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Drug treatment

Eye (Lond). 2016 May 20. [Epub ahead of print]

Variability of disease activity in patients treated with ranibizumab for neovascular age-related macular degeneration.

Enders P, Scholz P, Muether PS, Fauser S.

Purpose: To analyze choroidal neovascularization (CNV) activity and recurrence patterns in patients with neovascular age-related macular degeneration (nAMD) treated with ranibizumab, and the correlation with individual intraocular vascular endothelial growth factor (VEGF) suppression time (VST).

Methods: Post-hoc analysis of data from a prospective, non-randomized clinical study. Patients with nAMD treated with ranibizumab on a pro re nata regimen. Disease activity was analyzed monthly by spectral-domain optical coherence tomography and correlated with VSTs.

Results: Overall, 73 eyes of 73 patients were included in the study with a mean follow-up of 717 days (range: 412-1239 days). Overall, the mean CNV-activity-free interval was 76.5 days (range: 0-829 days). The individual range of the length of dry intervals was high. A total of 42% of patients had a range of more than 90 days. Overall, 16% of patients showed persistent activity. And 12% stayed dry after the initial ranibizumab treatment. No significant correlation was found between the CNV-recurrence pattern and VST ($P=0.12$).

Conclusions: CNV activity in nAMD is irregular, which is reflected in the range of the duration of dry intervals and late recurrences. The biomarker VST solely seems not to be sufficient to explain recurrence pattern of CNV in all AMD patients.

PMID: 27197870 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2016 May 1;47(5):458-65.

Factors Associated With Poor Response to Aflibercept After Switching From Ranibizumab or Bevacizumab in Neovascular Age-related Macular Degeneration.

Cheng S, Leng T.

BACKGROUND AND OBJECTIVE: The purpose of this study was to analyze demographic and ocular features of patients with age-related macular degeneration who failed aflibercept (Eylea; Regeneron, Tarrytown, NY) treatment after switching from ranibizumab (Lucentis; Genentech, South San Francisco, CA) or bevacizumab (Avastin; Genentech, South San Francisco, CA).

PATIENTS AND METHODS: Retrospective chart review of patients treated with aflibercept at the Byers

Eye Institute from November 2011 to August 2014. Patient visual acuity was noted prior to aflibercept; after 1, 3, and 12 months; and on the most recent visit. Patients who improved vision after switching were compared to patients who lost vision. Demographic and imaging features were analyzed using univariate and multivariate statistics.

RESULTS: Patients who lost vision had significantly higher BMI ($P = .013$, multivariate) and geographic atrophy ($P = .0381$, univariate; $P = .1$, multivariate) compared to patients who improved vision.

CONCLUSION: BMI and geographic atrophy may be considered as potential indicators for poor response to aflibercept after switching from ranibizumab or bevacizumab. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:458-465.].

PMID: 27183550 [PubMed - in process]

Eye (Lond). 2016 May 20. [Epub ahead of print]

Determinants of visual acuity outcomes in eyes with neovascular AMD treated with anti-VEGF agents: an instrumental variable analysis of the AURA study.

Holz FG, Tadayoni R, Beatty S, Berger AR, Cereda MG, Hykin P, Staurengi G, Wittrup-Jensen K, Nilsson J, Kim K, Sivaprasad S.

Purpose: To identify the strongest variable(s) linked with the number of ranibizumab injections and outcomes in AURA, and to identify ways to improve outcomes using this association.

Methods: AURA was a large observational study that monitored visual acuity over a 2-year period in patients with neovascular age-related macular degeneration (AMD) who received ranibizumab injections. Baseline characteristics, resource use, and outcomes were analyzed using an instrumental variable approach and regression analysis.

Results: Data were analyzed from 2227 patients enrolled in AURA. Optical coherence tomography (OCT) and ophthalmoscopy were the most common diagnostic tests used, and this combination was the strongest instrumental variable. Use of OCT and ophthalmoscopy affected the number of injections given and resulted in an increase in visual acuity gains from baseline of 17.6 letters in year 1 and 2.5 letters in year 2. Regression models using the instrumental variable (OCT and ophthalmoscopy combined) showed that ≥ 5.1 (95% CI: 3.3-11.4) ranibizumab injections were needed to maintain visual acuity from baseline to year 1 and ≥ 8.3 (95% CI: 5.3-18.8) injections were needed to maintain visual acuity from year 1 to year 2. To gain ≥ 15 letters, ≥ 7.9 (95% CI: 5.1-17.5) ranibizumab injections would be needed in year 1 and ≥ 16.1 (95% CI: 10.3-36.4) injections would be needed over 2 years.

Conclusions: These findings highlight the role that regular monitoring plays in guiding neovascular AMD therapy and they showed that the number of ranibizumab injections needed to maintain visual acuity is higher than that administered in AURA.

PMID: 27197868 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2016 May 1;47(5):477-81.

Progressive Release of Vitreomacular Traction With Aflibercept.

Schwartz SG, Flynn HW Jr.

Abstract: A patient with combined diabetic macular edema (DME) and vitreomacular traction (VMT) was treated with a series of intravitreal aflibercept (Eylea; Regeneron, Tarrytown, NY) injections. The VMT progressively released during the course of the five intravitreal injections. This release may have been spontaneous, due to a nonspecific mechanical effect from the injections, or due to a pharmacologic effect

from the aflibercept. While treating DME, anti-vascular endothelial growth factor agents may have an additional benefit in releasing VMT. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:477-481.].

PMID: 27183554 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2016 May 1;47(5):474-6.

Reduction of Diabetic Macular Edema in the Untreated Fellow Eye Following Intravitreal Injection of Aflibercept.

Calvo CM, Sridhar J, Shahlaee A, Ho AC.

Abstract: A 59-year-old patient with bilateral worsening diabetic macular edema received intravitreal injection of aflibercept (Eylea; Regeneron, Tarrytown, NY) to the left eye only. On 1-month follow-up, there was noted bilateral improvement of visual acuity and diabetic macular edema on spectral-domain optical coherence tomography imaging, reflecting bilateral effect of unilateral treatment with aflibercept. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:474-476.].

PMID: 27183553 [PubMed - in process]

PLoS One. 2016 May 20;11(5):e0153052. eCollection 2016.

Comparing the Effectiveness of Bevacizumab to Ranibizumab in Patients with Exudative Age-Related Macular Degeneration. The BRAMD Study.

Schauwvlieghe AM, Dijkman G, Hooymans JM, Verbraak FD, Hoyng CB, Dijkgraaf MG, Peto T, Vingerling JR, Schlingemann RO.

PURPOSE: To compare the effectiveness of bevacizumab and ranibizumab in the treatment of exudative age-related macular degeneration (AMD).

DESIGN: Multicentre, randomized, controlled, double-masked clinical trial in 327 patients. The non-inferiority margin was 4 letters.

PATIENTS: Patients ≥ 60 years of age with primary or recurrent sub- or juxtafoveal choroidal neovascularization (CNV) secondary to AMD with a total area of CNV < 12 disc areas and a best corrected visual acuity (BCVA) score between 20 and 78 letters on an EDTRS like chart in the study eye.

METHODS: Monthly intravitreal injections with 1.25 mg bevacizumab or 0.5 mg ranibizumab were given during one year. Intention to treat with last observation carried forward analysis was performed.

MAIN OUTCOME MEASURES: Primary outcome was the change in BCVA in the study eye from baseline to 12 months.

RESULTS: The mean gain in BCVA was 5.1 (± 14.1) letters in the bevacizumab group ($n = 161$) and 6.4 (± 12.2) letters in the ranibizumab group ($n = 166$) ($p = 0.37$). The lower limit of the 95% confidence interval of the difference in BCVA gain was 3.72. The response to bevacizumab was more varied; 24% of patients showed a gain of ≥ 15 letters, 11% a loss of ≥ 15 letters and 65% a gain or loss < 15 letters compared to 19%, 5% and 76% respectively for ranibizumab ($p = 0.038$). No significant differences in absolute CRT and CRT change ($p = 0.13$) or in the presence of subretinal or intraretinal fluid ($p = 0.14$ and 0.10 , respectively) were observed. However, the presence of any fluid on SD-OCT (subretinal and/or intraretinal) differed significantly ($p = 0.020$), with definite fluid on SD-OCT in 45% of the patients for bevacizumab versus 31% for ranibizumab. The occurrence of serious adverse events and adverse events was similar, with 34 SAEs and 256 AEs in the bevacizumab group and 37 SAEs and 299 AEs in the ranibizumab group ($p = 0.87$ and $p = 0.48$, respectively).

CONCLUSIONS: Bevacizumab was not inferior to ranibizumab. The response to bevacizumab was more varied with higher percentages of both gainers and losers and more frequently observed retinal fluid on SD-OCT at 12 months when compared to the ranibizumab group.

PMID: 27203434 [PubMed - in process]

J Ophthalmol. 2016;2016:7689862. Epub 2016 Apr 20.

Different Strategies for the Treatment of Age-Related Macular Degeneration in China: An Economic Evaluation.

Wu B, Li J, Lin H, Wu H.

Purpose: To assess the cost-effectiveness of bevacizumab compared to ranibizumab, verteporfin photodynamic therapy (PDT), and usual care for the treatment of age-related macular degeneration (AMD) in China.

Methods: A Markov model was developed according to patient visual acuity (VA) in the better-seeing eye (Snellen scale). Four cohorts of patients were treated with one of the following therapies: bevacizumab, ranibizumab, PDT, or usual care. Clinical data related to treatments were obtained from published randomized clinical trials. Direct medical costs and resource utilization in the Chinese health care setting were taken into account. Health and economic outcomes were evaluated over a lifetime horizon. Sensitivity analyses were performed.

Results: Treatment with ranibizumab provided the greatest gains in quality-adjusted life-years (QALYs). The cost per marginal QALY gained with bevacizumab over usual care was \$1,258, \$3,803, and \$2,066 for the predominantly classic, minimally classic, and occult lesions, respectively. One-way sensitivity analysis showed considerably influential factors, such as utility values and effectiveness data. Probabilistic sensitivity analysis indicated that, compared to usual care, PDT and ranibizumab most cases would be cost-effective in the bevacizumab arm at a threshold of \$7,480/QALY.

Conclusion: Bevacizumab can be a cost-effective option for the treatment of AMD in the Chinese setting.

PMID: 27200183 [PubMed] PMCID: PMC4855017

Br J Ophthalmol. 2016 May 17. [Epub ahead of print]

Three-month outcome of intravitreal ziv-aflibercept in eyes with diabetic macular oedema.

Mansour AM, Dedhia C, Chhablani J.

PURPOSE: We report the 3-month efficacy of monthly intravitreal ziv-aflibercept in patients with diabetic macular oedema (DME).

METHODS: Prospectively, consecutive patients with DME underwent intravitreal injection of 0.05 ml of compounded ziv-aflibercept (1.25 mg) from March 2015 to November 2015. Monitoring of best-corrected visual acuity (BCVA), intraocular inflammation, cataract progression and retinal structure by spectral domain optical coherence tomography was carried out at baseline, 1 week, 1 month, 2 months and 3 months after 3 monthly injections.

RESULTS: A total of 17 eyes (11 right eyes and 6 left eyes) were treated. The participants were divided into 10 Caucasians and 6 Indians, 11 men and 5 women, and had a mean age of 61.5 years. Five eyes were treatment-naïve cases and 12 eyes were treatment non-naïve with last treatment received at least more than 4-month interval. Mean BCVA in log MAR (equivalent Snellen visual acuity) improved from baseline 0.70 (20/100) to 0.49 (20/60) at 1 month, 0.43 (20/50) at 2 months and 0.42 (20/50) at 3 months ($p \leq 0.003$). Central macular thickness decreased from mean baseline 517.5 to 388.1 μm at 1 week, 355.4 μm

at 1 month, 351.4 μm at 2 months and 322.2 μm at 3 months ($p \leq 0.001$).

CONCLUSIONS: Off-label use of intravitreal ziv-aflibercept improves visual acuity, without detectable ocular toxicity or systemic side effects in DME. It offers a less expensive alternative to the approved intravitreal aflibercept (Eylea), especially in the low/middle-income countries and in countries where Eylea is not available.

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PMID: 27190127 [PubMed - as supplied by publisher]

Ophthalmol Ther. 2016 May 19. [Epub ahead of print]

Electronic Patient Records to Identify Patients in the United Kingdom with Diabetic Macular Oedema Suitable for ILUVIEN® (Fluocinolone Acetonide).

Butt F, Khan K, Chaudhry S, Khan R.

INTRODUCTION: We describe a proactive method using electronic patient records (EPR) to identify pseudophakic patients with diabetic macular oedema (DMO) that might benefit from treatment with 0.2 μg /day fluocinolone acetonide (FAC; ILUVIEN®) implant.

METHODS: Our EPR audit tool (Medisoft®) identified diabetic patients (May 2011-December 2014) with National Screening Committee-confirmed grade M1 maculopathy. Searches segmented this DMO patient population into patient groups who: (1) had received ranibizumab therapy, (2) had received ≥ 2 macular laser treatments, or (3) were unsuitable for macular laser or ranibizumab therapy. Pre-specified criteria identified patients insufficiently responsive to treatment, and their electronic case notes were flagged for clinicians to consider FAC, based on National Institute for Health and Care Excellence (NICE) TA301.

RESULTS: Using this methodology, 138 patients with DMO were identified, of whom 87 were assigned to group 1, 32 to group 2, and 29 to group 3 (10 patients were included in both groups 2 and 3). From these, 28 different pseudophakic eyes were identified as suitable for treatment with FAC, based on insufficient response to prior treatment.

CONCLUSION: EPR audit offers a real-world methodology to efficiently identify patients that might benefit from treatment with FAC. Limitations apply, and thorough documentation of lens status and ocular comorbidities is vital; however, this approach was more rapid than prospective recruitment through the clinic. Flagging patient records using EPR audit offers a practical process for application to clinical practice, thereby optimizing patient care in line with NICE TA301 guidelines.

PMID: 27192988 [PubMed - as supplied by publisher]

BioDrugs. 2016 May 17. [Epub ahead of print]

Choroidal Thickness Changes After Intravitreal Ranibizumab for Exudative Age-Related Macular Degeneration.

Minnella AM, Federici M, Falsini B, Barbano L, Gambini G, Lanza A, Caporossi A, Savastano MC.

BACKGROUND: The results regarding changes of choroidal thickness following intravitreal ranibizumab injections in the literature are controversial. Vascular endothelial growth factor A is implicated in pathogenesis of neovascular age-related macular degeneration (AMD). The suspected unchanged choroidal layer thickness after intravitreal injections of ranibizumab suggests a possible protection of the outer blood-retinal barrier in the human eye.

OBJECTIVE: The aim was to evaluate choroidal thickness following the first administration of the study drug ranibizumab into the eyes of naïve wet AMD patients (nAMD).

METHODS: In this open label, 3-month, prospective, single-center, interventional, single-arm pilot study, 20 nAMD eyes were included and underwent three consecutive monthly injections of ranibizumab (0.5 mg/0.05 ml). Vital signs (i.e., blood pressure and pulse), ophthalmic examinations, intraocular pressure, best correct visual acuity and subfoveal choroidal thickness as examined with optical coherence tomography using enhanced depth imaging (OCT-EDI) were assessed at each visit. All patients were evaluated at baseline and at 15, 30 60 and 90 days after intravitreal injection. Ten eyes with fibrotic AMD lesions were evaluated as the control group.

RESULTS: In all eyes, the choroidal thicknesses (μm) exhibited no significant changes from the baseline visit to the visits at 15, 30, 60 and 90 days post-injection ($P > 0.05$). The intravitreal treatment with ranibizumab was well tolerated, and no adverse events were registered.

CONCLUSION: Choroidal thickness appeared to be unmodified following the intravitreal injection of ranibizumab into nAMD eyes. Intravitreal ranibizumab injections probably elicit a pharmacologic effect only in the choroidal neovascularization and not in the choroid circulation under neovascular lesions. Clinical Trials Eudract Registration #: 2013-005091-17.

PMID: 27189458 [PubMed - as supplied by publisher]

J Ophthalmol. 2016;2016:8421940. Epub 2016 Apr 12.

Comparison of the Efficacy of Intravitreal Aflibercept and Bevacizumab for Macular Edema Secondary to Branch Retinal Vein Occlusion.

Wang JK, Su PY, Hsu YR, Chen YJ, Chen FT, Tseng YY.

Abstract: Fifty-two eyes of 52 patients with treatment-naïve macular edema associated with perfused branch retinal vein occlusion were retrospectively reviewed. Twenty-seven cases received PRN intravitreal bevacizumab, and 25 cases were treated by PRN intravitreal aflibercept with monthly follow-ups for 12 months. Both aflibercept and bevacizumab were effective in reduction of macular thickness and improvement of visual acuity for the participants. Both antivascular endothelial growth factor agents had similar efficacy and duration of treatment for these eyes with macular edema secondary to branch retinal vein occlusion during a 12-month period. No serious systemic or ocular adverse events were reported.

PMID: 27190640 [PubMed] PMCID: PMC4844878

Drug Deliv Transl Res. 2016 May 18. [Epub ahead of print]

Lipid-based drug delivery systems in the treatment of wet age-related macular degeneration.

Du JD, Fong WK, Caliph S, Boyd BJ.

Abstract: Recent advances in drug delivery technology have amplified potential opportunities to treat the debilitating diseases that affect the posterior segment of the eye in a less invasive and more efficient manner. Current methods for effective drug delivery to the back of the eye are hindered by many barriers and limitations. As a consequence, considerable efforts have been directed towards developing new materials to selectively deliver drug directly to the target site. This review focuses on lipid-based delivery systems which show promise in improving treatment for the most common disease of the posterior segment of the eye in the developed world, age-related macular degeneration, with an emphasis upon on-demand delivery systems as they have greater potential to overcome the current limitations.

PMID: 27194165 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Klin Monbl Augenheilkd. 2016 May;233(5):613-21. Epub 2016 May 17.

[New Possibilities in Retinal Diagnostics Using OCT Angiography]. [Article in German]

Lang GE, Enders C, Werner JU.

BACKGROUND: Instruments for using OCT angiography (OCTA) in daily clinical practice have recently become available. The aim of this paper is to report the possibilities, advantages and limitations of OCTA in the clinical diagnosis of diseases of the posterior segment of the eye.

PATIENTS/METHODS: Patients with diabetic retinopathy, retinal vascular occlusions, and age-related macular degeneration who had been assigned to fluorescein angiography (FA) additionally underwent an AngioPlex™-OCTA examination, which captures a 6 × 6 mm scanning area centred on the fovea. If deemed necessary, 3 × 3 mm volume scans were created in regions of interest. The findings of FA and OCTA were correlated and compared.

RESULTS: The OCTA procedure took only a few seconds, was easily integrated into the standard OCT diagnostic imaging procedure, and delivered highly detailed, three dimensional images of the entire microvasculature of the retina and choroid. Microvascular changes, such as microaneurysms, intraretinal microvascular abnormalities, non-perfused areas, alterations in the foveal avascular zone (FAZ) and neovascularization were reliably detected. Overall, OCTA results were in good agreement with the results of the FA. Additionally, OCTA provided more detailed and three dimensional information and thus permitted a better assessment of the spatial extension of microvascular abnormalities. Due to OCTA's limited scanning area, vascular alterations in the mid-periphery were detected only if their location had already been determined by FA. Although OCTA does not show leakage, macular oedema can be diagnosed from OCTA, together with OCT thickness measurements.

CONCLUSION: OCTA provides important three dimensional information on vascular alterations and is already an indispensable diagnostic method. As the procedure takes just a few seconds and can be performed non-invasively, OCTA is well suited as a monitoring method and may allow early diagnosis. In this sense, prospective studies are required to determine precise OCTA analytical strategies for specific diseases. It is very likely that OCTA will revolutionise the diagnosis of retinal and choroidal diseases; however, it is not yet clear estimated to what extent it will replace FA.

PMID: 27187882 [PubMed - in process]

Ophthalmology. 2016 May 17. [Epub ahead of print]

Automated Identification of Lesion Activity in Neovascular Age-Related Macular Degeneration.

Chakravarthy U, Goldenberg D, Young G, Haviilo M, Rafaeli O, Benyamini G, Loewenstein A.

PURPOSE: The objective of the study was to evaluate the accuracy of the Notal OCT Analyzer (NOA) versus that of a retina specialist (RS) in the automated detection of fluid on optical coherence tomography (OCT).

DESIGN: A study of the performance of the NOA compared with the results from 3 RSs.

PARTICIPANTS: A selection of 155 anonymized OCT scans (Zeiss Cirrus; Carl Zeiss Meditec, Dublin, CA) from an image repository at a single tertiary referral retina center (Belfast Health and Social Care Trust, Belfast, United Kingdom) after approval from the local data guardian of the clinical site.

METHODS: One hundred fifty-five OCT cube scans were stripped of all clinical identifiers and exported. The NOA and 3 independent RSs analyzed all 128 B-scans of each cube scan for the presence of intraretinal fluid, subretinal fluid, and sub-retinal pigment epithelium fluid. The NOA also ranked individual B

-scans of each volume scan for likelihood of CNV activity, which was subjected to a second grading session by the 3 RSs.

MAIN OUTCOME MEASURES: The NOA's sensitivity and specificity versus the RS grading and the NOA's performance in ranking B-scans for activity.

RESULTS: One hundred forty-two cube scans met the inclusion criteria for the primary analysis. On testing the RS grading versus the NOA, the accuracy was 91% (95% confidence interval [CI], $\pm 7\%$), sensitivity was 92% (95% CI, $\pm 6\%$), and specificity was 91% (95% CI, $\pm 6\%$), meeting the primary outcome. The graders' accuracy when compared with the majority of the other graders (including a fourth grader) was 93%. On average, the 3 graders could identify fluid in 95% of scans by just reviewing a single cross-section with the highest NOA score and 99.5% of scans with fluid by viewing the top 3 cross-sections.

CONCLUSIONS: Concordance between the NOA and the RS determination of lesion activity was extremely high. The level of discrepancy between the RS and the NOA results was similar to the NOA's mismatches. Our results show that automated delineation of the retinal contours combined with interpretation of disease activity is feasible and has the potential to become a powerful tool in terms of its clinical applications.

PMID: 27206840 [PubMed - as supplied by publisher]

Pak J Med Sci. 2016 Mar-Apr;32(2):516-8.

Delayed visual loss due to radiation retinopathy.

Uzun S, Toyran S, Akay F, Gundogan FC.

Abstract: Radiation retinopathy remains a devastating cause of visual morbidity in patients undergoing radiation for globe, orbit, and head and neck malignancies. A 65-year-old female was admitted with the complaint of low vision in the right eye for two months. Best corrected visual acuity was 20/32 in the right eye and 20/25 in the left eye. Slit lamp examination was normal in both eyes. Fundoscopic examination revealed perifoveolar hard exudates, paramacular microhemorrhages, telangiectasias, and macular degeneration in both eyes. Fundus fluorescein angiography showed enlargement of the foveal avascular zone, perifoveal capillary telangiectasia, and widespread venous beading bilaterally. Optical coherence tomography revealed bilateral cystoid macular edema. The prediagnosis of diabetic retinopathy was not confirmed because of the absence of diabetes mellitus after endocrinologic evaluation. Detailed medical history explored external beam radiotherapy to the head and neck region for nasopharyngeal cancer 10 years ago. The ultimate diagnosis was radiation retinopathy.

PMID: 27182273 [PubMed] PMCID: PMC4859056

Graefes Arch Clin Exp Ophthalmol. 2016 May 18. [Epub ahead of print]

Exploring choriocapillaris under reticular pseudodrusen using OCT-Angiography.

Alten F, Heiduschka P, Clemens CR, Eter N.

PURPOSE: To evaluate if choriocapillaris (CC) vessel density and CC decorrelation signal index are compromised in eyes with reticular pseudodrusen (RPD) using optical coherence tomography angiography (OCT-A).

METHODS: Decorrelation values in OCT-A CC images of 20 RPD patients were measured in the outer superior and the outer inferior sector of the EDTRS grid and compared to age-matched healthy controls. CC vessel density and CC decorrelation signal index were measured within a 30 μm and a 10 μm OCT-A CC slab. CC data were correlated to number of RPD lesions, predominantly present RPD stage, predominantly present RPD type, retinal area affected by RPD and choroidal thickness (CT).

RESULTS: CC vessel density and CC decorrelation signal index decreased in correlation to advancing age in healthy subjects particularly in subjects older than 60 years (CC vessel density: 30 μm : $p=0.0019$; 10 μm : $p=0.0014$; CC decorrelation signal index: 30 μm : $p=0.0005$; 10 μm : $p=0.0003$). In the RPD group, CC vessel density (outer superior sector, 10 μm : 98.299) and CC decorrelation signal index (89.07) were significantly reduced compared to controls (99.203, $p=0.0002$; 98.09, $p=0.0010$). The number of RPD lesions was correlated to a reduced CC vessel density (30 μm : $p=0.0355$) but not to changes in CC decorrelation signal index. No correlations were found between CC parameters and either RPD stage, RPD type, size of RPD affected area or CT.

CONCLUSIONS: OCT-A reveals a distinct reduction in CC vessel density and CC decorrelation signal index in eyes affected by RPD, which emphasizes the relevance of the CC layer in RPD pathogenesis.

PMID: 27193430 [PubMed - as supplied by publisher]

J Ophthalmol. 2016;2016:5893601. Epub 2016 Apr 14.

Automatic Screening and Grading of Age-Related Macular Degeneration from Texture Analysis of Fundus Images.

Phan TV, Seoud L, Chakor H, Cheriet F.

Abstract: Age-related macular degeneration (AMD) is a disease which causes visual deficiency and irreversible blindness to the elderly. In this paper, an automatic classification method for AMD is proposed to perform robust and reproducible assessments in a telemedicine context. First, a study was carried out to highlight the most relevant features for AMD characterization based on texture, color, and visual context in fundus images. A support vector machine and a random forest were used to classify images according to the different AMD stages following the AREDs protocol and to evaluate the features' relevance. Experiments were conducted on a database of 279 fundus images coming from a telemedicine platform. The results demonstrate that local binary patterns in multiresolution are the most relevant for AMD classification, regardless of the classifier used. Depending on the classification task, our method achieves promising performances with areas under the ROC curve between 0.739 and 0.874 for screening and between 0.469 and 0.685 for grading. Moreover, the proposed automatic AMD classification system is robust with respect to image quality.

PMID: 27190636 [PubMed] PMCID: PMC4848444

Int Med Case Rep J. 2016 Apr 19;9:95-9. eCollection 2016.

Progressive symmetric vertical macular wide angioid streak-like lacquer crack.

Mansour AM.

PURPOSE: We report an unusual case of bilateral vertical lacquer crack with no history of ocular trauma and with progressive marked enlargement and consequent visual loss.

METHODS: Three-year follow-up was completed using best-corrected visual acuity, serial fundus photographs, intravenous fluorescein angiography, and optical coherence tomography.

RESULTS: We report the occurrence of lacquer crack in a 43-year-old woman with no history of trauma except for laser in situ keratomileusis surgery for mild myopia (as reported by the patient) in the past 5 years and habitual ocular rubbing. Lacquer crack started in the right eye and became evident 1 year later in the left eye. Serial photography after repeated intravitreal injections of ranibizumab for subfoveal choroidal new vessel showed the lacquer crack widened gradually in both eyes. Axial length measurement revealed the presence of high myopia. Best-corrected visual acuity dropped to 20/200 bilaterally.

CONCLUSION: We hypothesize that a thin Bruch's membrane in high myopia is prone for small rupture

initially either spontaneously or following laser in situ keratomileusis and subsequent widening of the rupture by oculopression and intravitreal injections from rise in intraocular pressure.

PMID: 27186081 [PubMed] PMCID: PMC4847605

Am J Ophthalmol. 2016 May 14. [Epub ahead of print]

Retinal Sensitivity at the Junctional Zone of Eyes with Geographic Atrophy due to Age Related Macular Degeneration.

Hariri AH, Tepelus TC, Akil H, Nittala MG, Sadda SR.

PURPOSE: To compare the retinal sensitivity at the junctional zone and uninvolved retina of eyes with geographic atrophy (GA) due to age related macular degeneration (AMD).

DESIGN: Cross-sectional, observational study.

METHODS: Patients with dry AMD were evaluated by microperimetry and Cirrus optical coherence tomography (OCT). The GA lesion was segmented on en face OCT images and registered to color images with the microperimetric sensitivity values. The junctional zone, a ring 500 microns in width, surrounding the region of atrophy was further subdivided into "sub-zones": Zone 1 at the precise border of atrophy; Zone 2 as the center of this junctional region; Zone 3 at the border between the junctional zone and adjacent "normal" retina. An additional Zone 4 was defined as "normal" retina, at least 500 microns from the edge of the GA lesion. The mean sensitivities of all stimuli within each of these zones (across the entire cohort) were compared.

RESULT: In 36 eyes with GA, the mean retinal sensitivity in the various subzones was as follows: Zone 1 = 13.7 ± 4.7 , Zone 2 = 20.3 ± 3.9 , Zone 3 = 20.9 ± 3.9 , and Zone 4 = 21.1 ± 4.1 (all in dB). Zone 1 (atrophic margin) sensitivity was significantly lower than all other zones ($p < 0.001$ for all comparisons), but there were no differences between the other zones.

CONCLUSION: Retinal sensitivity appears to drop precipitously at the margins of GA lesions. The retinal sensitivity in the bulk of junctional zone is similar to apparently uninvolved distant regions.

PMID: 27189929 [PubMed - as supplied by publisher]

J Ophthalmic Vis Res. 2016 Jan-Mar;11(1):84-92.

Optical Coherence Tomography Angiography in Retinal Diseases.

Chalam KV, Sambhav K.

Abstract: Optical coherence tomography angiography (OCTA) is a new, non-invasive imaging system that generates volumetric data of retinal and choroidal layers. It has the ability to show both structural and blood flow information. Split-spectrum amplitude-decorrelation angiography (SSADA) algorithm (a vital component of OCTA software) helps to decrease the signal to noise ratio of flow detection thus enhancing visualization of retinal vasculature using motion contrast. Published studies describe potential efficacy for OCTA in the evaluation of common ophthalmologic diseases such as diabetic retinopathy, age related macular degeneration (AMD), retinal vascular occlusions and sickle cell disease. OCTA provides a detailed view of the retinal vasculature, which allows accurate delineation of microvascular abnormalities in diabetic eyes and vascular occlusions. It helps quantify vascular compromise depending upon the severity of diabetic retinopathy. OCTA can also elucidate the presence of choroidal neovascularization (CNV) in wet AMD. In this paper, we review the knowledge, available in English language publications regarding OCTA, and compare it with the conventional angiographic standard, fluorescein angiography (FA). Finally, we summarize its potential applications to retinal vascular diseases. Its current limitations include a relatively small field of view, inability to show leakage, and tendency for image artifacts. Further larger studies will

define OCTA's utility in clinical settings and establish if the technology may offer a non-invasive option of visualizing the retinal vasculature, enabling us to decrease morbidity through early detection and intervention in retinal diseases.

PMID: 27195091 [PubMed] PMCID: PMC4860994

Pathogenesis

Mol Ther. 2016 May 19. [Epub ahead of print]

Strand and cell-type specific function of microRNA-126 in angiogenesis.

Zhou Q, Anderson C, Hanus J, Zhao F, Ma J, Yoshimura A, Wang S.

Abstract: microRNAs (miRs) have been shown to be pivotal modulators of vascular development. The strand and cell-type specific function of miR-126 in angiogenesis, especially pathological angiogenesis, remains poorly defined. We characterized the retinal vascular phenotype of miR-126^{-/-} mice, and tested the function of miR-126 strands (miR-126-3p and -5p) using in vitro angiogenesis models and a mouse model of neovascular age-related macular degeneration. We found that miR-126 is critical for retinal vascular development but has dual function in pathological angiogenesis. miR-126^{-/-} mice showed defective postnatal retinal vascular development and remodeling, which is partially rescued by genetic knockout of its target gene *Spred-1*. Surprisingly, either silencing miR-126-3p by LNA-antimiR or overexpressing miR-126-3p by miRNA mimic repressed laser-induced choroidal neovascularization. To dissect the underlying mechanism, we found in endothelial cells, silencing of miR-126-3p repressed angiogenesis, while overexpression of miR-126-5p enhanced angiogenesis. However, in retinal pigment epithelial cells, miR-126-3p repressed VEGF-A expression via a novel mechanism of regulating α B-Crystallin promoter activity and by directly targeting VEGF-A 3'-untranslated region. These findings provide first genetic evidence that miR-126 is required for the development of different retinal vascular layers, and also uncover a strand and cell-type specific function of miR-126 in ocular pathological angiogenesis. *Molecular Therapy* (2016); doi:10.1038/mt.2016.108.

PMID: 27203443 [PubMed - as supplied by publisher]

Exp Eye Res. 2016 May 12;147:138-143. [Epub ahead of print]

Amyloid beta deposition and phosphorylated tau accumulation are key features in aged choroidal vessels in the complement factor H knock out model of retinal degeneration.

Aboelnour A, Kam JH, Elnasharty MA, Sayed-Ahmed A, Jeffery G.

Abstract: Extra-cellular deposition including amyloid beta (A β) is a feature of retinal ageing. It has been documented for Bruch's membrane (BM) where A β is elevated in complement factor H knockout mice (Cfh^{-/-}) proposed as a model for age related macular degeneration. However, arterial deposition in choroidal vessels prior to perfusion across BM has not been examined. A β is associated with tau phosphorylation and these are linked in blood vessels in Alzheimers Disease where they can drive perivascular pathology. Here we ask if A β , tau and phosphorylated tau are features of ageing in choroidal vessels in 12 month C57 BL/6 and Cfh^{-/-} mice, using immune staining and Western blot analysis. Greater levels of A β and phosphorylated tau are found in choroidal vessels in Cfh^{-/-} mice. Western blot revealed a 40% increase in A β in Cfh^{-/-} over C57 BL/6 mice. A β deposits coat around 55% of the luminal wall in Cfh^{-/-} compared to only about 40% in C57 BL/6. Total tau was similar in both groups, but phosphorylated tau increased by >100% in Cfh^{-/-} compared to C57 BL/6 and covered >75% of the luminal wall compared to 50% in C57 BL/6. Hence, phosphorylated tau is a marked choroidal feature in this mouse model. A β deposition was clumped in Cfh^{-/-} mice and likely to influence blood flow dynamics. Disturbed flow is associated with atherogenesis and may be related to the accumulation of membrane attack complex recently identified

between choroidal vessels in those at high risk of macular degeneration due to complement factor H polymorphisms.

PMID: 27181225 [PubMed - as supplied by publisher]

Front Cell Neurosci. 2016 Apr 28;10:103. eCollection 2016.

Retinal Remodeling and Metabolic Alterations in Human AMD.

Jones BW, Pfeiffer RL, Ferrell WD, Watt CB, Tucker J, Marc RE.

Abstract: Age-related macular degeneration (AMD) is a progressive retinal degeneration resulting in central visual field loss, ultimately causing debilitating blindness. AMD affects 18% of Americans from 65 to 74, 30% older than 74 years of age and is the leading cause of severe vision loss and blindness in Western populations. While many genetic and environmental risk factors are known for AMD, we currently know less about the mechanisms mediating disease progression. The pathways and mechanisms through which genetic and non-genetic risk factors modulate development of AMD pathogenesis remain largely unexplored. Moreover, current treatment for AMD is palliative and limited to wet/exudative forms. Retina is a complex, heterocellular tissue and most retinal cell classes are impacted or altered in AMD. Defining disease and stage-specific cytoarchitectural and metabolic responses in AMD is critical for highlighting targets for intervention. The goal of this article is to illustrate cell types impacted in AMD and demonstrate the implications of those changes, likely beginning in the retinal pigment epithelium (RPE), for remodeling of the the neural retina. Tracking heterocellular responses in disease progression is best achieved with computational molecular phenotyping (CMP), a tool that enables acquisition of a small molecule fingerprint for every cell in the retina. CMP uncovered critical cellular and molecular pathologies (remodeling and reprogramming) in progressive retinal degenerations such as retinitis pigmentosa (RP). We now applied these approaches to normal human and AMD tissues mapping progression of cellular and molecular changes in AMD retinas, including late-stage forms of the disease.

PMID: 27199657 [PubMed] PMCID: PMC4848316

Hum Mol Genet. 2016 May 18. [Epub ahead of print]

BESTROPHIN1 mutations cause defective chloride conductance in patient stem cell-derived RPE.

Moshfegh Y, Velez G, Li Y, Bassuk AG, Mahajan VB, Tsang SH.

Abstract: Bestrophin1 (BEST1) is expressed in human retinal pigment epithelium (RPE) and mutations in the BEST1 gene commonly cause retinal dysfunction and macular degeneration. BEST1 is presumed to assemble into a calcium-activated chloride channel and be involved in chloride transport but there is no direct evidence in live human RPE cells to support this idea. To test whether BEST1 functions as a chloride channel in living tissue, BEST1-mutant RPE (R218H, L234P, A243T) were generated from patient-derived induced pluripotent stem cells and compared with wild-type RPE in a retinal environment, using a biosensor that visualizes calcium-induced chloride ion flux in the cell. Calcium stimulation elicited chloride ion export in normal RPE but not in RPE derived from three patients with BEST1 mutations. These data, along with three-dimensional modeling, provide evidence that BEST1 assembles into a key calcium-sensing chloride channel in human RPE.

PMID: 27193166 [PubMed - as supplied by publisher]

Epidemiology

J Ophthalmic Vis Res. 2016 Jan-Mar;11(1):54-60.

Association of Age Related Macular Degeneration and Age Related Hearing Impairment.

Ghasemi H, Pourakbari MS, Entezari M, Yarmohammadi ME.

PURPOSE: To evaluate the association between age-related macular degeneration (ARMD) and sensory neural hearing impairment (SHI).

METHODS: In this case-control study, hearing status of 46 consecutive patients with ARMD were compared with 46 age-matched cases without clinical ARMD as a control group. In all patients, retinal involvements were confirmed by clinical examination, fluorescein angiography (FA) and optical coherence tomography (OCT). All participants were examined with an otoscope and underwent audiological tests including pure tone audiometry (PTA), speech reception threshold (SRT), speech discrimination score (SDS), tympanometry, reflex tests and auditory brainstem response (ABR).

RESULTS: A significant ($P = 0.009$) association was present between ARMD, especially with exudative and choroidal neovascularization (CNV) components, and age-related hearing impairment primarily involving high frequencies. Patients had higher SRT and lower SDS against anticipated presbycusis than control subjects. Similar results were detected in exudative, CNV and scar patterns supporting an association between late ARMD with SRT and SDS abnormalities. ABR showed significantly prolonged wave I and IV latency times in ARMD ($P = 0.034$ and 0.022 , respectively). Average latency periods for wave I in geographic atrophy (GA) and CNV, and that for wave IV in drusen patterns of ARMD were significantly higher than controls ($P = 0.030$, 0.007 and 0.050 , respectively).

CONCLUSION: The association between ARMD and age-related SHI may be attributed to common anatomical components such as melanin in these two sensory organs.

PMID: 27195086 [PubMed] PMCID: PMC4860988

Genetics

Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2763-9.

Sequence and Expression of Complement Factor H Gene Cluster Variants and Their Roles in Age-Related Macular Degeneration Risk.

Hughes AE, Bridgett S, Meng W, Li M, Curcio CA, Stambolian D, Bradley DT.

PURPOSE: To investigate how potentially functional genetic variants are coinherited on each of four common complement factor H (CFH) and CFH-related gene haplotypes and to measure expression of these genes in eye and liver tissues.

METHODS: We sequenced the CFH region in four individuals (one homozygote for each of four common CFH region haplotypes) to identify all genetic variants. We studied associations between the haplotypes and AMD phenotypes in 2157 cases and 1150 controls. We examined RNA-seq profiles in macular and peripheral retina and retinal pigment epithelium/choroid/sclera (RCS) from eight eye donors and three liver samples.

RESULTS: The haplotypic coinheritance of potentially functional variants (including missense variants, novel splice sites, and the CFHR3-CFHR1 deletion) was described for the four common haplotypes. Expression of the short and long CFH transcripts differed markedly between the retina and liver. We found no expression of any of the five CFH-related genes in the retina or RCS, in contrast to the liver, which is the main source of the circulating proteins.

CONCLUSIONS: We identified all genetic variants on common CFH region haplotypes and described their coinheritance. Understanding their functional effects will be key to developing and stratifying AMD therapies. The small scale of our expression study prevented us from investigating the relationships between CFH region haplotypes and their expression, and it will take time and collaboration to develop epidemiologic-scale studies. However, the striking difference between systemic and ocular expression of complement regulators shown in this study suggests important implications for the development of intraocular and systemic treatments.

PMID: 27196323 [PubMed - in process]

Diet, lifestyle and low vision

BMC Ophthalmol. 2016 May 17;16(1):56.

Patient-reported utilities in bilateral visual impairment from amblyopia and age-related macular degeneration.

van de Graaf ES, Despriet DD, Klaver CC, Simonsz HJ.

BACKGROUND: Utility of visual impairment caused by amblyopia is important for the cost-effectiveness of screening for amblyopia (lazy eye, prevalence 3-3.5 %). We previously measured decrease of utility in 35-year-old persons with unilateral persistent amblyopia. The current observational case-control study aimed to measure loss of utility in patients with amblyopia with recent decrease of vision in their better eye. As these patients are rare, the sample was supplemented by patients with bilateral age-related macular degeneration with similar decrease of vision.

METHODS: From our out-patient department, two groups of patients with recent deterioration to bilateral visual acuity less than Snellen 0.5 (bilateral visual impairment, BVI) were recruited, with either persistent amblyopia and age-related macular degeneration (AMB + AMD), or with bilateral age-related macular degeneration (BAMD). To measure utility, the time trade-off method and the standard gamble method were applied through interviews. Correlations were sought between utility values and visual acuity, age and Visual Function Questionnaire-25 scores.

RESULTS: Seventeen AMB + AMD patients (mean age 72.9 years), and 63 BAMD patients (mean age 79.6 years) were included in the study. Among AMB + AMD, 80 % were willing to trade lifetime in exchange for cure. The overall mean time trade-off utility was 0.925. Among BAMD, 75 % were willing to trade, utility was 0.917. Among AMB + AMD, 38 % accepted risk of death in exchange for cure, overall mean standard gamble utility was 0.999. Among BAMD, 49 % accepted risk of death, utility was 0.998. Utility was not related to visual acuity but it was to age ($p = 0.02$).

CONCLUSION: Elderly patients with BVI, caused by persistent amblyopia and age-related macular degeneration (AMD) or by bilateral AMD, had an approximately 8 % loss of TTO utility. Notably, the 8 % loss in elderly with BVI differs little from the 3.7 % loss we found previously in 35-year-old persons with unilateral amblyopia with good vision in the other eye. The moderate impact of BVI in senescence could be explained by adaptation, comorbidity, avoidance of risk and a changed percept of cure.

PMID: 27184381 [PubMed - in process] PMCID: PMC4869400

Adv Nutr. 2016 May 16;7(3):433-7.

Perspective: A Critical Look at the Ancillary Age-Related Eye Disease Study 2: Nutrition and Cognitive Function Results in Older Individuals with Age-Related Macular Degeneration.

Hammond BR Jr, Renzi-Hammond LM.

Abstract: A large body of literature suggests that the dietary carotenoids lutein and zeaxanthin and long-chain polyunsaturated fatty acids such as docosahexaenoic acid are related to improved cognitive function across the life span. A recent report by the Age-Related Eye Disease Study (AREDS) group appears to contradict the general findings of others in the field. In this review, we look critically at the methods, study designs, and analysis techniques used in the larger body of literature and compare them with the recent AREDS reports.

PMID: 27184270 [PubMed - in process]

IEEE Pulse. 2016 May-Jun;7(3):26-9.

A Better View: New Low-Vision Technology Helps Bring the World Into Focus.

Mertz L.

Abstract: Approximately 2% of Americans have a visual disability-vision that cannot be corrected even with the strongest prescription-and in developing countries where infectious disease or untreated cataracts are more common, the percentage is often higher. Many different diseases and conditions can cause low vision, including age-related macular degeneration, diabetic retinopathy, and cone dystrophy (a genetic mutation affecting the cone cells of the retina). People with low vision find everyday activities more challenging. They may not be able to decipher small type, especially text on busy or colored backgrounds; see a plastic toy or other trip hazard left lying on the sidewalk; distinguish faces from more than a few feet away; or read street signs or the route number on a bus to help them get around town.

PMID: 27187537 [PubMed - in process]

Nutrients. 2016 May 11;8(5).

Nutraceutical with Resveratrol and Omega-3 Fatty Acids Induces Autophagy in ARPE-19 Cells.

Koskela A, Reinisalo M, Petrovski G, Sinha D, Olmiere C, Karjalainen R, Kaarniranta K.

Abstract: Impaired autophagic and proteasomal cleansing have been documented in aged retinal pigment epithelial (RPE) cells and age-related macular degeneration (AMD). Omega-3 fatty acids and resveratrol have many positive homeostatic effects in RPE cells. In this work, ARPE-19 cells were treated with 288 ng of Resvega, containing 30 mg of trans resveratrol and 665 mg of omega-3 fatty acids, among other nutrients, with proteasome inhibitor MG-132 or autophagy inhibitor bafilomycin A1 up to 48 h. Autophagy markers p62/SQSTM1 (p62) and LC3 (microtubule-associated protein 1A/1B-light chain 3) were analyzed by Western blotting. Fluorescence microscopy with mCherry-GFP-LC3 plasmid was applied to study the autophagy flux, and cytoprotective effects were investigated with colorimetric MTT and LDH assays. Resvega induced autophagy by showing increased autolysosome formation and autophagy flux, and the change in the p62 and LC3 protein levels further confirmed the fluorescent microscopy results. Moreover, Resvega provided a clear cytoprotection under proteasome inhibition. These findings highlight the potential of the nutraceuticals containing resveratrol, omega-3 fatty acids and other nutrients in the prevention of ARPE-19 cell damage.

PMID: 27187449 [PubMed - in process]

PLoS One. 2016 May 18;11(5):e0155509. eCollection 2016.

The Impact of Vision Impairment (IVI) Questionnaire; Validation of the Thai-Version and the Implementation on Vision-Related Quality of Life in Thai Rural Community.

Ratanasukon M, Tongsomboon J, Bhurayanontachai P, Jirarattanasopa P.

Abstract: The objective of this study is to validate the Thai-version of the impact of vision impairment (IVI) questionnaire and to evaluate its impact on vision-related quality of life (VRQoL) in southern Thailand. The IVI questionnaire was translated into Thai according to WHO translation guidelines. In addition to the routine ophthalmological examinations, a Thai version of the IVI questionnaire was administered to all participants. A total of 120 patients with visual impairment who presented at Songklanagarind hospital, Songkhla province, were enrolled in the study; 30 had age-related macular degeneration (AMD), 30 had cataract, 30 had diabetic retinopathy, 30 had glaucoma, and 30 non-visually impaired individuals comprised the control group. Statistical analysis demonstrated the Thai-version IVI questionnaire is valid and reliable to evaluate the VRQoL of the Thai patients through three subscales: (i) mobility and independence, (ii) reading and accessing information, and (iii) emotional well-being. The results demonstrated high consistency in all subscales with Cronbach's alpha ranging from 0.787 to 0.849. Rasch analysis revealed the validity of the Thai-version IVI to assess VRQoL through all three subscales. Test-retest reliability was also high (intraclass correlation coefficient = 0.96). The composite score of the IVI was significantly higher in participants with visual impairment compared with healthy participants. Moreover, the subscale scores of reading and accessing information, and emotional well-being were highest in participants with AMD. While the subscale scores of mobility and independence were highest among those with either cataracts or diabetic retinopathy. The symptoms of the common vision impairment diseases are associated with an adverse impact on VRQoL in a clinic-based population as demonstrated in this study.

PMID: 27191960 [PubMed - in process]

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