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MD Research News

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Drug treatment

Clin Ophthalmol. 2012;6:1175-86. Epub 2012 Jul 26.

Clinical and differential utility of VEGF inhibitors in wet age-related macular degeneration: focus on aflibercept.

Stewart MW.

College of Medicine, Mayo Clinic, Jacksonville, FL, USA.

Abstract

Age-related macular degeneration (AMD) has become a major public health problem and a leading cause of blindness in industrialized nations. AMD results from the ageing eye's inability to metabolize and dispose completely of photoreceptor outer segments and other waste products. As a result, lipids, particularly apolipoproteins, accumulate within Bruch's membrane, leading to chronic ischemia and inflammation. The subsequent upregulation of inflammatory cytokines and growth factors, including vascular endothelial growth factor (VEGF), induces the growth of neovascular membranes from the choriocapillaris into the subretinal or subretinal pigment epithelium spaces. To counter this, intravitreally administered drugs (pegaptanib, bevacizumab, ranibizumab) that specifically target VEGF have become the standard treatment for exudative AMD. Aflibercept, a recently approved fusion protein, binds to all isoforms of both VEGF-A and placental growth factor with high affinity. Phase III trials showed that monthly or every other month injections of aflibercept prevent vision loss (fewer than 15 letters) in 95% of patients. Additionally, aflibercept injections every 4 or 8 weeks produce average vision gains of 6.9 letters to 10.9 letters, comparable with those achieved with monthly ranibizumab. After one year of regularly administered aflibercept injections, patients required an average of only 4.2 injections during the second year. Aflibercept promises to decrease the injection frequency required for many patients and appears to serve as an effective "salvage" therapy for patients who respond poorly to other anti-VEGF drugs.

PMID: 22973088 [PubMed - in process]

Clin Ophthalmol. 2012;6:1149-57. Epub 2012 Jul 19.

Comparative study of 1+PRN ranibizumab versus bevacizumab in the clinical setting.

Carneiro AM, Mendonça LS, Falcão MS, Fonseca SL, Brandão EM, Falcão-Reis FM.

Department of Ophthalmology of Hospital de São João, Porto, Portugal.

PURPOSE: We compared the efficacy of intravitreal ranibizumab and bevacizumab for treating neovascular age-related macular degeneration using an on-demand regimen.

METHODS: A total of 186 wet age-related macular degeneration eyes of 186 treatment-naïve patients were compared retrospectively (67 eyes treated with ranibizumab with 91 treated with bevacizumab). At baseline, mean age, best corrected visual acuity, and angiographic lesion types were similar in both groups. Best corrected visual acuity and ocular coherence tomography were evaluated.

RESULTS: Sixty eyes treated with ranibizumab and 85 eyes treated with bevacizumab completed a 12-month evaluation. At 12 months, mean best corrected visual acuity increased by +6.65 letters with ranibizumab treatment and by +5.59 with bevacizumab treatment (P = 0.64). Visual acuity improved by ≥15 letters in 15 eyes treated with ranibizumab and in 21 eyes treated with bevacizumab (P = 0.75). An overall reduction in ocular coherence tomography central thickness occurred for all time points. The mean number of injections per eye was 5.97 with ranibizumab and 5.92 with bevacizumab (P = 0.90).

CONCLUSION: Intravitreal therapies with ranibizumab or bevacizumab have similar visual and anatomical results. These results confirm those of comparison of Age-Related Macular Degeneration Treatment Trials in as-needed cohorts in clinical practice. Randomized long-term clinical trials are necessary to examine the systemic safety of these treatments.

PMID: 22973087 [PubMed - in process

Arch Ophthalmol. 2012 Sep 1;130(9):1153-1161.

Factors Associated With Changes in Visual Acuity and Central Subfield Thickness at 1 Year After Treatment for Diabetic Macular Edema With Ranibizumab.

Bressler SB, Qin H, Beck RW, Chalam KV, Kim JE, Melia M, Wells JA; for the Diabetic Retinopathy Clinical Research Network.

OBJECTIVE: To identify factors that predict the success or failure of treatment with intravitreal ranibizumab for patients with diabetic macular edema.

METHODS: A total of 37 baseline demographic, systemic, ocular, optical coherence tomographic, and fundus photographic variables were assessed for association with change in visual acuity or central subfield thickness between baseline and 1 year in 361 eyes that were randomly assigned to intravitreal ranibizumab with prompt or deferred laser treatment within a trial of ranibizumab, triamcinolone acetonide, and laser treatment for center-involved diabetic macular edema. A categorical variable describing follow-up anatomic responses to therapy was added to the visual acuity outcome model.

RESULTS: After adjusting for baseline visual acuity, a larger visual acuity treatment benefit was associated with younger age (P < .001), less severe diabetic retinopathy on clinical examination (P = .003), and absence of surface wrinkling retinopathy (P < .001). The reduction in central subfield thickness during the first treatment year also predicted better visual acuity outcomes (P < .001). After adjusting for baseline central subfield thickness, the presence of hard exudates was associated with more favorable improvement on optical coherence tomographic scan (P = .004). Because only 11 eyes experienced vision loss and 6 eyes experienced an increase in central subfield thickness, factors for poor outcomes could not be evaluated.

CONCLUSIONS: A review of baseline factors and anatomic responses during the first year of ranibizumab therapy for association with visual acuity outcome did not identify any features that would preclude ranibizumab treatment. However, baseline central subfield thickness is the strongest predictor of anatomic outcome, and reduction in central subfield thickness during the first treatment year is associated with better visual acuity outcomes.

PMID: 22965591 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Sep 1;130(9):1145-52.

Long-term Effects of Ranibizumab on Diabetic Retinopathy Severity and Progression.

Ip MS, Domalpally A, Hopkins JJ, Wong P, Ehrlich JS.

OBJECTIVE: To evaluate effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity over time in 2 phase 3 clinical trials (RIDE, NCT00473382; RISE, NCT00473330) of ranibizumab for diabetic macular edema.

METHODS: Participants with diabetic macular edema (n = 759) were randomized to monthly sham, 0.3-mg ranibizumab, or 0.5-mg ranibizumab intravitreal injections. Macular laser was available per protocol-specified criteria. Fundus photographs, taken at baseline and periodically, were graded by a central reading center; clinical examinations were performed monthly. The main outcome measures of this report are secondary/exploratory analyses including a 2-step or more and 3-step or more change on the Early Treatment Diabetic Retinopathy Study severity scale in the study eye and a composite DR progression outcome including photographic changes plus clinically important events such as occurrence of vitreous hemorrhage or need for panretinal laser.

RESULTS: At 2 years, the percentage of participants with DR progression (worsening by ≥2 or ≥3 steps) was significantly reduced in ranibizumab-treated eyes compared with sham-treated eyes, and DR regression (improving by ≥2 or ≥3 steps) was significantly more likely. The cumulative probability of clinical progression of DR as measured by the composite outcome at 2 years was 33.8% of sham-treated eyes compared with 11.2% to 11.5% of ranibizumab-treated eyes.

CONCLUSIONS: Intravitreal ranibizumab reduced the risk of DR progression in eyes with diabetic macular edema, and many ranibizumab-treated eyes experienced improvement in DR severity. Because these results are exploratory, the use of intravitreal ranibizumab specifically to reduce DR progression or cause DR regression requires further study.

PMID: 22965590 [PubMed - in process

Clin Ophthalmol. 2012;6:1399-402. Epub 2012 Aug 28.

Exogenous group G Streptococcus endophthalmitis following intravitreal ranibizumab injection.

Kugu S, Sevim MS, Kaymak NZ, Erdogan G, Kandemir B, Dogan OK.

Lutfi Kırdar Kartal Training and Research Hospital, Eye Clinic, Istanbul.

Abstract

We report a case of group G Streptococcus endophthalmitis following an intravitreal ranibizumab injection for a choroidal neovascular membrane. Pars plana vitrectomy was applied for endophthalmitis and group G Streptococcus cultures were isolated in the vitreous samples taken from the patient. Twenty-four hours following pars plana vitrectomy the patient underwent myocardial infarction and cardiac arrest. To our knowledge this is the first reported case of group G Streptococcus endophthalmitis following an intravitreal injection.

PMID: 22969285 [PubMed - in process] PMCID: PMC3437953

Arch Ophthalmol. 2012 Sep 1;130(9):1226-7.

Reduction of vascular endothelial growth factor a in human breast milk after intravitreal injection of bevacizumab but not ranibizumab.

Ehlken C, Martin G, Stahl A, Agostini HT.

PMID: 22965611 [PubMed - in process]

Other treatment & diagnosis

Jpn J Ophthalmol. 2012 Sep 13. [Epub ahead of print]

Novel automated screening of age-related macular degeneration.

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PURPOSE: To determine the objective and quantitative hyperspectral parameters for distinguishing between age-related macular degeneration (AMD) and a normal macula.

METHODS: Near-infrared hyperspectral images were taken of 71 eyes of 62 AMD patients with exudative AMD and 21 eyes of 12 control subjects without AMD. The spatial information included a 480 × 321-pixel image in a 50° field located at the ocular fundus and a 720-950-nm-per-pixel reflectance spectrum. Macular vectors were determined as the average spectrum for each macula, and reference vectors were used as average macular vectors for healthy volunteers. Variations in vector length and angle were calculated based on comparison with the reference vector. The AMD differentiation index was a parameter that minimized the plot overlap between AMD patients and controls.

RESULTS: Statistically significant differences between the AMD patients and controls were noted. Receiver-operating characteristic curve analysis revealed an area under the curve of 0.888. The appropriate threshold values were attained for the proposed discrimination index, including 68 % sensitivity, 95 % specificity and 74 % accuracy.

CONCLUSIONS: This study presents a simplified diagnostic index for the determination of age-related macular degeneration based on near-infrared spectra.

PMID: 22968294 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Sep 8. [Epub ahead of print]

Spectral-Domain Optical Coherence Tomography Characteristics of Intermediate Age-Related Macular Degeneration.

Leuschen JN, Schuman SG, Winter KP, McCall MN, Wong WT, Chew EY, Hwang T, Srivastava S, Sarin N, Clemons T, Harrington M, Toth CA.

Duke Eye Center, Durham, North Carolina.

PURPOSE: Describe qualitative spectral-domain optical coherence tomography (SD-OCT) characteristics of eyes classified as intermediate age-related macular degeneration (nonadvanced AMD) from Age-Related Eye Disease Study 2 (AREDS2) color fundus photography (CFP) grading.

DESIGN: Prospective cross-sectional study.

PARTICIPANTS: We included 345 AREDS2 participants from 4 study centers and 122 control participants who lack CFP features of intermediate AMD.

METHODS: Both eyes were imaged with SD-OCT and CFP. The SD-OCT macular volume scans were graded for the presence of 5 retinal, 5 subretinal, and 4 drusen characteristics. In all, 314 AREDS2 participants with ≥1 category-3 AMD eye and all controls each had 1 eye entered into SD-OCT analysis, with 63 eyes regraded to test reproducibility.

MAIN OUTCOME MEASURES: We assessed SD-OCT characteristics at baseline.

RESULTS: In 98% of AMD eyes, SD-OCT grading of all characteristics was successful, detecting drusen in 99.7%, retinal pigment epithelium (RPE) atrophy/absence in 22.9%, subfoveal geographic atrophy in 2.5%, and fluid in or under the retina in 25.5%. Twenty-eight percent of AMD eyes had characteristics of possible advanced AMD on SD-OCT. Two percent of control eyes had drusen on SD-OCT. Vision loss was not correlated with foveal drusen alone, but with foveal drusen that were associated with other foveal pathology and with overlying focal hyperreflectivity. Focal hyperreflectivity over drusen, drusen cores, and hyper- or hyporeflectivity of drusen were also associated with RPE atrophy.

CONCLUSIONS: Macular pathologies in AMD can be qualitatively and reproducibly evaluated with SD-OCT, identifying pathologic features that are associated with vision loss, RPE atrophy, and even possibly the presence of advanced AMD not apparent on CFP. Qualitative and detailed SD-OCT analysis can contribute to the anatomic characterization of AMD in clinical studies of vision loss and disease progression.

PMID: 22968145 [PubMed - as supplied by publisher]

Ophthalmology. 2012 Sep 8. [Epub ahead of print]

Rasch Analysis Reveals Problems with Multiplicative Scoring in the Macular Disease Quality of Life Questionnaire.

Finger RP, Fenwick E, Pesudovs K, Marella M, Lamoureux EL, Holz FG.

Center for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Melbourne, Australia; Department of Ophthalmology, University of Bonn, Germany.

PURPOSE: To evaluate validity and psychometric characteristics of the Macular Disease Quality of Life questionnaire (MacDQoL), a multiplicative rating scale designed to measure vision-related quality of life (VRQoL) in macular diseases and age-related macular degeneration (AMD).

DESIGN: Cross-sectional study.

PARTICIPANTS: We included 108 patients with neovascular AMD at baseline before ranibizumab treatment.

METHODS: The psychometric properties of the MacDQoL were assessed using Rasch analysis, exploring key indices such as response category functioning, instrument unidimensionality, discriminant ability, and targeting of item difficulty to patient ability.

MAIN OUTCOME MEASURES: Measurement characteristics of the MacDQoL.

RESULTS: In the MacDQoL's native form, the majority of response categories were underutilized and thresholds disordered. This could not be remedied without eliminating the importance ratings owing to the ambiguous nature of the response categories. Scaling problems were resolved by using the impairment rating scale only and collapsing response categories to 4. However, the MacDQoL was multidimensional, necessitating the omission of a number of items and splitting it into an activity limitation and mobility and a socioemotional well-being scale. This improved the psychometric parameters of the revised MacDQoL, although no correlation with clinical measures such as visual acuity was found.

CONCLUSIONS: The multiplicative rating scale of the MacDQoL is flawed and does not provide scientific measurement of VRQoL. Measurement can be restored with a series of revisions to the instrument. This study reinforces the importance of considering rating scale design when choosing patient reported outcomes instruments for healthcare research.

PMID: 22968142 [PubMed - as supplied by publisher]

Int J Radiat Oncol Biol Phys. 2012 Sep 10. pii: S0360-3016(12)03296-8. doi: 10.1016/j.ijrobp.2012.07.2352. [Epub ahead of print]

Radiation Therapy for Neovascular Age-related Macular Degeneration.

Kishan AU, Modjtahedi BS, Morse LS, Lee P.

Harvard Medical School, Boston, Massachusetts.

Abstract

In the enormity of the public health burden imposed by age-related macular degeneration (ARMD), much effort has been directed toward identifying effective and efficient treatments. Currently, anti-vascular endothelial growth factor (VEGF) injections have demonstrated considerably efficacy in treating neovascular ARMD, but patients require frequent treatment to fully benefit. Here, we review the rationale and evidence for radiation therapy of ARMD. The results of early photon external beam radiation therapy are included to provide a framework for the sequential discussion of evidence for the usage of stereotactic radiation therapy, proton therapy, and brachytherapy. The evidence suggests that these 3 modern modalities can provide a dose-dependent benefit in the treatment of ARMD. Most importantly, preliminary data suggest that all 3 can be used in conjunction with anti-VEGF therapeutics, thereby reducing the frequency of anti-VEGF injections required to maintain visual acuity.

PMID: 22975610 [PubMed - as supplied by publisher]

J Ophthalmol. 2012;2012:542417. Epub 2012 Aug 30.

En Face OCT Imaging for the Diagnosis of Outer Retinal Tubulations in Age-Related Macular Degeneration.

Wolff B, Matet A, Vasseur V, Sahel JA, Mauget-Faÿsse M.

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Purpose: "En face" is an emerging imaging technique derived from spectral domain optical coherence tomography (OCT). It produces frontal sections of retinal layers, also called "C-scan OCT." Outer retinal tubulations (ORTs) in age-related macular degeneration (AMD) are a recent finding evidenced by spectral-domain OCT. The aim of this study is to characterize the morphology of ORT according to the form of AMD, using "en-face" spectral domain OCT.

Methods: "En face" OCT imaging was prospectively performed in 26 consecutive eyes with AMD that also had ORT.

Results: There were 15 neovascular, 8 atrophic, and 3 eyes with a mixed (fibrotic and atrophic) form of AMD. Among the neovascular group, the most frequent tubulation pattern on "en-face" OCT was a branching network emanating from a fibrovascular scar; we term this pattern as "pseudodendritic." It did not require treatment when observed as an isolated finding. In all cases of atrophic AMD, the tubular network was located at the edge of the geographic atrophy area, and formed a "perilesional" pattern. Six atrophic cases showed tubular invaginations inside this area.

Conclusion: "En face" OCT is a valuable technique in the diagnosis and followup of macular disease. It revealed the main characteristic patterns of ORT associated with neovascular and atrophic AMD.

PMID: 22970349 [PubMed] PMCID: PMC3437289

Acta Ophthalmol. 2012 Sep 12. doi: 10.1111/j.1755-3768.2012.02532.x. [Epub ahead of print]

Need to consensus for novel findings by optical coherence tomography in patients with age-related macular degeneration.

Gallego-Pinazo R, Dolz-Marco R, Pinazo Durán MD, Díaz-Llopis M.

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PMID: 22970835 [PubMed - as supplied by publisher]

Mol Vis. 2012;18:2300-8. Epub 2012 Sep 3.

Nano chitosan peptide as a potential therapeutic carrier for retinal delivery to treat age-related macular degeneration.

Jayaraman MS, Bharali DJ, Sudha T, Mousa SA.

Pharmaceutical Research Institute at Albany College of Pharmacy and Health Sciences, One Discovery Drive, Rensselaer, NY.

PURPOSE: We describe the synthesis and use of an efficient nano carrier molecule for retinal delivery of a nano chitosan peptide that has potential application for treating age-related macular degeneration (AMD). We chose serine-threonine-tyrosine as the peptide sequence because it is well known to act as a transduction signaling agent within and between retinal pigmented epithelium cells.

METHODS: A nanoformulation of a water-soluble chitosan conjugated with a peptide (serine-threonine-tyrosine) was synthesized by a method developed in our laboratory and characterized with dynamic light scattering, zeta potential, transmission electron microscopy, nuclear magnetic resonance, and Fourier transform infrared spectroscopy. The in vitro efficacy of the formulation was evaluated in retinal cells with confocal microscopy by studying the formulation's action on tyrosine kinase activity.

RESULTS: The conjugated nano chitosan peptide showed evidence of tyrosine kinase activity as seen by fluorescent signals under confocal microscopy, while nano chitosan or peptide alone did not show such activity.

CONCLUSIONS: Conjugated nano chitosan peptide may promote binding and engulfment. This molecule is an excellent carrier for retinal drug delivery and has the potential to treat age-related macular degeneration.

PMID: 22977298 [PubMed - in process]

Acta Ophthalmol. 2012 Sep 12. doi: 10.1111/j.1755-3768.2012.02503.x. [Epub ahead of print]

Reduction in the drusenoid retinal pigment epithelium detachment area in the dry form of age-related macular degeneration 2.5 years after rheohemapheresis.

Rencová E, Bláha M, Studnička J, Bláha V, Brožík J, Pazderová M, Rozsíval P, Langrová H.

Department of Ophthalmology, Medical Faculty and Faculty Hospital, Charles University, Hradec Králové, Czech Republic Second Department of Internal Medicine, Haematology, Medical Faculty and Faculty Hospital, Charles University, Hradec Králové, Czech Republic Department of Gerontology and Metabolic Care, Medical Faculty and Faculty Hospital, Charles University, Hradec Králové, Czech Republic Department of Radiology, Medical Faculty and Faculty Hospital, Charles University, Hradec Králové, Czech Republic Department of Ophthalmology, Regional Hospital, Pardubice, Czech Republic.

PMID: 22971248 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Sep 6. [Epub ahead of print]

Medical Decision-Making Capacity and Cataract Surgery.

Swanson MW.

School of Optometry, University of Alabama at Birmingham, Birmingham, Alabama.

BACKGROUND: Medical decision making has evolved from a paternalistic, "doctor knows best system" to one of shared decision making between health care providers and patients. Shared decision making involves informed consent related to the proposed health care options and medical decision-making capacity by patients. Adults aged 90 and older are the fastest growing segment of the US population. Dementia prevalence increases dramatically among this group. Dementia may affect the ability of patients to participate in shared decision making.

CASE REPORT: The case of a 91-year-old female rehabilitation inpatient with mild cognitive impairment, cataracts, and macular degeneration is presented. The case highlights key issues of informed decision making and medical decision-making capacity related to cataract surgery. Video examples of the assessment of cognitive and medical decision-making capacity are presented.

PMID: 22960617 [PubMed - as supplied by publisher]

Brain. 2012 Sep 7. [Epub ahead of print]

Microcystic macular degeneration from optic neuropathy.

Abegg M, Zinkernagel M, Wolf S.

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PMID: 22960546 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2012 Sep 4. [Epub ahead of print]

Risk of Age-related Macular Degeneration 3 Years after Cataract Surgery: Paired Eye Comparisons.

Wang JJ, Fong CS, Rochtchina E, Cugati S, de Loryn T, Kaushik S, Tan JS, Arnold J, Smith W, Mitchell P.

Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia; Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia.

OBJECTIVE: To clarify possible associations between cataract surgery and progression of age-related macular degeneration (AMD).

DESIGN: Clinic-based cohort.

PARTICIPANTS: We followed cataract surgical patients aged 65+ years in the Australian Cataract Surgery and Age-related Macular Degeneration (CSAMD) study. Patients who remained unilaterally phakic for at least 24 months after recruitment were included.

METHODS: We performed annual examinations with retinal photography. We assessed AMD using side-by-side grading of images from all visits. Paired comparisons between operated and nonoperated fellow eyes (defined as nonoperated or operated <12 months previously) were made using generalized estimating equation models.

MAIN OUTCOME MEASURES: Incident early AMD was defined as the new appearance of soft indistinct/reticular drusen or coexisting retinal pigmentary abnormality and soft distinct drusen in eyes at risk of early AMD. Incident late AMD was defined as the new appearance of neovascular AMD or geographic atrophy (GA) in eyes at risk of late AMD.

RESULTS: Among 2029 recruited, eligible participants, 1851 had cataract surgery performed at Westmead Hospital, Sydney, and 1244 (70.7%) had 36-month postoperative visits. Of these participants, 1178 had gradable photographs at baseline and at least 1 follow-up visit. Of 308 unilaterally operated participants at risk of late AMD, this developed in 4 (1.3%) operated and 7 (2.3%) nonoperated fellow eyes (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.23-2.36) after adjusting for the presence of early AMD at baseline. Of 217 unilaterally operated participants at risk of early AMD, this developed in 23 (10.6%) operated and 21 (9.7%) nonoperated fellow eyes (OR, 1.07; 95% CI, 0.74-1.65). Incident retinal pigment abnormalities were more frequent in operated than nonoperated fellow eyes (15.3% vs. 9.9%; OR, 1.64; 95% CI, 1.07-2.52). There was no difference in the 3-year incidence of large soft indistinct or reticular drusen between the 2 eyes (8.8% vs. 7.9%; OR, 1.12; 95% CI, 0.79-1.60).

CONCLUSIONS: Prospective follow-up data and paired eye comparisons of this older surgical cohort showed no increased risk of developing late AMD, early AMD, or soft/reticular drusen over 3 years. There was a 60% increased detection of retinal pigmentary changes in surgical eyes.

PMID: 22959104 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2012 Sep 7. doi:

Acta Ophthalmol. 2012 Sep 11. doi: 10.1111/j.1755-3768.2012.02511.x. [Epub ahead of print]

The Tromsø Eye Study: study design, methodology and results on visual acuity and refractive errors.

Bertelsen G, Erke MG, von Hanno T, Mathiesen EB, Peto T, Sjølie AK, Njølstad I.

Department of Ophthalmology and Neurosurgery, University Hospital of North Norway, Tromsø, Norway Research Group of Epidemiology of Chronic Diseases, Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway Brain and Circulation Research Group, Department of Clinical Medicine, Faculty of Health Sciences, University of Tromsø, Tromsø, Norway Department of Ophthalmology, Nordland Hospital, Bodø, Norway Department of Neurology and Neurophysiology, University Hospital of North Norway, Tromsø, Norway NIHR Biomedical Research Centre for Ophthalmology, Moorfields Eye Hospital, NHS Foundation Trust, London, UK UCL Institute of Ophthalmology, Head of Reading Centre, London, UK Department of Ophthalmology, Odense University Hospital, Odense, Denmark.

Purpose: To describe the study design and methodology of the Tromsø Eye Study (TES), and to describe visual acuity and refractive error in the study population.

Methods: The Tromsø Eye Study is a sub-study of the Tromsø Study, a population-based multipurpose longitudinal study in the municipality of Tromsø, Norway. The Tromsø Eye Study was a part of the sixth survey of the Tromsø Study, conducted from October 2007 through December 2008. The eye examination included information on self-reported eye diseases, assessment of visual acuity and refractive errors, retinal photography and optical coherence tomography. Retinal images were graded for diabetic retinopathy and age-related macular degeneration, and with computer-assisted measurements of arteriolar and venular diameters. In addition, TES researchers have access to the large comprehensive Tromsø Study database including physical examination results, carotid artery ultrasound, electrocardiogram, bone densitometry, cognitive tests, questionnaires, DNA, blood and urine samples and more from the present and the five previous surveys.

Results: Visual acuity was assessed in 6459 subjects and refraction in 6566 subjects aged 38-87 years. Snellen visual acuity <20/60 was found in 1.2% (95% CI 0.95-1.5) of the participants and there was no gender difference. Visual impairment increased with age, and in the age group 80-87 years, the overall visual acuity <20/60 was 7.3% (95% CI 3.3-11.2). Spherical equivalent showed an increasing trend with age and there was no clinically relevant difference between men and women. Retinal photography was performed in 6540 subjects.

Conclusion: Prevalence of visual impairment was low but increased with age. There was a trend towards hyperopia with age and no clinically relevant difference in refraction between the sexes. TES aims to provide epidemiological research on several eye and eye-related diseases. Owing to a comprehensive data collection, it

has the opportunity to explore issues related to environmental factors, cognition and their interaction with diseases in this community.

PMID: 22963377 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2012 Sep 8. [Epub ahead of print]

Prevalence and causes of visual impairment in elderly Amis aborigines in eastern Taiwan (the Amis Eye Study).

Chen N, Huang TL, Tsai RK, Sheu MM.

Department of Ophthalmology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung-Yang Road, Hualien, 97002, Taiwan.

PURPOSE: To investigate the prevalence and causes of visual impairment in elderly Amis aborigines in Eastern Taiwan.

METHODS: Population-based cross-sectional study of visual impairment of elderly Amis (65 years of age or older). We conducted ocular examinations on 2,316 participants, which represent 61.2 % of the elderly population. We used WHO criteria to identify visual impaired subjects, and the causes were analyzed.

RESULTS: Ninety-four subjects were identified with low vision and nineteen were blind. The prevalence of low vision was 4.06 % (95 % confidence interval, 3.26, 4.56 %); that of blindness was 0.82 % (95 % confidence interval, 0.45, 1.19 %). Cataracts (47.79 %) were the main cause of visual impairment, followed by age-related macular degeneration (15.93 %), corneal opacity (7.96 %), optic neuropathy (7.96 %), diabetic retinopathy (5.31 %), and retinitis pigmentosa (2.65 %). Glaucoma was a minor cause of visual impairment. There were no significant gender differences in the prevalence and specific causes of visual impairment.

CONCLUSION: The prevalence of treatable causes of vision impairment, for example cataracts and corneal opacity, is high among the elderly Amis aborigines. They would, therefore, benefit from a more aggressive and in-depth eye-care program as a blindness-prevention strategy.

PMID: 22961342 [PubMed - as supplied by publisher]

Pathogenesis

Exp Eye Res. 2012 Aug 31. [Epub ahead of print]

Melatonin: An underappreciated player in retinal physiology and pathophysiology.

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Abstract

In the vertebrate retina, melatonin is synthesized by the photoreceptors with high levels of melatonin at night and lower levels during the day. Melatonin exerts its influence by interacting with a family of G-protein-coupled receptors that are negatively coupled with adenylyl cyclase. Melatonin receptors belonging to the subtypes MT(1) and MT(2) have been identified in the mammalian retina. MT(1) and MT(2) receptors are found in all layers of the neural retina and in the retinal pigmented epithelium. Melatonin in the eye is believed to be involved in the modulation of many important retinal functions; it can modulate the electroretinogram (ERG), and administration of exogenous melatonin increases light-induced photoreceptor degeneration. Melatonin may also have protective effects on retinal pigment epithelial cells, photoreceptors and ganglion cells. A series of studies have implicated

melatonin in the pathogenesis of age-related macular degeneration, and melatonin administration may represent a useful approach to prevent and treat glaucoma. Melatonin is used by millions of people around the world to retard aging, improve sleep performance, mitigate jet lag symptoms, and treat depression. Administration of exogenous melatonin at night may also be beneficial for ocular health, but additional investigation is needed to establish its potential.

PMID: 22960156 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Sep 13. doi: 10.1111/j.1755-3768.2012.02539.x. [Epub ahead of print]

Physiological vitreous changes may contribute to the pathogenesis of macular degeneration.

Polak BC, Ringens PJ, Worst JG.

Department of Ophthalmology, VU University Medical Center, Amsterdam, The Netherlands Jan Worst Research Group, Haren, The Netherlands.

PMID: 22973902 [PubMed - as supplied by publisher]

Genetics

Ocul Immunol Inflamm. 2012 Sep 13. [Epub ahead of print]

Susceptibility Genes and Pharmacogenetics in Ocular Inflammatory Disorders.

Liu B, Nida Sen H, Nussenblatt R.

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Abstract

Ocular inflammatory disorders encompass uveitis, scleritis, keratitis, and other ocular diseases where inflammation may play a role. Although age-related macular degeneration (AMD) is clinically characterized by degenerative changes in the macula, accumulating evidence suggests that inflammation plays an important role in its pathogenesis. Pharmacogenetics is the study of the influence of genetic variation and its effects on drug efficacy or toxicity. There are no pharmacogenetic studies in uveitis and very few in AMD therapies. In this review, the authors describe the susceptibility genes related to uveitis and AMD and the important advances in pharmacogenetic research in relation to AMD and uveitis therapy. They propose polygenic and composite models of treatment responses to fulfill individualized drug therapy in intraocular inflammatory disorders.

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Plasma levels of complement proteins from the alternative pathway in patients with age-related macular degeneration are independent of Complement Factor H Tyr(402)His polymorphism.

Silva AS, Teixeira AG, Bavia L, Lin F, Velletri R, Belfort R Jr, Isaac L.

PURPOSE: To investigate the influence of the Factor H (CFH) Tyr(402)His polymorphism on the plasma levels of the alternative pathway proteins CFH, C3, Factor B (FB), Factor D (FD), and Factor I (FI) and the inflammatory marker C-reactive protein (CRP) in 119 patients with age-related macular degeneration (AMD) and 152 unrelated control individuals.

METHODS: Patients with AMD and the control group were separated according to CFH polymorphism, age, and gender. Plasma complement proteins and CRP concentrations were determined with enzyme-linked immunosorbent assay, immunodiffusion, or nephelometry.

RESULTS: Significant differences in the concentrations of FD and FI were observed between the patients with AMD and the control individuals. We observed significantly reduced FD plasma levels in patients with AMD. We also identified a significant decrease in CFH plasma levels in female patients with AMD in relation to female controls. Plasma FI levels were significantly increased in patients with AMD compared to the control group. Regarding gender, a significant increase in FI plasma levels was observed in male patients. Finally, we found no significant correlation between the CFH Tyr(402)His polymorphism and the CFH, C3, FB, FD, FI, and CRP plasma levels.

CONCLUSIONS: Patients with AMD present altered levels of FD and FI in a manner independent of this CFH polymorphism, and gender apparently contributes to the plasma levels of these two proteins in patients with AMD and control individuals.

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Effect of the Y402H Variant in the Complement Factor H Gene on the Incidence and Progression of Age-Related Macular Degeneration: Results From Multistate Models Applied to the Beaver Dam Eye Study.

Gangnon RE, Lee KE, Klein BE, Iyengar SK, Sivakumaran TA, Klein R.

OBJECTIVES: To investigate the effect of age, sex, and the Y402H variant in the complement factor H (CFH) gene on the incidence, progression, and regression of age-related macular degeneration (AMD) as well as the effect of these factors and AMD on mortality, using multistate models.

METHODS: Analyses included 4379 persons aged 43 to 84 years at the time of the census. The status of AMD on a 5-level severity scale was graded from retinal photographs taken at up to 5 study visits between 1988 and 2010. Multistate models in continuous time were used to model the effects of age, sex, and CFH genotype on the incidence, progression, and regression of AMD and mortality.

RESULTS: The CFH Y402H genotype CC was associated, relative to genotype TT (reported as hazard ratio; 95% CI), with increased incidence of AMD (no to minimally severe early AMD, 1.98; 1.57-2.49), progression of AMD (minimally severe early to moderately severe early AMD, 1.73; 1.29-2.33; moderately severe early to severe early AMD, 1.30; 0.86-1.94; and severe early to late AMD, 1.72; 1.01-2.91) but not with regression of AMD or mortality. Late AMD was associated with increased mortality (1.37; 1.15-1.62) relative to no AMD, but earlier stages of AMD were not.

CONCLUSIONS: Using the multistate models, we show that the Y402H risk variant is associated with lifetime incidence of early AMD and progression of early to late AMD and that late AMD is associated with mortality risk.

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Single nucleotide polymorphism in the cholesterol-24S-hydroxylase (CYP46A1) gene and its association with CFH and LOC387715 gene polymorphisms in AMD.

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Purpose: To investigate the association of single nucleotide polymorphism (SNP) in the cholesterol-24S-hydroxylase (CYP46A1) gene, according to CFH and LOC387715 SNPs, with age-related macular degeneration (AMD).

Methods: 1388 AMD patients with neovascular AMD or geographic atrophy and 487 unrelated control subjects were enrolled. SNPs were genotyped in the CYP46A1 (rs754203), LOC387715 (rs10490924) and CFH (rs1061170) genes. Plasma 24S-hydroxycholesterol, the metabolic product of CYP46A1, was quantified by gas chromatography-mass spectrometry using an authentic deuterated internal standard in sub-groups of patients and controls. The χ² test was used to compare categorical allelic and genotype distributions between cases and controls. The odds ratio (OR) with a 95% confidence interval (95% CI) was calculated for AMD risk and adjusted for age and gender. Significance levels were set at $p<0.05$.

Results: The rs754203 SNP in the CYP46A1 gene was not associated with AMD (crude OR=1.2, 95% CI=0.9-1.4, p=0.2). The crude OR for risk of AMD was 2.9 (95% CI=2.4-3.4, $p<0.0001$) according to the number of rs10490924 T alleles in the LOC387715 gene, and 2.0 (95% CI=1.7-2.3, $p<0.0001$) according to the number of rs1061170 C alleles in the CFH gene. After adjustment for age and gender, an OR of 2.2 (95% CI=1.1-4.1, p=0.04) was obtained for AMD cases with the C allele in the CYP46A1 gene and carrying no risk alleles in the CFH and LOC387715 genes.

Conclusions: The rs754203 C allele in the CYP46A1 gene may confer a higher risk for exudative AMD in patients who carry no risk alleles in the CFH and LOC387715 genes. Additional studies with larger sample sizes are needed in AMD subjects at no risk in CFH and LOC387715.

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Lack of association between SMOC2 polymorphism and age-related macular degeneration in Jordanian Arabs.

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