ranibizumab (P>0.50 for each pairwise comparison). When the initial letter score was less than 69 (approximately 20/50 or worse), the mean improvement was 18.9 with aflibercept, 11.8 with bevacizumab, and 14.2 with ranibizumab (P<0.001 for aflibercept vs. bevacizumab, P=0.003 for aflibercept vs. ranibizumab, and P=0.21 for ranibizumab vs. bevacizumab). There were no significant differences among the study groups in the rates of serious adverse events (P=0.40), hospitalization (P=0.51), death (P=0.72), or major cardiovascular events (P=0.56).

Conclusions: Intravitreous aflibercept, bevacizumab, or ranibizumab improved vision in eyes with center-involved diabetic macular edema, but the relative effect depended on baseline visual acuity. When the initial visual-acuity loss was mild, there were no apparent differences, on average, among study groups. At worse levels of initial visual acuity, aflibercept was more effective at improving vision. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT01627249.)

PMID: 25692915 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Feb 13. [Epub ahead of print]

UK AMD EMR USERS GROUP REPORT V: benefits of initiating ranibizumab therapy for neovascular AMD in eyes with vision better than 6/12.

Lee AY, Lee CS, Butt T, et al; on behalf of UK AMD EMR Users Group.

BACKGROUND/AIMS: To study the effectiveness and clinical relevance of eyes treated with good (better than 6/12 or >70 Early Treatment Diabetic Retinopathy Study letters) visual acuity (VA) when initiating treatment with ranibizumab for neovascular age-related macular degeneration (nAMD) in the UK National Health Service. Currently eyes with VA better than (>) 6/12 are not routinely funded for therapy.

METHODS: Multicentre national nAMD database study on patients treated 3-5 years prior to the analysis. Anonymised structured data were collected from 14 centres. The primary outcome was the mean VA at year 1, 2 and 3. Secondary measures included the number of clinic visits and injections.

RESULTS: The study included 12 951 treatment-naive eyes of 11 135 patients receiving 92 976 ranibizumab treatment episodes. A total of 754 patients had baseline VA better than 6/12 and at least 1-year of follow up. Mean VA of first treated eyes with baseline VA>6/12 at year 1, 2, 3 were 6/10, 6/12, 6/15, respectively and those with baseline VA 6/12 to >6/24 were 6/15, 6/17, 6/20, respectively (p values <0.001 for comparing differences between 6/12 and 6/12-6/24 groups). For the second eyes with baseline VA>6/12, mean VA at year 1, 2, 3 were 6/9, 6/9, 6/10 and those with baseline VA 6/12 to >6/24 were 6/15, 6/15, 6/27, respectively (p values <0.001-0.005). There was no significant difference in the average number of clinic visits or injections between those with VA better and worse than 6/12.

CONCLUSIONS: All eyes with baseline VA>6/12 maintained better mean VA than the eyes with baseline VA 6/12 to >6/24 at all time points for at least 2 years. The significantly better visual outcome in patients who were treated with good baseline VA has implications on future policy regarding the treatment criteria for nAMD patients' funding.

PMID: 25680619 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2015 Feb 12;25(2):163-7.

Occurrence of macular hematoma after ranibizumab treatment for age-related macular degeneration.

Azar G, Mauget-Faÿsse M, Nyouma J, et al.

PURPOSE: To report the occurrence and study the characteristics of macular hematoma after ranibizumab (anti-VEGF) intravitreal injection for subfoveal choroidal neovascularization in age-related macular degeneration (AMD).

METHODS: The charts of 6000 patients treated with ranibizumab (0.5 mg) for exudative AMD were reviewed. Inclusion criteria were a minimum follow-up of 1 year after the first injection and the occurrence of a large macular hematoma involving the fovea in patients with macular lesions considered stabilized or still active. All patients had a complete ophthalmologic assessment including Early Treatment of Diabetic Retinopathy Study visual acuity (VA) measurement, fundus photography, fundus fluorescein angiography, scanning laser ophthalmoscopy-infracyanine green angiography, and spectral-domain optical coherence tomography.

RESULTS: Of the 6000 eyes, 24 (0.4%) developed macular hematoma during follow-up. There were 8 men (33.3%) and 16 women (66.7%). The mean age at the time of initial presentation was 76.7 ± 3.8 years (range 61-81 years). The mean time to occurrence of macular hematoma after the last injection was 4.8 months. Spectral-domain optical coherence tomography showed the presence of a retinal pigment epithelium (RPE) tear in 19 eyes (79.1%). Vitreomacular traction (VMT) was only present in 4 eyes (17%). Final VA after macular hematoma resorption was <20/50 in 17 cases (70.9%) and ≥20/50 in 7 cases

(29.1%).

CONCLUSIONS: Macular hematoma may follow intravitreal anti-VEGF injection for exudative AMD with large occult neovascularization, especially if a large RPE tear is found. The occurrence does not seem to be linked to anticoagulation treatment or the presence of VMT.

PMID: 25684081 [PubMed - in process]

J Fr Ophtalmol. 2015 Feb 12. [Epub ahead of print]

[Management of macular edema secondary to retinal vein occlusion.][Article in French]

Girmens JF, Glacet-Bernard A, Kodjikian L, et al

BACKGROUND: In recent years, intravitreal injections have added to the treatment modalities available for macular edema (ME) secondary to retinal vein occlusion (RVO). This article aims to provide an update regarding the management of ME secondary to RVO.

METHODS: A work group met in order to analyze the literature available on Embase/PubMed, regarding treatments for venous occlusion that have received market approval and are reimbursed in France. In total, 33 articles were selected. Consensus within the group for recommendations was based on this data from the literature review and clinical experience and was reported in this article.

RESULTS: The management of ME secondary to branch retinal vein occlusion (BRVO) or central vein occlusion of the retina (CRVO) differs on a number of points. Methods of best practice were discussed separately for BRVO and CRVO, taking into account various ocular and associated parameters.

DISCUSSION: Ranibizumab and dexamethasone implant are the first-line treatments for visual impairment due to ME secondary to RVO. The choice of either of these drugs may take into account various ocular and extraocular parameters. A change of treatment to one or the other or to laser may also be considered during follow-up.

PMID: 25683131 [PubMed - as supplied by publisher]

Nepal J Ophthalmol. 2014 Jul;6(12):145-52.

Comparison of intravitreal bevacizumab treatment between phakic and pseudophakic neovascular age-related macular degeneration.

Ozkaya A, Alkin Z, Perente I, et al.

INTRODUCTION: Before the era of intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment, only prevention for visual loss might have been achieved in a limited number of neovascular age -related macular generation (nAMD) patients with different treatment options.

OBJECTIVE: To compare the efficacy of intravitreal bevacizumab (IVB) for the treatment of nAMD between phakic and pseudophakic eyes.

MATERIALS AND METHODS: The newly diagnosed nAMD patients were included in this retrospective study. The patients were divided into the phakic and pseudophakic groups. Initially, the patients received three consecutive, monthly, IVB injections, and then the treatment was continued on an as-needed regimen. The patients were examined monthly, and the data at the baseline, at 3, 6, 9, and 12 months and at the last follow-up were evaluated. The changes in the visual acuity (VA), central retinal thickness (CRT) and the number of injections were compared between the two groups.

RESULTS: The study included 62 eyes of 62 patients (39 phakic, and 23 pseudophakic patients). The mean follow-up time was 19.7 and 17.2 months in the phakic and pseudophakic groups, respectively (p =

0.06). The mean Log MAR VA at the baseline, 12 months and the last follow-up was 0.82, 0.72 and 0.75 in the phakic group and 0.77, 0.67, and 0.68 in the pseudophakic group, respectively. The change in the mean BCVA from the baseline to 12 months and at the last follow-up was not statistically different between the two groups (p = 0.9 and p = 0.7, respectively). The mean injection number at 12 months was 4.5 and 4.9 in the phakic and pseudophakic group, respectively (p = 0.2).

CONCLUSION: The beneficial effect of IVB is equal in both the phakic and pseudophakic group of nAMD patients. The functional and anatomical outcomes of the treatment and the number of injections were similar in the two groups.

PMID: 25680245 [PubMed - in process]

Am J Ophthalmol. 2015 Mar;159(3):607-8.

Intravitreal Aflibercept for Macular Edema Secondary to Central Retinal Vein Occlusion: 18-Month Results of the Phase 3 GALILEO Study.

Călugăru D, Călugăru M.

PMID: 25681022 [PubMed - in process]

Acta Ophthalmol. 2015 Mar;93(2):103-4.

Translational public health care perspective: Intravitreal treatment of neovascular age-related macular degeneration has revolutionized clinical ophthalmology.

Bloch SB, Larsen M.

PMID: 25688486 [PubMed - in process]

Other treatment & diagnosis

Quant Imaging Med Surg. 2015 Feb;5(1):63-8.

In vivo imaging rhodopsin distribution in the photoreceptors with nano-second pulsed scanning laser ophthalmoscopy.

Liu T, Liu X, Wen R, et al.

BACKGROUND: Rhodopsin is a biomarker for the function of rod photoreceptors, the dysfunction of which is related to many blinding diseases like retinitis pigmentosa and age-related macular degeneration. Imaging rhodopsin quantitatively may provide a powerful clinical tool for diagnosis of these diseases. To map rhodopsin distribution accurately in the retina, absorption by rhodopsin intermediates need to be minimized.

METHODS AND MATERIALS: We developed nano-second pulsed scanning laser ophthalmoscopy (SLO) to image rhodopsin distribution in the retina. The system takes advantage of the light-induced shift of rhodopsin absorption spectra, which in turn affects the fundus spectral reflection before and after photo-bleaching. By imaging the retina twice, one in the dark-adapted state and the other one in the light-adapted state, the rhodopsin absorption change can be calculated from the differential image, which is a function of the rhodopsin concentration in the rod photoreceptors.

RESULTS: The system was successfully applied to in vivo imaging of rat retina in different bleaching conditions to verify its feasibility. Our studies showed that the differential image between the dark- and light-adapted states represents rhodopsin distribution in the retina. We also conducted a dynamic bleaching

experiment to prove the importance of reducing light absorption of rhodopsin intermediates.

CONCLUSIONS: The preliminary results showed that our nano-second pulsed-light SLO is promising in imaging the functional biomarker of the rod photoreceptors. By using nanosecond pulsed laser, in which one laser pulse generates one pixel of the image, the absorption of rhodopsin intermediates can be reduced.

PMID: 25694955[PubMed]

Transl Vis Sci Technol. 2015 Feb 10;4(1):7. eCollection 2015.

A Subsequent Human Neural Progenitor Transplant into the Degenerate Retina Does Not Compromise Initial Graft Survival or Therapeutic Efficacy.

Lu B, Lin Y, Tsai Y, et al

PURPOSE: Stem and progenitor cell transplantation provides a promising clinical application for treating degenerative retinal diseases, including age-related macular degeneration (AMD) and retinitis pigmentosa (RP). Our previous studies have shown that a single subretinal injection of human cortical-derived neural progenitor cells (hNPCctx) into cyclosporine-treated Royal College of Surgeons (RCS) rats preserved both photoreceptors and visual function. However, it is still unknown whether nonautologous progenitor cell readministration for sustained vision is efficacious and safe in terms of the initial graft initiating an immune response to a subsequent graft.

METHODS: A cell suspension containing 3×104 hNPCctx into one eye of cyclosporine-treated RCS rats at postnatal day 21 (P21), followed by a second transplantation at P95 into the previously untreated fellow eye.

RESULTS: hNPCctx delayed photoreceptor degeneration and preserved visual function, as measured by electroretinography (ERG), optokinetic response (OKR), and luminance threshold recordings (LTRs). Visual function and photoreceptors of the initially treated eye were still preserved 6 weeks after hNPCctx were injected into the second eye. Antibodies against T-cell markers showed that CD3, CD4, and CD8 T cells were not detected at P90 and P140 in most cases. No detectable level of anti-nestin antibody was found in serum by enzyme-linked immunosorbent assay (ELISA).

CONCLUSIONS: This xenograft study with cyclosporine-treated animals demonstrates that readministration of hNPCctx into the fellow eye did not induce anti-graft immune responses or lower therapeutic efficacy of hNPCctx in preserving vision. Thus, readministration of progenitor cells to sustain long-term efficacy may be an option for long-term therapies of retinal degeneration.

TRANSLATIONAL RELEVANCE: Redosing neural progenitors do not affect the efficacy of the initial grafts in protecting vision or induce unwanted immune responses.

PMID: 25694843 [PubMed]

Prog Retin Eye Res. 2015 Feb 11. [Epub ahead of print]

Adult-onset foveomacular vitelliform dystrophy: A fresh perspective.

Chowers I, Tiosano L, Audo I, et al.

Abstract: Adult-onset foveomacular vitelliform dystrophy (AFVD) was first described by Gass four decades ago. AFVD is characterized by subretinal vitelliform macular lesions and is usually diagnosed after the age of 40 years. The lesions gradually increase and then decrease in size over the years, leaving an area of atrophic outer retina and retinal pigment epithelium. This process is accompanied by a loss of visual acuity. Vitelliform lesions manifest as autoflourescence and initially have a dome-shape subretinal appearance on

optical coherence tomography. Electro-oculogram and full-field electroretinogram finding are typically normal. A similar phenotype is also associated with systemic disorders such as cancer, drug toxicity, and mitochondrial diseases. Phenocopies are also associated with ocular disorders, including vitreomacular traction, age-related macular degeneration, pseudodrusen, and central serous choroidopathy. A minority of AFVD patients have a mutation in the PRPH2, BEST1, IMPG1, or IMPG2 genes. A single-nucleotide polymorphism in the HTRA1 gene has also been associated with this phenotype. Accordingly, the phenotype can arise from alterations in the photoreceptors, retinal pigment epithelium, and/or interphotoreceptor matrix. Excess outer segment production and/or impaired outer segment uptake due to impaired phagocytosis are the likely underlying mechanisms. At present, no cure is available for AFVD. Thus, the current challenges in the field include identifying the underlying cause in the majority of AFVD cases and the development of effective therapeutic approaches.

PMID: 25681578 [PubMed - as supplied by publisher]

Nepal J Ophthalmol. 2014 Jul;6(12):170-6.

Effectiveness of measuring the central field with the Berkeley field test.

Mishra SK, Shrestha GS, Korani H.

INTRODUCTION: There are several limitations of the Amsler chart as a screening tool due to its low sensitivity and high false-negative results. The Berkeley central visual field test (BCFT), which is a simple power-point presentation of a 50-point scoring system for the central 10-degree of the visual field, was devised as an alternative to the Amsler chart.

OBJECTIVES: To compare the efficacy of measuring the central visual field using the Berkeley central field test (BCFT) and the Amsler grid test.

MATERIALS AND METHODS: In a comparative and validity study, 30 subjects with maculopathy and 35 controls were recruited. The maculopathy subjects with the best corrected visual acuity of 20/200 or better and 2.5M for distant and near vision respectively, were included. All the subjects under went a complete eye examination where visual assessment was done using the distant and near vision Log MAR Chart. The subjects were assessed with the Amsler chart-II at a distance of 30 cm. The BCFT was used as a 50- point scoring system. The effectiveness of BCFT was compared with that of the Amsler grid regarding the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

RESULTS: Out of 65 subjects, 30 subjects had maculopathy and 35 were normal. The mean age of the 65 subjects was 49.8±9.1 years. Of the 30 subjects with maculopathy, the majority (54%) had age- related macular degeneration. The sensitivity, specificity, PPV and NPV of the Amsler grid test were found to be 80%, 100%, 100% and 87%, respectively, whereas those of the BCFT were 71%, 99%, 98% and 82% (p=0.37).

CONCLUSION: The BCFT test was as good as the Amsler grid test at detecting the presence of maculopathy.

PMID: 25680247 [PubMed - in process]

Pathogenesis

Acta Ophthalmol. 2015 Feb 12. [Epub ahead of print]

Impact of visceral fat and pro-inflammatory factors on the pathogenesis of age-related macular degeneration.

Haas P, Kubista KE, Krugluger W, et al.

PURPOSE: Previous studies have indicated that the immune system is involved in the pathogenesis of the AMD. Increased visceral fat, in addition, has a pro-inflammatory effect on the organism by producing or influencing different kinds of inflammatory factors. The aim of this study is to determine the relationship of body fat distribution in patients with age-related macula degeneration in comparison to a control group in the Austrian population.

METHODS: In this case-control study, body weight and height, and body mass index (BMI) were measured for each subject in 54 patients with exudative AMD and compared to 46 gender- and age-matched healthy control subjects. Body composition and abdominal fat areas were measured using dual-energy X-ray absorptiometry (DEXA). Data on age, gender distribution, smoking history and systemic diseases, respectively, were compared. The inflammatory markers CRP, tumour necrosis factor-alpha (TNF-alpha), leptin, amyloid A, amyloid beta and interleukin-6 (IL-6) were assayed by ELISA (R&D).

RESULTS: DEXA revealed central-abdominal-to-total body fat ratio of 0.073 +/- 0.011 in AMD patients compared to 0.061 +/- 0.013 in the controls ($p < 0.001$; $d = 0.98$). The calculation of BMI has provided a significant result ($p = 0.045$). U-test results for Aß1-42, IL-6, SAA and CRP each were significant ($p < 0.05$), with higher values in AMD patients. Leptin, TNF-alpha and Aß1-40 showed no significant differences between the groups.

CONCLUSION: Our results suggest that abdominal fat distribution is significantly associated with age-related macular degeneration. Analysis of patients with exudative AMD revealed higher levels of CRP, amyloid ß1-42, IL-6 and amyloid alpha.

PMID: 25683020 [PubMed - as supplied by publisher]

Wound Repair Regen. 2015 Feb 14. [Epub ahead of print]

Effect of substance P on recovery from laser-induced retinal degeneration.

Hong HS, Kim S, Nam S, et al

Abstract: Retinal degeneration is caused by neovascularization and persistent inflammation in the retinal pigment epithelium and choroid, and causes serious eye disease including age-related macular degeneration. Thus, inhibiting inflammation and neovascularization may be a primary approach to protect the retina from degeneration. The purpose of this study was to determine whether substance P, which can suppress inflammation and mobilize stem cells, can protect the retinal pigment epithelium from degeneration. The effect of substance P was evaluated by analyzing systemic inflammation, cell survival, and neovascularization within the argon laser-injured retina of mice. At 1 week post-injury, the substance P-treated group had lower tumor necrosis factor-alpha and higher interleukin-10 serum concentrations, and a more intact retinal structure compared to the vehicle-treated group. In mice administered substance P repeatedly for 4 weeks, the retinal structure appeared normal and showed sparse neovascularization, whereas the vehicle-treated group showed severe retinal destruction and dense neovascularization. Moreover, the efficacy of substance P was identical to that of mesenchymal stem cells that were transplanted into the vitreous after retinal injury. This study highlights the potential for the endogenous neuropeptide substance P as a treatment for retinal damage to prevent conditions such as age-related macular degeneration. This article is protected by copyright. All rights reserved.

PMID: 25682893 [PubMed - as supplied by publisher]

Epidemiology

JAMA Ophthalmol. 2015 Feb 19. [Epub ahead of print]

Association of Smoking and CFH and ARMS2 Risk Variants With Younger Age at Onset of Neovascular Age-Related Macular Degeneration.

Lechanteur YT, van de Camp PL, Smailhodzic D, et al

Importance: The age at which the first signs of age-related macular degeneration (AMD) manifest is variable. Better insight into factors that influence disease onset has direct implications for preventive measures and patient counseling.

Objective: To identify risk factors for an earlier age at onset of neovascular AMD.

Design, Setting, and Participants: Retrospective cohort study, including patient data from the European Genetic Database collected between April 2006 and July 2010. All patients had at least 1 documented visit to the outpatient AMD clinic of the Radboud University Medical Center, Nijmegen, the Netherlands, a tertiary referral center for retinal disorders. In total, 275 patients with a known age at onset of neovascular AMD and a genetic risk analysis were included.

Main Outcomes and Measures: Effects of several genetic, sociodemographic, behavioral, and ocular factors on the age at onset of neovascular AMD. The mean differences in the age at onset were determined using general linear models with the age at onset as the dependent variable.

Results: Past smokers and current smokers developed neovascular AMD on average 4.9 (95% CI, 3.0-6.8) and 7.7 (95% CI, 5.3-10.0) years earlier, respectively, than never smokers ($P < .001$ for both). Compared with the reference group, the age at onset was 5.2 (95% CI, 2.8-7.7) years earlier for homozygous carriers of the A69S risk allele in the age-related maculopathy susceptibility 2 (ARMS2) gene ($P < .001$). Homozygous carriers of the Y402H risk variant in the complement factor H (CFH) gene developed neovascular AMD 2.8 (95% CI, 0.5-5.0) years earlier ($P = .02$). Patients carrying 4 risk alleles in CFH and ARMS2 developed neovascular AMD 12.2 (95% CI, 6.2-18.3) years earlier than patients with zero risk alleles ($P < .001$).

Conclusions and Relevance: Genetic and environmental risk factors influence the age at onset of neovascular AMD. Individuals at risk could be identified at an early age if and when preventive or therapeutic options become available. Insight into individual risk profiles might influence patients' consideration of interventions to increase their chance of avoiding vision loss from AMD.

PMID: 25695752 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Feb 11. [Epub ahead of print]

Changes in Lens Opacities on the Age-Related Eye Disease Study Grading Scale Predict Progression to Cataract Surgery and Vision Loss: Age-Related Eye Disease Study Report No. 34.

Indaram M, Agrón E, Clemons TE, et al; Age-Related Eye Disease Study Research Group.

PURPOSE: To investigate whether the 2-year change in lens opacity severity on the Age-Related Eye Disease Study (AREDS) lens grading scale predicts progression to cataract surgery or loss of visual acuity by 5 years.

DESIGN: Prospective cohort study within a randomized clinical trial of oral supplements.

PARTICIPANTS: The AREDS participants whose eyes were phakic at baseline and free of late age-related macular degeneration throughout the study.

METHODS: Baseline and annual lens photographs of AREDS participants (n = 3466/4757; 73%) were graded for severity of cataracts using the AREDS system for classifying cataracts from photographs. Clinical examinations conducted semiannually collected data on cataract surgery and visual acuity. Association of the change in lens opacities at 2 years with these outcomes at 5 years was analyzed with adjusted Cox proportional hazard models.

MAIN OUTCOME MEASUREMENTS: Progression of lens opacities on stereoscopic lens photographs at 2 years, cataract surgery, and visual acuity loss of 2 lines or more at 5 years.

RESULTS: The adjusted hazard ratios (HRs) for association of progression to cataract surgery at 5 years were: nuclear cataract increase of 1.0 unit or more compared with less than 1.0-unit change at 2 years, 2.77 (95% confidence interval [CI], 2.07-3.70; P < 0.001); cortical cataract increase of 5% or more in lens opacity in the central 5 mm of the lens compared with less than 5% increase at 2 years, 1.91 (95% CI, 1.27-2.87; P = 0.002); and posterior subcapsular cataract increase of 5% or more versus less than 5% in the central 5 mm of the lens, 8.25 (95% CI, 5.55-12.29; P < 0.001). Similarly, HRs of vision loss of 2 lines or more at 5 years for this degree of lens changes at 2 years were the following: nuclear, 1.83 (95% CI, 1.49-2.25; P < 0.001); cortical, 1.13 (95% CI, 0.78-1.65; P = 0.519); and posterior subcapsular cataract, 3.05 (95% CI, 1.79-5.19; P < 0.001).

CONCLUSIONS: Two-year changes in severity of lens opacities on the AREDS lens grading scale are predictive of long-term clinically relevant outcomes, making them potential surrogate end points in follow-up studies.

PMID: 25682177 [PubMed - as supplied by publisher]

Public Health. 2015 Feb 13. [Epub ahead of print]

Area deprivation and age related macular degeneration in the EPIC-Norfolk Eye Study.

Yip JL, Khawaja AP, Chan MP, et al

OBJECTIVES: To investigate the relationship between area deprivation, individual socio-economic status (SES) and age related macular degeneration (AMD).

STUDY DESIGN: Cross sectional study nested within a longitudinal cohort study.

METHODS: Data were collected in the EPIC-Norfolk Eye Study by trained nurses, using standardized protocols and lifestyle questionnaires. The English Index of multiple deprivation 2010 (IMD) was derived from participants' postcodes. AMD was identified from standardized grading of fundus photographs. Logistic regression was used to examine associations between IMD, SES and AMD.

RESULTS: 5344 pairs (62.0% of total 8623) of fundus photographs were of sufficient quality for grading of AMD. Of 5182 participants with complete data, AMD was identified in 653 participants (12.60%, 95%CI = 11.7-13.5%). Multivariable logistic regression showed that people living in the most affluent 5% of areas had nearly half the odds of AMD compared to those living in comparatively more deprived areas (OR = 0.56, 95% CI = 0.36-0.89, P = 0.02), after adjusting for age, sex, education, social class and smoking.

CONCLUSIONS: The authors found that living in the most affluent areas exerted a protective effect on AMD, independently of education and social class. Further investigation into underlying mechanisms will inform potential interventions to reduce health inequalities relating to AMD.

PMID: 25687711 [PubMed - as supplied by publisher]

F1000Res. 2014 Dec 2;3:293. eCollection 2014.

Slow progression of exudative age related macular degeneration associated with hypertrophy of the retinal pigment epithelium.

Stern J, Eveleth D, Masula J, Temple S.

RATIONALE: Choroidal neovascular (CNV) lesions in younger patients are often accompanied by the appearance of a surrounding ring of pigment that is associated with disease regression or slowed disease progression. In older patients with age-related macular degeneration (AMD), however, hypertrophy of the retinal pigment epithelium (RPE) is known to occur but has not previously been reported to be associated with CNV regression. This report describes the clinical course of a case series of AMD patients with

pigment hypertrophy adjacent to CNV associated with stabilization of the CNV lesion.

METHODS: A retrospective analysis of exudative AMD patients seen by a single retina specialist over a 7-year period.

RESULTS: Retrospective analysis of 955 exudative AMD patients revealed pigment hypertrophy associated with CNV in 33 patients. A ring of pigment surrounded CNV in 6 of these. Three representative patients are presented to illustrate the decrease in macular edema, reduced fluorescein leakage and slowed CNV progression that was associated with a pigment ring around CNV in AMD. Pigment hypertrophy was associated with blocked fluorescein leakage and exudative AMD patients with a complete pigment ring maintained stable visual acuity, macular edema, fluorescein leakage and CNV lesion size without treatment for intervals of up to 21 months.

CONCLUSION: We report slowed disease progression in AMD patients who develop pigment around CNV. The slow rate of disease progression in the AMD patient subgroup having a pigment ring is a factor to consider in determining the treatment interval for exudative AMD patients.

PMID: 25685325 [PubMed] PMCID: PMC4314661

Genetics

Gene. 2015 Feb 15. [Epub ahead of print]

Nonsynonymous single nucleotide polymorphisms in the complement component 3 gene are associated with risk of age-related macular degeneration: A meta-analysis.

Qian-Qian Y, Yong Y, Jing Z, et al.

Abstract: Nonsynonymous single nucleotide polymorphisms (SNPs) in complement component 3 (CC3) are associated with the risk of age-related macular degeneration (AMD), however, this association is not consistent among studies. To thoroughly address this issue, we performed an updated meta-analysis to evaluate the association between nine SNPs in the CC3 gene and AMD risk. A search was conducted of the PubMed database through 3rd Aug, 2014. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of associations. Based on the search criteria for manuscripts reporting AMD susceptibility related to CC3 in nine SNPs, 57 case-control studies from 22 different articles were retrieved. Significantly positive associations were found for the rs2230199 C/G SNP and AMD in the Caucasian population, as well as for the rs1047286 C/T SNP. Moreover, a relationship between the rs11569536 G/A SNP and AMD was detected. By contrast, a negative association was observed between rs2250656 A/G SNP and AMD risk. The present meta-analysis suggests that these four SNPs in the CC3 gene are potentially associated with the risk of AMD development. Further studies using larger sample sizes and accounting for gene-environment interactions should be conducted to elucidate the role of CC3 gene polymorphisms in AMD risk.

PMID: 25688879 [PubMed - as supplied by publisher]

Neuromolecular Med. 2015 Feb 14. [Epub ahead of print]

A Candidate Gene Association Study Identifies DAPL1 as a Female-Specific Susceptibility Locus for Age-Related Macular Degeneration (AMD).

Grassmann F, Friedrich U, Fauser S, et al

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among white caucasians over the age of 50 years with a prevalence rate expected to increase markedly with an anticipated increase in the life span of the world population. To further expand our knowledge of the genetic

architecture of the disease, we pursued a candidate gene approach assessing 25 genes and a total of 109 variants. Of these, synonymous single nucleotide polymorphism (SNP) rs17810398 located in death-associated protein-like 1 (DAPL1) was found to be associated with AMD in a joint analysis of 3,229 cases and 2,835 controls from five studies [combined P ADJ = 1.15 × 10-6, OR 1.332 (1.187-1.496)]. This association was characterized by a highly significant sex difference (P diff = 0.0032) in that it was clearly confined to females with genome-wide significance [P ADJ = 2.62 × 10-8, OR 1.541 (1.324-1.796); males: P ADJ = 0.382, OR 1.084 (0.905-1.298)]. By targeted resequencing of risk and non-risk associated haplotypes in the DAPL1 locus, we identified additional potentially functional risk variants, namely a common 897-bp deletion and a SNP predicted to affect a putative binding site of an exonic splicing enhancer. We show that the risk haplotype correlates with a reduced retinal transcript level of two, less frequent, non-canonical DAPL1 isoforms. DAPL1 plays a role in epithelial differentiation and may be involved in apoptotic processes thereby suggesting a possible novel pathway in AMD pathogenesis.

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Retinal pigment epithelial cells display specific transcriptional responses upon TNF-α stimulation.

Korthagen NM, van Bilsen K, Swagemakers SM, et al

BACKGROUND/AIMS: Tumour necrosis factor-α (TNF-α) is a key mediator of ocular inflammation and its interaction with the retinal pigment epithelium (RPE) may be a driving force in vitreoretinal disorders such as age-related macular degeneration, proliferative vitreoretinopathy (PVR) and diabetic retinopathy. Under inflammatory conditions, the ability of RPE cells to maintain the blood-retinal barrier and immune privilege may be lost and proliferation of RPE cells is facilitated. To gain insight into the effects of TNF-α on RPE cells, a gene expression study was performed.

METHODS: ARPE-19 and HT-29 cells were stimulated with 50 ng/mL TNF-α for 6 h. Gene expression patterns were compared between stimulated and control cells using whole genome gene expression arrays. Data were analysed using Partek and OmniViz and validated using quantitative RT-PCR. Functional annotation analysis was performed using Ingenuity and DAVID.

RESULTS: A total of 97 genes were uniquely modulated by TNF-α in ARPE-19 cells compared with HT-29 cells (86 upregulated and 11 downregulated). Most commonly affected biological processes were apoptosis, cell motility and cell signalling. The highest upregulated gene was EFNA1. Among the downregulated genes were transcription factors implicated in ocular development (SIX3, PAX6) and modulation of p53-mediated apoptosis (CITED2).

CONCLUSIONS: This study provides insight into the unique responses of RPE cells to TNF-α stimulation and suggests a role for genes involved in apoptosis and retinal epithelial development. These findings contribute to our understanding of the behaviour of RPE cells under inflammatory conditions and the crucial role of RPE cells in vitreoretinal diseases.

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