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MD Research News

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Drug treatment

Retina. 2015 Jan 29. [Epub ahead of print]

PHARMACOGENOMICS OF RESPONSE TO ANTI-VEGF THERAPY IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Dedania VS, Grob S, Zhang K, Bakri SJ.

PURPOSE: To determine whether there is an association between response to intravitreal anti-vascular endothelial growth factor agents and genotype in patients with neovascular age-related macular degeneration.

METHODS: Analysis of the current literature evaluating pharmacogenetics of treatment response in patients with neovascular age-related macular degeneration.

RESULTS: Studies have demonstrated associations between various genotypes and response to intravitreal anti-vascular endothelial growth factor agents. Lower-risk genotypes of the CFH, ARMS2, HTRA1, and VEGF-A genes may be associated with improved visual outcomes. Additionally, frequency of injections may be associated with certain genotypes.

CONCLUSION: Genetic background may influence an individual's response to treatment of neovascular age-related macular degeneration. Further studies to investigate biologic pathways of neovascular age-related macular degeneration and gene products that are directly involved might lead to better understanding of contribution of various genes to treatment response.

PMID: 25635578 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Jan 28. pii: bjophthalmol-2014-306543. doi: 10.1136/bjophthalmol-2014-306543. [Epub ahead of print]

A randomised, double-masked, controlled study of the efficacy and safety of intravitreal bevacizumab versus ranibizumab in the treatment of macular oedema due to branch retinal vein occlusion: MARVEL Report No. 1.

Narayanan R, Panchal B, Das T, et al; on behalf of MARVEL study group.

PURPOSE: To assess the efficacy and safety of intravitreal bevacizumab (IVB) compared with ranibizumab (IVR) in the treatment of macular oedema due to branch retinal vein occlusion (BRVO).

METHODS: In this prospective, randomised, non-inferiority trial, 75 participants with macular oedema due

to BRVO received intravitreal injections of ranibizumab or bevacizumab after 1:1 block randomisation. The primary outcome measure was the difference in mean changes in best-corrected visual acuity (BCVA) at 6 months. Secondary outcome measures included mean change in central retinal thickness (CRT), the proportion of patients improving by >15 letters and the proportion of patients developing neovascularisation.

RESULTS: Participants received either IVR (n=37) or IVB (n=38). The mean BCVA at baseline was 52.8±14.4 letters (20/80) and 56.1±10.0 letters (20/80) (p=0.24) in the ranibizumab and bevacizumab groups, respectively. At 6 months, the mean gains in BCVA were +18.1 letters (p<0.0001; 95% CI, +12.8 to +22.6) in the ranibizumab group and +15.6 letters (p<0.0001; 95% CI +12.0 to +20.5) in the bevacizumab group. The difference between the mean visual gains of the treated groups (bevacizumab-ranibizumab) was -2.5 letters (95% CI -8.0 to +5.0; p=0.74). Mean reductions in CRT at 6 months were 177.1±122.3 µm in the ranibizumab group (p<0.0001) and 201.7±166.2 µm in the bevacizumab group (p<0.0001), with no significant difference between the two groups (p=0.48). The mean numbers of ranibizumab and bevacizumab injections were 3.2±1.5 and 3.0±1.4, respectively (p=0.55). Two serious adverse events occurred in the ranibizumab group and one in the bevacizumab group but both were unrelated to intravitreal injections.

CONCLUSIONS: This study demonstrated significant gain in visual acuity in eyes with BRVO treated with either bevacizumab or ranibizumab. Pro-re-nata strategy was effective in maintaining the visual gain.

PMID: 25631483 [PubMed - as supplied by publisher]

Retina. 2015 Jan 26. [Epub ahead of print]

RESPONSE OF PIGMENT EPITHELIAL DETACHMENTS TO INTRAVITREAL AFLIBERCEPT AMONG PATIENTS WITH TREATMENT-RESISTANT NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Broadhead GK, Hong T, Zhu M, et al

PURPOSE: To assess the effect of intravitreal aflibercept on pigment epithelial detachment (PED) in patients with treatment-resistant neovascular age-related macular degeneration.

METHODS: Forty-six patients with vascularized PEDs participating in a wider, prospective clinical trial of treatment-resistant neovascular age-related macular degeneration received 2-mg aflibercept as 3 loading doses 1 month apart, followed by further 2-monthly doses over a total 12-month period. Change in PED dimensions and reflective properties were assessed by optical coherence tomography. Reflectivity was subclassified as solid (hyperreflective), hollow (hyporeflective), or mixed (elements of both).

RESULTS: Aflibercept reduced PED height, width, and length at 48 weeks compared with baseline values ($P \leq 0.01$ for all). Reductions in PED height were correlated with reductions in central macular thickness at 48 weeks ($R = 0.36$, $P < 0.001$). There was no significant correlation between PED height decrease and visual acuity changes at 48 weeks. Solid PEDs were less likely to experience reductions in all three dimensions than either hollow or mixed PEDs.

CONCLUSION: Aflibercept is effective in reducing PED dimensions in treatment-resistant patients and is most effective in PEDs demonstrating some hyporeflective optical coherence tomography characteristics. Reduction in PED dimensions correlated with central macular thickness, but not with visual acuity changes. The role of PEDs as markers of disease requires further investigation; however, lesions should be monitored for retinal fluid recurrence.

PMID: 25627086 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Jan 26. [Epub ahead of print]

One year result of aflibercept treatment on age-related macular degeneration and predictive factors for visual outcome.

Oishi A, Tsujikawa A, Yamashiro K, et al

PURPOSE: To investigate the efficacy of periodic injection of aflibercept in each subtype of age-related macular degeneration (AMD) and to explore the predictive factors for visual outcome in clinical settings.

DESIGN: Prospective non-randomized interventional case series.

METHODS: Patients with AMD were recruited and were administered aflibercept injections once a month for 3 months followed by once every 2 months for 8 months. The logarithm of the minimum angle of resolution (logMAR) at 12 months and improvement of vision from baseline were compared among polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), and typical AMD. Regression rate of polypoidal lesions was assessed. We also performed regression analysis with logMAR at 12 months as the dependent variable.

RESULTS: The study sample consisted of 98 patients: 46 had typical AMD, 42 had PCV, and 10 had RAP. Mean logMAR improved from 0.36 to 0.21 in 12 months. While there was no difference in visual improvement between typical AMD and PCV, final logMAR was better in PCV (0.32 ± 0.09 vs. 0.08 ± 0.04, P = .016). Thirty-nine PCV patients underwent follow-up angiography, and regression of polyps was observed in 27 cases (69.2%). Multiple regression analysis showed that the presence of external limiting membrane (ELM), smaller greatest linear dimension (GLD), and the presence of polypoidal lesion were associated with better visual outcome (R2 = 0.53, P = 2.73 × 10-14).

CONCLUSIONS: Periodic injection of aflibercept is effective for PCV as well as for typical AMD. The statuses of ELM, GLD, and polypoidal lesion are predictive for visual outcome.

PMID: 25634529 [PubMed - as supplied by publisher]

Retina. 2015 Jan 23. [Epub ahead of print]

MICROPERIMETRIC ASSESSMENT OF RETINAL SENSITIVITY IN EYES WITH DIABETIC MACULAR EDEMA FROM A PHASE 2 STUDY OF INTRAVITREAL AFLIBERCEPT.

Gonzalez VH, Boyer DS, Schmidt-Erfurth U, et al

PURPOSE: To evaluate retinal sensitivity in patients with diabetic macular edema who received intravitreal aflibercept injection (IAI) or laser.

METHODS: A substudy included 46 patients from DA VINCI (a randomized, double-masked Phase 2 study) receiving either laser, 0.5 mg IAI every 4 weeks, 2 mg IAI every 4 weeks, 2 mg IAI every 8 weeks after 3 monthly doses (2q8), or 2 mg IAI as-needed after 3 monthly doses for 52 weeks. Retinal sensitivity was measured in one (central), five (one central and four inner), and eight (four inner and four outer) optical coherence tomography subfields.

RESULTS: Mean best-corrected visual acuity improvement in the subgroup at Week 52 was 3.3 letters with laser and ranged from 5.4 to 16.3 letters in the IAI groups. Retinal sensitivity of laser patients at Week 52 was comparable with baseline in the central optical coherence tomography subfield but decreased in the five and eight optical coherence tomography subfields. Compared with laser, retinal sensitivity significantly increased with IAI in the 2q8 and pooled IAI groups in the 5 and 8 optical coherence tomography subfields at Week 52 (P < 0.05).

CONCLUSION: Intravitreal aflibercept injection improved best-corrected visual acuity and retinal sensitivity in this subgroup of patients. Laser may cause a deterioration of macular function that is not detectable with

best-corrected visual acuity testing.

PMID: 25621943 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Jan 30. [Epub ahead of print]

Residual edema evaluation with ranibizumab 0.5 mg and 2.0 mg formulations for diabetic macular edema (REEF study).

Dhoot DS, Pieramici DJ, Nasir M, et al

Purpose: To compare the efficacy of ranibizumab 0.5-mg and 2.0-mg intravitreal injections for persistent diabetic macular edema (DME) previously treated with bevacizumab.

Methods: In all, 43 patients with residual center-involved DME following intravitreal bevacizumab were included in this 12-month prospective, nonrandomized, multicenter study. Enrolled patients received three monthly ranibizumab 0.5-mg injections. At month 3, patients with residual macular edema switched to three monthly injections of ranibizumab 2.0-mg. Assessments included monthly visual acuity and spectral-domain optical coherence tomography.

Results: Mean visual acuity improved by +6.4 letters at month 3 and +8.8 letters at month 6. Mean central subfield thickness (CST) decreased by -113 μm at month 3 and -165 μm at month 6. Before enrollment, 29/43 (67.4%) patients showed <10% CST reduction following monthly bevacizumab treatment. After three monthly ranibizumab 0.5-mg injections, 22/29 (75.9%) patients showed >10% reduction in CST, whereas 6 showed <10% reduction. Of these six, three (50%) showed >10% reduction in CST after switching to three monthly ranibizumab 2.0-mg doses. No serious adverse events were observed to month 6.

Conclusion: Ranibizumab 0.5-mg or 2.0-mg may improve visual and anatomic outcomes in patients with DME who demonstrated minimal or no response to bevacizumab therapy. Moreover, increased dosage of ranibizumab (2.0-mg) may provide additional benefit over ranibizumab 0.5-mg in some patients. However, 2.0-mg ranibizumab is not currently commercially licensed or available. .

PMID: 25633882 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2015 Jan 22. [Epub ahead of print]

Oct parameters as predictive factors for the visual outcome after ranibizumab therapy in neovascular age related macular degeneration.

Valverde-Megías A, Donate-López J, García-Gil-de-Bernabé J, et al

OBJECTIVE: To evaluate macular morphological parameters measured by spectral domain optical coherence tomography (SD-OCT) as predictive factors of visual outcome in patients with exudative age-related macular degeneration (AMD) treated with ranibizumab.

METHODS: A retrospective study was conducted on 47 patients diagnosed with exudative AMD and treated with intravitreal ranibizumab for twelve months. Central retinal thickness (CRT), extension and thickness of modifications secondary to neovascular process, and status of the bands corresponding to the external limiting membrane (ELM) and to the ellipsoid region of the photoreceptors (ISe) were evaluated by means of SD-OCT. The relationship between these variables and visual acuity was analyzed by statistical methods.

RESULTS: At the time of the diagnosis, preservation of ELM and ISe bands, and CRT were correlated with initial visual acuity. Twelve months later, CRT and visual acuity were independent parameters. Bivariate relationship analysis showed a correlation between final visual acuity and the following parameters: initial

CRT, initial ISe and ELM status, and ISe and ELM integrity after loading dose. Multiple regression analysis indicated that initial visual acuity and ISe band status after loading dose have a predictive value for final visual acuity.

CONCLUSIONS: The status of ISe and ELM bands after twelve months of treatment with ranibizumab was associated with visual outcome. Initial visual acuity and status of the ISe band after loading dose are prognostic factors of final visual acuity.

PMID: 25620678 [PubMed - as supplied by publisher]

Other treatment & diagnosis

JAMA Ophthalmol. 2015 Jan 29. [Epub ahead of print]

Longitudinal Changes in Microperimetry and Low Luminance Visual Acuity in Age-Related Macular Degeneration.

Wu Z, Ayton LN, Luu CD, Guymer RH.

Importance: There is a need for more sensitive measures of disease in intermediate age-related macular degeneration (AMD) to evaluate novel interventions more effectively and expediently.

Objective: To determine if microperimetry and low luminance visual acuity can detect functional changes over a short duration of follow-up.

Design, Setting, and Participants: Prospective longitudinal examination of 49 participants with consecutive AMD and 10 healthy participants in a research clinic from May 1, 2012, to December 31, 2013. Forty-one participants had intermediate AMD, 8 had nonfoveal geographic atrophy due to AMD. Participants underwent microperimetry examinations in 1 eye during a 12-month period at 6-month intervals for participants with AMD and at baseline and 12 months for control participants; low luminance visual acuity was performed at baseline and at 12 months for all participants. Changes in pathological features of intermediate AMD eyes were determined using side-by-side comparisons of color fundus photographs from the initial and final visit as remaining stable, progressed, or improved.

Main Outcomes and Measures: Microperimetric sensitivity and low luminance visual acuity.

Results: A reduction in mean (SE) microperimetric pointwise sensitivity was identified at 12 months compared with the baseline for intermediate AMD eyes graded as stable (-0.31 dB [0.10 dB]; $P = .003$) or worsened (-0.42 dB [0.12 dB]; $P < .001$) and an improvement in mean (SE) pointwise sensitivity was identified in eyes graded as improved (1.13 dB [0.23 dB]; $P < .001$). A reduction in mean (SE) pointwise sensitivity was identified in eyes with nonfoveal geographic atrophy at both 6 months (-1.41 dB [0.22 dB]; $P < .001$) and 12 months compared with the baseline (-2.56 dB [0.22 dB]; $P < .001$) while a change in mean (SE) pointwise sensitivity was not identified over the 12-month period for control participants (-0.11 dB [0.11 dB]; $P = .34$). No changes in best-corrected visual acuity or low luminance visual acuity were identified in all groups over the 12-month period ($P \geq .07$).

Conclusions and Relevance: Microperimetry detected subtle changes in visual function over a 12-month period in eyes with intermediate AMD but visual acuity measures did not identify any such changes. These findings suggest that microperimetry is worth exploring as a method for assessing the efficacy of novel interventions for intermediate AMD potentially requiring a shorter duration of follow-up.

PMID: 25632841 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Jan 8;56(1):633-9.

Automatic identification of reticular pseudodrusen using multimodal retinal image analysis.

van Grinsven MJ, Buitendijk GH, Brussee C, et al

PURPOSE: To examine human performance and agreement on reticular pseudodrusen (RPD) detection and quantification by using single- and multimodality grading protocols and to describe and evaluate a machine learning system for the automatic detection and quantification of reticular pseudodrusen by using single- and multimodality information.

METHODS: Color fundus, fundus autofluoresence, and near-infrared images of 278 eyes from 230 patients with or without presence of RPD were used in this study. All eyes were scored for presence of RPD during single- and multimodality setups by two experienced observers and a developed machine learning system. Furthermore, automatic quantification of RPD area was performed by the proposed system and compared with human delineations.

RESULTS: Observers obtained a higher performance and better interobserver agreement for RPD detection with multimodality grading, achieving areas under the receiver operating characteristic (ROC) curve of 0.940 and 0.958, and a κ agreement of 0.911. The proposed automatic system achieved an area under the ROC of 0.941 with a multimodality setup. Automatic RPD quantification resulted in an intraclass correlation (ICC) value of 0.704, which was comparable with ICC values obtained between single-modality manual delineations.

CONCLUSIONS: Observer performance and agreement for RPD identification improved significantly by using a multimodality grading approach. The developed automatic system showed similar performance as observers, and automatic RPD area quantification was in concordance with manual delineations. The proposed automatic system allows for a fast and accurate identification and quantification of RPD, opening the way for efficient quantitative imaging biomarkers in large data set analysis.

PMID: 25574052 [PubMed - in process]

BMC Ophthalmol. 2015 Jan 27;15(1):10. [Epub ahead of print]

Combining macula clinical signs and patient characteristics for age-related macular degeneration diagnosis: a machine learning approach.

Fraccaro P, Nicolo M, Bonetto M, et al

BACKGROUND: To investigate machine learning methods, ranging from simpler interpretable techniques to complex (non-linear) "black-box" approaches, for automated diagnosis of Age-related Macular Degeneration (AMD).

METHODS: Data from healthy subjects and patients diagnosed with AMD or other retinal diseases were collected during routine visits via an Electronic Health Record (EHR) system. Patients' attributes included demographics and, for each eye, presence/absence of major AMD-related clinical signs (soft drusen, retinal pigment epitelium, defects/pigment mottling, depigmentation area, subretinal haemorrhage, subretinal fluid, macula thickness, macular scar, subretinal fibrosis). Interpretable techniques known as white box methods including logistic regression and decision trees as well as less interpreitable techniques known as black box methods, such as support vector machines (SVM), random forests and AdaBoost, were used to develop models (trained and validated on unseen data) to diagnose AMD. The gold standard was confirmed diagnosis of AMD by physicians. Sensitivity, specificity and area under the receiver operating characteristic (AUC) were used to assess performance.

RESULTS: Study population included 487 patients (912 eyes). In terms of AUC, random forests, logistic regression and adaboost showed a mean performance of (0.92), followed by SVM and decision trees

(0.90). All machine learning models identified soft drusen and age as the most discriminating variables in clinicians' decision pathways to diagnose AMD.

CONCLUSIONS: Both black-box and white box methods performed well in identifying diagnoses of AMD and their decision pathways. Machine learning models developed through the proposed approach, relying on clinical signs identified by retinal specialists, could be embedded into EHR to provide physicians with real time (interpretable) support.

PMID: 25623470 [PubMed - as supplied by publisher]

Retina. 2015 Jan 26. [Epub ahead of print]

CORRELATION BETWEEN NEOVASCULAR LESION TYPE AND CLINICAL CHARACTERISTICS OF NONNEOVASCULAR FELLOW EYES IN PATIENTS WITH UNILATERAL, NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Marsiglia M, Boddu S, Chen CY, et al

PURPOSE: To investigate the association between the type of neovascularization (NV) and the clinical characteristics of nonneovascular fellow eyes in patients with unilateral, neovascular age-related macular degeneration.

METHODS: Eighty-three patients with treatment-naive, unilateral, neovascular age-related macular degeneration were retrospectively analyzed. Neovascular lesions were classified using both fluorescein angiography and optical coherence tomography as Type 1 (subretinal pigment epithelium), 2 (subretinal), 3 (intraretinal), or mixed NV. The associations between NV lesion type and baseline clinical and imaging characteristics of the fellow eye, including central geographic atrophy, noncentral geographic atrophy, pigmentary changes, soft drusen, cuticular drusen, reticular pseudodrusen, and subfoveal choroidal thickness, were examined. Subfoveal choroidal thickness was defined as thin if thickness was <120 μm.

RESULTS: In the fellow eyes of patients with treatment-naive, unilateral, neovascular age-related macular degeneration, Type 3 NV had an increased adjusted odds ratio of reticular pseudodrusen (15.361, $P < 0.001$) and thin subfoveal choroidal thickness (21.537, $P < 0.001$) as well as a tendency toward an increased adjusted odds ratio of central geographic atrophy (4.775, $P = 0.028$). Fellow eyes of patients with Type 1 NV showed a decreased adjusted odds ratio of reticular pseudodrusen (0.233, $P = 0.007$) and thin subfoveal choroidal thickness (0.080, $P = 0.005$).

CONCLUSION: In patients with unilateral, neovascular age-related macular degeneration, certain nonneovascular features of the fellow eye correlate with the NV lesion composition based on type, as anatomically classified utilizing both fluorescein angiography and optical coherence tomography. Patients with Type 3 NV were more likely to have reticular pseudodrusen and/or thin subfoveal choroidal thickness in the fellow eye compared with those with Type 1 NV. Patients with Type 3 NV also showed a trend toward increased central geographic atrophy in the fellow eye.

PMID: 25627089 [PubMed - as supplied by publisher]

Ophthalmologica. 2015 Jan 27. [Epub ahead of print]

Evaluation of Carotid Atherosclerosis, Peripheral Arterial Disease, and Chronic Kidney Disease in Patients with Exudative Age-Related Macular Degeneration without Coronary Artery Disease or Stroke.

Taniguchi H, Shiba T, Maeno T, Takahashi M.

Purpose: To evaluate the risk factors for acute atherothrombotic events in patients with exudative age-

related macular degeneration (AMD) without a history of coronary artery disease or stroke.

Methods: Two hundred fifty-nine patents with exudative AMD were evaluated for carotid atherosclerosis, peripheral arterial disease, and chronic kidney disease (CKD).

Results: A mean intima-media thickness of ≥1.0 mm was found in 28.2% of patients; 8.9% of patients had severe carotid artery stenosis. The prevalence rates of severe atherosclerosis with a plaque score >10, peripheral arterial disease, and CKD were 16.6, 5.4, and 32%, respectively. Diabetes mellitus and AMD affecting eyes bilaterally were identified as risk factors for abnormal carotid artery thickening, and age and body mass index were identified as risk factors for CKD.

Conclusion: The current study confirmed that potentially 30% of patients with exudative AMD without a history of coronary artery disease or stroke have a high risk of acute atherothrombotic events. © 2015 S. Karger AG, Basel.

PMID: 25633305 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2015 Jan 23. [Epub ahead of print]

A CASE OF HYPOTRICHOSIS WITH JUVENILE MACULAR DYSTROPHY.

Mason JO 3rd, Patel SA.

PURPOSE: To report a very rare case of hypotrichosis with juvenile macular dystrophy.

METHODS: Clinical case report and literature review.

RESULTS: A 6-year-old boy was referred to us for a retinal evaluation after retinal defects were found bilaterally by his optometrist. His ocular symptoms included decreased visual acuity and light sensitivity. His ocular history was unremarkable. Review of systems was positive for hypotrichosis. Fundus examination revealed bull's eye maculopathy bilaterally. The patient was found to have a cadherin-3 genetic defect, which is associated with hypotrichosis with juvenile macular dystrophy. In follow-up, fundus autofluorescence revealed severe hypoautofluorescence with severe retinal pigment epithelium loss, and spectral domain optical coherence tomography showed evidence of retinal pigment epithelium, photoreceptor, and inner segment/outer segment disruption bilaterally.

CONCLUSION: Hypotrichosis with juvenile macular dystrophy is a very rare genetic disorder that should be in the differential for macular degeneration during the first 4 decades of life. A detailed review of systems should always be performed on these patients.

PMID: 25621871 [PubMed - as supplied by publisher]

World J Stem Cells. 2015 Jan 26;7(1):160-4.

Stem cell therapy for retinal diseases.

Garcia JM, Mendonça L, Brant R, et al.

Abstract: In this review, we discuss about current knowledge about stem cell (SC) therapy in the treatment of retinal degeneration. Both human embryonic stem cell and induced pluripotent stem cell has been growth in culture for a long time, and started to be explored in the treatment of blinding conditions. The Food and Drug Administration, recently, has granted clinical trials using SC retinal therapy to treat complex disorders, as Stargardt's dystrophy, and patients with geographic atrophy, providing good outcomes. This study's intent is to overview the critical regeneration of the subretinal anatomy through retinal pigment epithelium transplantation, with the goal of reestablish important pathways from the retina to the occipital cortex of the

brain, as well as the differentiation from pluripotent quiescent SC to adult retina, and its relationship with a primary retinal injury, different techniques of transplantation, management of immune rejection and tumorigenicity, its potential application in improving patients' vision, and, finally, approaching future directions and challenges for the treatment of several conditions.

PMID: 25621115 [PubMed] PMCID: PMC4300926

Retina. 2015 Jan 29. [Epub ahead of print]

OUTER RETINAL TUBULATION IN ADVANCED AGE-RELATED MACULAR DEGENERATION: Optical Coherence Tomographic Findings Correspond to Histology.

Schaal KB, Freund KB, Litts KM, et al

PURPOSE: To compare optical coherence tomography (OCT) and histology of outer retinal tubulation (ORT) secondary to advanced age-related macular degeneration in patients and in postmortem specimens, with particular attention to the basis of the hyperreflective border of ORT.

METHOD: A private referral practice (imaging) and an academic research laboratory (histology) collaborated on two retrospective case series. High-resolution OCT raster scans of 43 eyes (34 patients) manifesting ORT secondary to advanced age-related macular degeneration were compared to high-resolution histologic sections through the fovea and superior perifovea of donor eyes (13 atrophic age-related macular degeneration and 40 neovascular age-related macular degeneration) preserved ≤4 hours after death.

RESULTS: Outer retinal tubulation seen on OCT correlated with histologic findings of tubular structures consisted largely of cones lacking outer segments and lacking inner segments. Four phases of cone degeneration were histologically distinguishable in ORT lumenal walls, nascent, mature, degenerate, and end stage (inner segments and outer segments, inner segments only, no inner segments, and no photoreceptors and only Müller cells forming external limiting membrane, respectively). Mitochondria, which are normally long and bundled within inner segment ellipsoids, were small and scattered within shrunken inner segments and cell bodies of surviving cones. A lumenal border was delimited by an external limiting membrane. Outer retinal tubulation observed in closed and open configurations was distinguishable from cysts and photoreceptor islands on both OCT and histology. Hyperreflective lumenal material seen on OCT represents trapped retinal pigment epithelium and nonretinal pigment epithelium cells.

CONCLUSION: The defining OCT features of ORT are location in the outer nuclear layer, a hyperreflective band differentiating it from cysts, and retinal pigment epithelium that is either dysmorphic or absent. Histologic and OCT findings of outer retinal tubulation corresponded in regard to composition, location, shape, and stages of formation. The reflectivity of ORT lumenal walls on OCT apparently does not require an outer segment or an inner/outer segment junction, indicating an independent reflectivity source, possibly mitochondria, in the inner segments.

PMID: 25635579 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Feb;122(2):222-3. .

Optical coherence tomography, fluorescein angiography, and the management of neovascular age-related macular degeneration.

Schachat AP, Thompson JT.

PMID: 25618425 [PubMed - in process]

Pathogenesis

Neuropharmacology. 2015 Jan 26. [Epub ahead of print]

MRZ-99030 - a novel modulator of Aβ aggregation: I - mechanism of action (MoA) underlying the potential neuroprotective treatment of Alzheimer´s disease, glaucoma and age-related macular degeneration (AMD).

Parsons CG, Ruitenberg M, Freitag CE, et al

Abstract: Therapeutic approaches addressing β-amyloid1-42 (Aβ1-42) aggregation represent a promising neuroprotective strategy for the treatment of Alzheimer´s disease, dry age-related macular degeneration (AMD) and glaucoma. MRZ-99030 is a dipeptide containing D-tryptophan and 2-amino-2-methylpropionic acid in clinical development for the topical treatment of glaucoma and AMD. MRZ-99030 is an Aβ aggregation modulator, previously reported to prevent the formation of soluble toxic oligomeric Aβ species. The present study confirmed that MRZ-99030 prevents the formation of oligomeric Aβ species using similar SDS-PAGE experiments. However, additional data from TR-FRET, DLS and AFM experiments revealed that MRZ-99030 does not directly prevent early protein/protein interactions between monomeric Aβ, but rather promotes the formation of large, non-amyloidogenic, amorphous Aβ aggregates and thereby reduces the amount of intermediate toxic soluble oligomeric Aβ species. The affinity of MRZ-99030 to Aβ1-42 determined by SPR was 28.4nM but the ratio of compound to Aβ is also important: a 10-20 fold excess of MRZ-99030 over Aβ is probably required for effective inhibition of protein/protein interactions. For example, in glaucoma, assuming a maximal Aβ concentration of 1-15nM in the retina, up to 150nM MRZ-99030 could be required at the protein target. In line with this consideration, MRZ-99030 was able to prevent Aβ-induced toxicity on PC12 cells, retinal ganglion cells and retinal pigment epithelium cells when present at a 10-20 fold stoichiometric excess over Aβ. Moreover, in vivo studies demonstrate the neuroprotective potential of MRZ-99030 after systemic and topical administration in animal models of Alzheimer's disease and glaucoma/AMD respectively.

PMID: 25634238 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Jan 27. [Epub ahead of print]

THE EFFECT OF AMA0428, A NOVEL AND POTENT ROCK INHIBITOR, IN A MODEL OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Hollanders K, Van Bergen T, Kindt N, et al

Purpose: Rho kinase (ROCK) is associated with VEGF-driven angiogenesis, as well as with inflammation and fibrosis. Therefore, the effect of AMA0428, a novel ROCK inhibitor, was studied in these processes, which highly contribute to the pathogenesis of neovascular age-related macular degeneration (AMD).

Methods: The effect of AMA0428 (0.5 - 5µM) on human umbilical vein endothelial cells (HUVEC), human brain microvascular endothelial cells (HBMEC) and human brain microvascular pericytes (HBVP) was determined using cell viability (WST-1), apoptosis (caspase 3/7) and migration (scratch and under-agarose) assays. The in vivo response was investigated using a laser-induced choroidal neovascularization (CNV) mouse model, in which intravitreal injections of AMA0428, murine anti-VEGF-R2 mAb (DC101) or placebo were given. Outcome was assessed by analysis of inflammation (CD45), angiogenesis (FITC-dextran), vessel leakage (Texas Red-conjugated Dextran and FITC-labeled lectin) and fibrosis (Sirius Red/Collagen I).

Results: AMA0428 dose-dependently reduced proliferation and VEGF-induced migration of HUVEC and HBMEC ($P<0.05$). No significant effect was seen on HBVP proliferation; however, migration and pericyte recruitment were enhanced ($P<0.05$) by AMA0428 administration. There was no apoptosis induction. AMA0428 significantly reduced CNV and vessel leakage 2 weeks after laser treatment, comparable to

DC101. In addition, AMA0428 inhibited inflammation on day 5 by 42% (P<0.05) and collagen deposition on day 30 by 43% (P<0. 05), while DC101 had no effect on inflammation nor on fibrosis.

Conclusions: The results suggest that targeting ROCK with AMA0428 not only reduces neo-angiogenesis, but also blocks inflammation and fibrosis (contrary to VEGF-suppression). These results point to a potential therapeutic benefit of ROCK-inhibition in neovascular AMD.

PMID: 25626969 [PubMed - as supplied by publisher]

Biomaterials. 2015 Mar;44:103-10.

Prolonged prevention of retinal degeneration with retinylamine loaded nanoparticles.

Puntel A, Maeda A, Golczak M, et al

Abstract: Retinal degeneration impairs the vision of millions in all age groups worldwide. Increasing evidence suggests that the etiology of many retinal degenerative diseases is associated with impairment in biochemical reactions involved in the visual cycle, a metabolic pathway responsible for regeneration of the visual chromophore (11-cis-retinal). Inefficient clearance of toxic retinoid metabolites, especially all-trans-retinal, is considered responsible for photoreceptor cytotoxicity. Primary amines, including retinylamine, are effective in lowing the concentration of all-trans-retinal within the retina and thus prevent retina degeneration in mouse models of human retinopathies. Here we achieved prolonged prevention of retinal degeneration by controlled delivery of retinylamine to the eye from polylactic acid nanoparticles in Abca4(-/-)Rdh8(-/-) (DKO) mice, an animal model of Stargardt disease/age-related macular degeneration. Subcutaneous administration of the nanoparticles containing retinylamine provided a constant supply of the drug to the eye for about a week and resulted in effective prolonged prevention of light-induced retinal degeneration in DKO mice. Retinylamine nanoparticles hold promise for prolonged prophylactic treatment of human retinal degenerative diseases, including Stargardt disease and age-related macular degeneration.

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Epidemiology

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PERIODONTAL DISEASE AND AGE-RELATED MACULAR DEGENERATION: Results From the National Health and Nutrition Examination Survey III.

Wagley S, Marra KV, Salhi RA, et al

PURPOSE: To study the association between periodontal disease (PD) and age-related macular degeneration (AMD).

METHODS: For this cross-sectional analysis, 8,208 adults aged 40 years or older with retinal photographs graded for AMD were used from the National Health and Nutrition Examination Survey III. National Health and Nutrition Examination Survey III standardized dental measurements of PD status (defined as loss of >3 mm of attachment between the gum and tooth in at least 10% of sites measured). Participants were stratified into 60 years or younger and older than 60 years of age groups. Association between PD and AMD was assessed while controlling for sex, race, education, poverty income ratio, smoking, hypertension, body mass index, cardiovascular disease, and C-reactive protein.

RESULTS: In this population, a total of 52.30% had PD, and the prevalence of AMD was 11.45%. Logistic regression model controlled for confounders and stratified by age 60 years or younger versus older than 60 years showed PD to be independently associated with an increased risk for AMD (odds ratio = 1.96, 95%

confidence interval = 1.22-3.14, P = 0.006) for those aged 60 years or younger but not for subjects older than 60 years (odds ratio = 1.32, confidence interval = 0.93-1.90, P = 0.120).

CONCLUSION: In this population-based study, PD is independently associated with AMD in those aged 60 years or younger.

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Genetics

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AGE-RELATED MACULAR DEGENERATION PHENOTYPES ASSOCIATED WITH MUTUALLY EXCLUSIVE HOMOZYGOUS RISK VARIANTS IN CFH AND HTRA1 GENES.

Chong EW, Amirul Islam FM, Robman LD, et al.

PURPOSE: To determine age-related macular degeneration (AMD) phenotypes associated with mutually exclusive homozygotic risk variants in rs1061170 (CFH) and rs11200638 (HTRA1).

METHODS: Nested case-control study of 2,982 eyes (2,129 control, 809 drusen ≥125 μm, 44 advanced AMD) homozygous for CFH [TT or CC] and HTRA1 [GG or AA] were analyzed using logistic regression and generalized estimating equations specifically regards to homozygous risk variants in one but homozygous no-risk in the other gene.

RESULTS: In early AMD, [CFH HTRA1] and [CFH HTRA1] were associated with central drusen (odds ratio [95% confidence interval] = 4.13 [2.97-5.73] and 3.65 [1.88-7.09], respectively). However, only [CFH HTRA1] was associated with central drusen occupying ≥50% area (13.9 [2.97-64.7]). In advanced AMD, [CFH HTRA1] was associated with geographic atrophy (4.04 [1.57-10.4]), whereas [CFH HTRA1] was associated with neovascular AMD (36.5 [8.3-160.9]). In doubly homozygous risk groups [CFH HTRA1], odds ratios were multiplicative.

CONCLUSION: Central but not peripheral drusen location was strongly associated with both [CFH HTRA1] and [CFH HTRA1]. Only [CFH HTRA1] was significantly associated with increased central drusen area.

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New loci and coding variants confer risk for age-related macular degeneration in East Asians.

Cheng CY, Yamashiro K, Jia Chen L, et al

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness, but presents differently in Europeans and Asians. Here, we perform a genome-wide and exome-wide association study on 2,119 patients with exudative AMD and 5,691 controls, with independent replication in 4,226 patients and 10,289 controls, all of East Asian descent, as part of The Genetics of AMD in Asians (GAMA) Consortium. We find a strong association between CETP Asp442Gly (rs2303790), an East Asian-specific mutation, and increased risk of AMD (odds ratio (OR)=1.70, P=5.60 × 10(-22)). The AMD risk allele (442Gly), known to protect from coronary heart disease, increases HDL cholesterol levels by 0.17 mmol l(-1) (P=5.82 × 10(-21)) in East Asians (n=7,102). We also identify three novel AMD loci: C6orf223 Ala231Ala (OR=0.78, P=6.19 × 10(-18)), SLC44A4 Asp47Val (OR=1.27, P=1.08 × 10(-11)) and FGD6 Gln257Arg (OR=0.87, P=2.85 × 10(-8)). Our findings suggest that some of the genetic loci conferring AMD susceptibility in East Asians are shared with Europeans, yet AMD in East Asians may also have a distinct genetic signature.

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Diet, lifestyle & low vision

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Is vitamin supplementation appropriate in the healthy old?

Dharmarajan TS.

PURPOSE OF REVIEW: Vitamin supplements are used by large numbers of older adults. Although vitamins serve several functions in the body, the benefits or harm of routine supplementation are far from clear. Data from studies over the last decade are reviewed to enable an understanding.

RECENT FINDINGS: Summarized data from studies conducted over the last few years, pertinent to the use of vitamins, as multivitamin combinations and as individual vitamins specifically A, D, E, C, and the B group, are presented. This review targets the benefits and harm of multivitamins when used to lower the risk of cancer, cardiovascular and cerebrovascular disease, visual disorders (e.g., cataracts and age-related macular degeneration), and bone disease. The effects of vitamins on total mortality are discussed. In addition, isolated or multiple vitamin deficiencies, their predisposing settings and manifestations from mild-to-life-threatening illness are discussed.

SUMMARY: Data from studies demonstrate considerable variations, most confirming little to no benefit following supplementation in healthy adults. However, clear roles exist for vitamin supplementation in states of deficiency and in subgroups of older adults at high risk for deficiency of specific or multiple vitamins. In these settings, vitamin supplements help prevent or correct deficiency and related manifestations.

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[Supplements in age-related macular degeneration : Recommendations by the German Ophthalmological Society, the German Retina Society and the German Professional Association of Ophthalmologists - October 2014.][Article in German]

Deutsche Ophthalmologische Gesellschaft.

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