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MD Research News

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Drug treatment

Retina. 2015 Feb 2. [Epub ahead of print]

REFRACTORY INTRARETINAL OR SUBRETINAL FLUID IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH INTRAVITREAL RANIZUBIMAB: Functional and Structural Outcome.

Gianniou C, Dirani A, Jang L, Mantel I.

PURPOSE: To investigate the visual acuity results of eyes with neovascular age-related macular degeneration and refractory fluid despite monthly treatment with ranibizumab, and to investigate differences between refractory subretinal fluid and intraretinal cystic changes.

METHODS: Retrospective chart review of consecutive treatment-refractory neovascular age-related macular degeneration, defined as persistent intraretinal or subretinal fluid despite monthly ranibizumab injections during 12 months or more. Data were evaluated for baseline characteristics, type and location of the refractory fluid, mean visual acuity change, number of injections, and the time point of first complete disappearance of all fluid on spectral domain optical coherence tomography.

RESULTS: Seventy-six eyes (74 patients, mean age, 76.8 years) were identified. The mean follow-up was 33.6 months (range, 12-73 months). The mean number of injections was 11.4 in the first year and 27.7 over follow-up. The refractory fluid was located subfoveally in 61.8%. In 27 eyes (35.5%), the fluid resolved after a mean of 21.8 months (range, 13-49 months). Mean visual acuity increased by 9.0, 7.9, and 7.9 letters by Month 12, Month 24, and Month 36, respectively. Subgroup analysis revealed a higher risk for fibrosis (odds ratio, 3.30) or atrophy (odds ratio, 3.34) in patients with refractory cysts as compared with refractory subretinal fluid. Furthermore, refractory cysts showed a higher risk for a 10-letter visual acuity loss (P = 0.018).

CONCLUSION: Fluid refractory to monthly treatment with ranibizumab for neovascular age-related macular degeneration still allowed for well-maintained visual improvement, even in subfoveal location. Late fluid resolution may occur. However, refractory cysts were associated with poorer anatomical and functional outcome than subretinal fluid.

PMID: 25650710 [PubMed - as supplied by publisher]

Trans Am Ophthalmol Soc. 2014 Jul;112:160-98.

Optical coherence tomographic and visual results at six months after transitioning to aflibercept for

patients on prior ranibizumab or bevacizumab treatment for exudative age-related macular degeneration (an american ophthalmological society thesis).

Chan CK, Jain A, Sadda S, Varshney N.

PURPOSE: To study optical coherence tomographic (OCT) results and vision at 6 months after transition (post-Tx) from intravitreal bevacizumab and/or ranibizumab to aflibercept for treatment of neovascular age-related macular degeneration (nAMD). The null hypothesis was the lack of improvements in OCT metrics and vision outcome in study eyes at 6 months after transitioning from bevacizumab or ranibizumab to aflibercept.

METHODS: This retrospective study assessed 6 monthly OCT (Cirrus) data after transitioning to aflibercept for eyes on prior Legacy-ranibizumab, Legacy-bevacizumab, or mixed treatment for nAMD. Outcome measures were subretinal fluid (SRF), cystoid macular edema (CME), pigment epithelial detachment (PED) heights and volumes, central 1- and 3-mm subfield, Macular Volume, and best spectacle and pinhole visual acuity (VA). A single masked investigator performed all OCT measurements.

RESULTS: One hundred eighty-nine eyes in 172 patients in Legacy-bevacizumab (95 eyes), Legacy-ranibizumab (84 eyes), or Mixed Group(10 eyes) were switched to aflibercept and followed for 6 months. Significant post-Tx reductions were noted in SRF/CME heights and volumes (all P<.001). Similar findings were noted for PED heights (122.8 μm vs 79.4 μm) and PED volumes (all P<.001). Post-Tx VA was better (20/43 vs 20/51, P<.001). There were no differences between Legacy-bevacizumab and Legacy-ranibizumab groups in OCT and VA changes. Post-Tx VA, SRF/CME, and PED heights and volumes were improved for Nonresponders (suboptimal response to bevacizumab/ranibizumab) (P=.001 to <.001), but not Responders (good responses to same). The only adverse event was a retinal pigment epithelial tear in one eye.

CONCLUSIONS: Significant improvements in vision and OCT metrics developed in Nonresponders but not in Responders. Post-Tx VA and OCT measures were similar for eyes on prior bevacizumab or ranibizumab. Post-Tx adverse events were uncommon.

PMID: 25646034 [PubMed - in process] PMCID: PMC4307397

Trans Am Ophthalmol Soc. 2014 Jul;112:142-59.

Retinal pigment epithelial tears in the era of intravitreal pharmacotherapy: risk factors, pathogenesis, prognosis and treatment (an american ophthalmological society thesis).

Sarraf D, Joseph A, Rahimy E.

PURPOSE: To describe the risk factors, pathogenesis, and prognosis of retinal pigment epithelial (RPE) tears and to demonstrate our hypothesis that continued anti-vascular endothelial growth factor (VEGF) therapy after an RPE tear has occurred correlates with improved long-term visual and anatomical outcomes.

METHODS: We searched a database of 10,089 patients and retrospectively identified a large case series of 56 eyes with neovascular age-related macular degeneration (AMD) complicated by an RPE tear over an 8-year period. Baseline visual acuity (VA) was tabulated and analysis of the RPE tear was performed with multimodal imaging. Follow-up VA, progression of the tear, and severity of fibrosis were evaluated, and each was correlated with number of anti-VEGF injections.

RESULTS: Average follow-up for the 56 eyes was 42 months, and mean logMAR VA at baseline was 0.88 (Snellen VA 20/150) with minimal decline over 3 years. LogMAR VA plotted against number of anti-VEGF injections demonstrated that more frequent and cumulative injections correlated with better VA (P<.0001). A greater number of anti-VEGF injections was associated with minimal progression of the RPE tear, reduced

fibrosis, and lower risk of a large, end-stage exudative disciform scar.

CONCLUSIONS: Fifteen to 20% of vascularized pigment epithelial detachments (PEDs) may develop RPE tears after anti-VEGF therapy due to progressive contraction of the type 1 choroidal neovascular membrane in a PED at risk. Continued monitoring of RPE tears for exudative changes warranting anti-VEGF therapy may stabilize VA, improve anatomical outcomes, reduce fibrosis, and decrease the risk of developing a large blinding end-stage exudative disciform scar.

PMID: 25646033 [PubMed - in process] PMCID: PMC4310706

Trans Am Ophthalmol Soc. 2014 Jul;112:74-93.

Prospective Evaluation of Subretinal Vessel Location in Polypoidal Choroidal Vasculopathy (PCV) and Response of Hemorrhagic and Exudative PCV to High-Dose Antiangiogenic Therapy (An American Ophthalmological Society Thesis).

Kokame GT.

PURPOSE: The purpose of this study was to determine the following: (1) Is polypoidal choroidal vasculopathy (PCV) a subretinal neovascular process, rather than a choroidal vascular anomaly? and (2) Is a higher dose of ranibizumab (2.0 mg/0.05 mL) more effective in treating PCV than the current dose (0.5 mg/0.05 mL) approved for treatment of age-related macular degeneration?

METHODS: Retrospective evaluation of PCV in 104 eyes of 86 patients was accomplished with use of indocyanine green angiography plus optical coherence tomography to localize the branching vascular network and the polyps. Nineteen eyes of 19 patients with active leaking and exudation underwent a prospective open-label trial of monthly high-dose intravitreal ranibizumab (2.0 mg/0.05 mL). The primary outcome was prevention of major vision loss (≤15 ETDRS letters). Secondary outcomes included adverse events, improved vision, and changes in subretinal hemorrhage, subretinal fluid, macular edema, and polypoidal complexes at 6 months.

RESULTS: The PCV vessels were localized beneath the retinal pigment epithelium (RPE) and above Bruch's membrane in 103 (99%) of 104 eyes. In the high-dose ranibizumab trial at 6 months, none of the patients lost ≥15 letters in visual acuity, and 5 (26%) of 19 gained ≥15 letters. Decreases were noted in subretinal fluid in 14 (82%) of 17 eyes, subretinal hemorrhage in 12 (100%) of 12, RPE detachment in 14 (88%) of 16, macular edema in 11 (92%) of 12, and polyps in 15 (79%) of 19 eyes.

CONCLUSIONS: PCV vessels are a subtype of subretinal neovascularization located above Bruch's membrane and below RPE. High-dose ranibizumab (2.0 mg/0.05 mL) decreased exudation and hemorrhage and resulted in significant polyp regression, although branching vascular networks persisted.

PMID: 25646029 [PubMed - in process] PMCID: PMC4307886

Am J Ophthalmol. 2015 Jan 29. [Epub ahead of print]

Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA and HORIZON studies (SEVEN-UP Study).

Bhisitkul RB1, Mendes TS2, Rofagha S2, Enanoria W3, Boyer DS4, Sadda SR5, Zhang K6.

PURPOSE: To assess the incidence and progression of macular atrophy and other key anatomic outcomes over 7-8 years in an early cohort of ranibizumab-treated exudative age-related macular degeneration (AMD) patients.

DESIGN: Follow up analysis of long-term outcomes in a multicenter treatment cohort.

METHODS: 14 study sites enrolled 65 previous subjects from the ranibizumab treatment arms of the ANCHOR, MARINA and HORIZON trials. In a single update visit, clinical assessment and retinal imaging studies were performed, with comparison to each subject's prior results from the previous trials. ETDRS visual acuity was the primary outcome. Secondary outcomes, including area of macular atrophy and selected anatomic factors, were analyzed for associations with long-term vision outcomes.

RESULTS: At a mean 7.3 years after ANCHOR/MARINA enrollment, mean visual acuity was 54 letters, study eyes having received a mean 1.6 injections/year since the HORIZON study. Macular atrophy was present in 98% of study eyes, the mean area increasing from 0.82 ± 1.0 mm2 at ANCHOR/MARINA Year 2 Exit to 2.22 ± 1.6 mm2 at the SEVEN-UP visit, a growth rate of 0.28 mm2/year. Progression of macular atrophy was significantly associated with visual decline over this 5-year period ($p < 0.001$), and final macular atrophy lesion size was significantly related to final vision ($p < 0.001$). Other key anatomic outcomes (macular thickening, thinning, or fluid; submacular fibrosis) did not have significant effects on vision outcomes.

CONCLUSIONS: Seven years after initiation of intensive ranibizumab therapy for exudative AMD, macular atrophy progression and severity were the primary anatomic determinants of visual outcomes.

PMID: 25640411 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Jan 27. [Epub ahead of print]

Anti-vascular endothelial growth factor with or without pneumatic displacement for submacular hemorrhage.

Shin JY, Lee JM, Byeon SH.

PURPOSE: To compare the treatment outcomes of a combination of pneumatic displacement and intravitreal anti-vascular endothelial growth factor (VEGF), and anti-VEGF monotherapy for submacular hemorrhage from exudative age-related macular degeneration (AMD).

DESIGN: Retrospective comparative interventional case series.

METHODS: Forty eyes treated with a combination therapy, and 42 eyes treated with monotherapy for submacular hemorrhage from exudative AMD with no significant difference in baseline central foveal thickness were compared. Central foveal thickness and best-corrected visual acuity (BCVA) at baseline, 1, 3, and 6 months after initial treatment were measured and compared between the two groups after adjustment of baseline central foveal thickness.

RESULTS: Central foveal thickness ($P < 0.0001$) and BCVA (combination $P < 0.0001$, monotherapy $P = 0.022$) were improved after both treatments. Combination therapy showed more rapid improvement of central foveal thickness ($P = 0.009$) and BCVA ($P = 0.007$) within 1 month than monotherapy, but there was no difference at 6 months ($P = 0.385$, $P = 0.303$, respectively). In eyes with subretinal hemorrhage thicker than 450 μm, visual outcome at 6 months was better in the combination therapy group than in the monotherapy group ($P = 0.021$), while BCVA showed no significant difference between groups in eyes with subretinal hemorrhage less than 450 μm ($P = 0.930$).

CONCLUSIONS: Both treatments are useful options for submacular hemorrhage from exudative AMD. Combination therapy may yield a better treatment outcome than monotherapy in eyes with thick subretinal hemorrhage. Nevertheless, the potential for adverse events from pneumatic displacement should be considered.

PMID: 25637179 [PubMed - as supplied by publisher]

J Nutr Health Aging. 2015;19(2):228-31.

Influence of Anti-VEGF about Cardiovascular Biomarkers in Age Related Macular Degeneration.

Manresa N, Mulero J, Losada M, Zafrilla P.

Abstract: Systemic VEGF inhibition disrupts endothelial homeostasis and accelerates the atherogenesis, suggesting that these events contribute to the clinical cardiovascular adverse events of VEGF-inhibiting therapies. The objective of the current study was to analyze the effect of anti-VEGF therapy on cardiovascular risk factors in patients with exudative age related macular degeneration. A total of 73 patients with exudative age related macular degeneration (without previous anti-VEGF therapy) were treated with two anti-VEGF: Ranibizumab and Pegaptanib sodium. The follow up was 6 months. The following parameters were determined before and after treatment: homocysteine, lipids (total cholesterol, triglycerides, HDL-c, LDL-c), C-Reactive Protein and fibrinogen. There were not statistically significant differences in parameters studied before and after treatment with both Pegaptanib sodium and Ranibizumab, except C-Reactive Protein. Of all patients analyzed, only 3 of them have initially C-Reactive Protein levels above normal levels and after antiangiogenic therapy, there was a significant increase in C-Reactive Protein. We have not found results in our study who to suspect that treatment with anti-VEGF in the patients with exudative age related macular degeneration increases cardiovascular risk predictors. However, after therapy was increased the CRP and fibrinogen may mean that anti-VEGF contribute an alteration of endothelial homeostasis in exudative AMD.

PMID: 25651450 [PubMed - in process]

Int Ophthalmol. 2015 Feb 3. [Epub ahead of print]

The safety of bevacizumab and ranibizumab in clinical studies.

De Rosa M, Messori A.

Abstract: In comparing the safety of ranibizumab versus bevacizumab in age-related macular degeneration, the meta-analyses published thus far have given conflicting results, particularly about the risk of venous thrombotic events and ocular inflammation. From the comparison of the design and the findings of these meta-analysis, we tried to identify the potential explanations to account for these discrepancies. We separately evaluated the incidence of ocular inflammation with the two agents between randomized studies and non-randomized studies. While no increase in risk was found in randomized studies, non-randomized studies showed an increase in risk for bevacizumab versus ranibizumab. One interpretation of these findings is that bevacizumab itself does not represent any increase in risk of ocular inflammation and/or cardiovascular events under the rigorous conditions of a randomized study, but this agent can be at the origin of an increase in risk when administered in the "real world"; this setting could in fact leave space for less strictly controlled preparation of aliquots for intravitreal injection.

PMID: 25646753 [PubMed - as supplied by publisher]

Other treatment & diagnosis

J Vis Exp. 2015 Jan 23;(95).

Performing subretinal injections in rodents to deliver retinal pigment epithelium cells in suspension.

Westenskow PD, Kurihara T, Bravo S, et al

Abstract: The conversion of light into electrical impulses occurs in the outer retina and is accomplished

largely by rod and cone photoreceptors and retinal pigment epithelium (RPE) cells. RPE provide critical support for photoreceptors and death or dysfunction of RPE cells is characteristic of age-related macular degeneration (AMD), the leading cause of permanent vision loss in people age 55 and older. While no cure for AMD has been identified, implantation of healthy RPE in diseased eyes may prove to be an effective treatment, and large numbers of RPE cells can be readily generated from pluripotent stem cells. Several interesting questions regarding the safety and efficacy of RPE cell delivery can still be examined in animal models, and well-accepted protocols used to inject RPE have been developed. The technique described here has been used by multiple groups in various studies and involves first creating a hole in the eye with a sharp needle. Then a syringe with a blunt needle loaded with cells is inserted through the hole and passed through the vitreous until it gently touches the RPE. Using this injection method, which is relatively simple and requires minimal equipment, we achieve consistent and efficient integration of stem cell-derived RPE cells in between the host RPE that prevents significant amount of photoreceptor degeneration in animal models. While not part of the actual protocol, we also describe how to determine the extent of the trauma induced by the injection, and how to verify that the cells were injected into the subretinal space using in vivo imaging modalities. Finally, the use of this protocol is not limited to RPE cells; it may be used to inject any compound or cell into the subretinal space.

PMID: 25651341 [PubMed - in process]

Retina. 2015 Feb 2. [Epub ahead of print]

TYPE 3 NEOVASCULARIZATION: Evolution, Association With Pigment Epithelial Detachment, and Treatment Response as Revealed by Spectral Domain Optical Coherence Tomography.

Nagiel A1, Sarraf D, Sadda SR, Spaide RF, Jung JJ, Bhavsar KV, Ameri H, Querques G, Freund KB.

PURPOSE: To demonstrate the evolution and treatment response of Type 3 neovascularization using spectral domain optical coherence tomography.

METHODS: We retrospectively analyzed 40 eyes treated with intravitreal anti-vascular endothelial growth factor therapy for Type 3 neovascularization over a variable follow-up period.

RESULTS: In 17 eyes, spectral domain optical coherence tomography captured the development of Type 3 neovascularization from punctate hyperreflective foci that preceded any outer retinal defect. The more mature Type 3 lesions were associated with outer retinal disruption and adjacent cystoid macular edema. In addition, 37 of 40 Type 3 lesions (93%) were associated with an underlying pigment epithelial detachment, of which 26 (70%) were drusenoid, 6 (16%) serous, and 5 (14%) mixed. Type 3 vessels appeared to leak fluid into the pigment epithelial detachment cavity, creating serous pigment epithelial detachments as large as 925 μm in maximal height. Treatment with anti-vascular endothelial growth factor agents led to prompt involution of the lesion and resorption of the intraretinal and subretinal pigment epithelium fluid after one or two injections (median = 1).

CONCLUSION: In some eyes with age-related macular degeneration, the earliest sign of Type 3 neovascularization is punctate hyperreflective foci above the external limiting membrane. The mature Type 3 lesions and associated serous pigment epithelial detachments are highly responsive to anti-vascular endothelial growth factor therapy.

PMID: 25650713 [PubMed - as supplied by publisher]

Retina. 2015 Feb 2. [Epub ahead of print]

LASER RESENSITIZATION OF MEDICALLY UNRESPONSIVE NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Efficacy and Implications.

Luttrull JK, Chang DB, Margolis BW, Dorin G, Luttrull DK.

PURPOSE: Drug tolerance is the most common cause of treatment failure in neovascular age-related macular degeneration. "Low-intensity/high-density" subthreshold diode micropulse laser (SDM) has been reported effective for a number of retinal disorders without adverse effects. It has been proposed that SDM normalizes retinal pigment epithelial function. On this basis, it has been postulated that SDM treatment might restore responsiveness to anti-vascular endothelial growth factor drugs in drug-tolerant eyes.

METHODS: Subthreshold diode micropulse laser treatment was performed in consecutive eyes unresponsive to all anti-vascular endothelial growth factor drugs, including at least three consecutive ineffective aflibercept injections. Monthly aflibercept was resumed 1 month after SDM treatment.

RESULTS: Thirteen eyes of 12 patients, aged 73 to 97 years (average, 84 years), receiving 16 to 67 (average, 34) anti-vascular endothelial growth factor injections before SDM treatment were included and followed for 3 months to 7 months (average, 5 months) after SDM treatment. After SDM treatment and resumption of aflibercept, 92% (12 of 13) of eyes improved, with complete resolution of macular exudation in 69% (9 of 13). Visual acuity remained unchanged. Central and maximum macular thicknesses significantly improved.

CONCLUSION: Subthreshold diode micropulse laser treatment restored drug response in drug-tolerant eyes with neovascular age-related macular degeneration. Based on these findings, a theory of SDM action is proposed, suggesting a wider role for SDM as retinal reparative/protective therapy.

PMID: 25650711 [PubMed - as supplied by publisher]

Retina. 2015 Feb 5. [Epub ahead of print]

COMPARISON OF SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY SCAN PATTERNS AND CLINICAL REVIEW STRATEGIES IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Courtney RJ, McClintic JI, Ehlers JP.

PURPOSE: To compare various spectral domain optical coherence tomography scan patterns and review strategies to identify an optimal imaging workflow for neovascular age-related macular degeneration.

METHODS: (Zeiss Cirrus), including horizontal/vertical five-line rasters, and macular cube analysis. For each scan pattern, a single report was independently reviewed in a masked fashion within the clinical image review software, whereas the cube was reviewed line-by-line in the reader software for the presence of fluid.

RESULTS: One hundred and fifty-six reports and 39 cube scans of 39 patients were included. Among all spectral domain optical coherence tomography scans, 64% (25/39) had definitive fluid and 95% (37/39) had possible fluid. Sensitivities for definite fluid detection for horizontal, combined horizontal/vertical, and horizontal/vertical/map reviews were 68%, 76%, and 88%, respectively. When assessing for possible fluid, sensitivities for the detection for horizontal, combined horizontal/vertical, and horizontal/vertical/map reviews were 76%, 92%, and 97%, respectively. Line-by-line review of the cube scan had a sensitivity for definite and possible fluid detection of 96% and 86%, respectively.

CONCLUSION: Optimizing both clinical accuracy and workflow are important factors in managing neovascular age-related macular degeneration. A zero-tolerance strategy with vertical/horizontal raster scans and thickness maps was comparable with line-by-line review of the cube to detect possible fluid.

PMID: 25658176 [PubMed - as supplied by publisher]

Retina. 2015 Feb 5. [Epub ahead of print]

EVALUATING CONTRAST SENSITIVITY IN AGE-RELATED MACULAR DEGENERATION USING A NOVEL COMPUTER-BASED TEST, THE SPAETH/RICHMAN CONTRAST SENSITIVITY TEST.

Faria BM, Duman F, Zheng CX, et al

BACKGROUND: Contrast sensitivity (CS) is a valuable measure of visual function in patients with age-related macular degeneration (AMD). The authors aimed to compare a novel computer-based test (the Spaeth/Richman Contrast Sensitivity test) with Pelli-Robson test for evaluating CS in patients with AMD.

METHODS: In this prospective cross-sectional study, CS was evaluated in patients with various stages of AMD and healthy controls using Spaeth/Richman Contrast Sensitivity test and Pelli-Robson test. Spaeth/Richman Contrast Sensitivity test determined CS scores for 5 areas of vision for each eye (central, superonasal, superotemporal, inferonasal, and inferotemporal) and the total score. Test scores between the two methods were compared using mixed-effects linear regression. Spearman's rank correlation coefficient was used to determine correlations. Test-retest reliability was determined using the intraclass correlation coefficient.

RESULTS: Of 35 participants with AMD (54 eyes) and 34 controls (66 eyes), 51% were female and 93% were of European descent. The mean Spaeth/Richman Contrast Sensitivity test score for the central area and each of the 4 peripheral quadrants was significantly lower for patients with AMD versus controls ($P < 0.001$ for all). The mean Pelli-Robson score was also significantly lower in patients with AMD versus controls ($P < 0.001$). The intraclass correlation coefficient for Spaeth/Richman Contrast Sensitivity test total score and Pelli-Robson score was 0.87 and 0.92, respectively.

CONCLUSION: Spaeth/Richman Contrast Sensitivity test, a novel Internet-based method of testing CS, had significantly lower scores for patients with AMD compared with controls for central and peripheral vision. This test is a valuable tool for assessing CS in AMD.

PMID: 25658175 [PubMed - as supplied by publisher]

Retina. 2015 Feb 5. [Epub ahead of print]

MORPHOLOGY SCORE AS A MARKER OF RETINAL FUNCTION IN DRUSENOID PIGMENT EPITHELIAL DETACHMENT.

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

PURPOSE: To evaluate a morphology score for drusenoid pigment epithelial detachment (dPED) regarding predictability of a decline in retinal function beyond best-corrected visual acuity.

METHODS: Thirteen eyes of 10 patients with dPED due to age-related macular degeneration (AMD) were included (age 72.8 ± 4.2 years). All underwent volume spectral domain optical coherence tomography, fluorescence angiography, and confocal scanning laser ophthalmoscopy infrared imaging as well as multifocal electroretinography and microperimetry. The dPED morphology score suggested consists of five parameters: hyperreflective spots in infrared, lesion diameter, lesion height, presence of vitelliform-like material in the subretinal space or subretinal fluid, and integrity of the ellipsoid zone in spectral domain optical coherence tomography. Subsequently, a score value between 0 and 1 according to the extent of morphologic changes was correlated to foveal multifocal electroretinography and microperimetry measurements.

RESULTS: The mean best-corrected visual acuity was 20/40. The mean height and mean diameter of dPED were 312.2 ± 111 μm and 2,535 ± 805 μm. Two dPED showed no hyperreflective spots in confocal scanning laser ophthalmoscopy infrared images, three displayed a moderate stage of hyperreflective spots, and eight had severe hyperreflective spots. Two eyes showed subretinal fluid, and five patients showed

vitelliform-like material in the subretinal space. Eight eyes revealed a severe disruption of the ellipsoid zone. Although no correlation was found between dPED morphology score and best-corrected visual acuity, eyes with a dPED morphology score >0.5 revealed distinctly decreased values in functional measurements compared with those with a score ≤0.5.

CONCLUSION: The dPED morphology score aggregates all currently known morphologic changes in dPED and represents a valuable tool for clinical lesion evaluation. Furthermore, it allows for assessing an estimate of functional decline beyond best-corrected visual acuity.

PMID: 25658174 [PubMed - as supplied by publisher]

Transl Vis Sci Technol. 2014 Dec 1;3(6):5.

Implantable MicroPump for Drug Delivery in Patients with Diabetic Macular Edema.

Humayun M, Santos A, Altamirano JC, et al.

PURPOSE: To demonstrate the safety and surgical feasibility of the first-in-man ocular implant of a novel Posterior MicroPump Drug Delivery System (PMP) in patients with diabetic macular edema (DME) and to report on the device capabilities for delivering a programmable microdose.

METHODS: This was a single center, single arm, open-label, prospective study. Eleven patients with DME and visual acuity equal to or worse than 20/40 were included. The PMP prefilled with ranibizumab was implanted into the subconjunctival space. After implantation, the PMP was wirelessly controlled to deliver a programmed microdose. Comprehensive ophthalmic exams and optical coherence tomography were performed biweekly for 90 days. At the end of the study, the PMP was explanted and the subjects thereafter received standard of care for DME (i.e., laser or intravitreal injections).

RESULTS: All 11 surgical implantations were without complications and within the skill sets of a retinal surgeon. No serious adverse events occurred during the follow-up period. At no point were visual acuity and central foveal thickness worse than baseline in the implanted eye. The PMP delivered the programmed ranibizumab dosage in seven subjects. The remaining four patients received a lower than target dose, and the treatment was complemented with standard intravitreal injection.

CONCLUSIONS: This study demonstrates the first-in-man safety of the Replenish MicroPump implant for a period of 90 days and its capability to deliver a microdose into the vitreous cavity. Further studies to enable longer-term safety and to demonstrate the feasibility of multiple programmable drug delivery are necessary.

PMID: 25653883 [PubMed] PMCID: PMC4315583

Pathogenesis

J Inflamm Res. 2015 Jan 16;8:15-27.

Targeting the NLRP3 inflammasome in chronic inflammatory diseases: current perspectives.

Ozaki E, Campbell M, Doyle SL.

Abstract: The inflammasome is a molecular platform formed by activation of an innate immune pattern recognition receptor seed, such as NLRP3. Once activated, NLRP3 recruits the adapter ASC (apoptosis-related speck-like protein containing a caspase recruitment domain), which in turn recruits procaspase-1. Procaspase-1 autocatalyzes its cleavage and activation, resulting in maturation of the precursor forms of interleukin (IL)-1β and IL-18 into active proinflammatory cytokines and initiation of pyroptotic cell death. The NLRP3 inflammasome has been implicated in the pathogenesis of a wide variety of diseases, including

genetically inherited autoinflammatory conditions as well as chronic diseases in which NLRP3 is abnormally activated. The NLRP3 inflammasome has been linked to diseases such as Alzheimer's disease, atherosclerosis, metabolic syndrome, and age-related macular degeneration. In this review, we describe the NLRP3 inflammasome complex and its activation in disease, and detail the current therapies that modulate either the NLRP3 inflammasome complex itself or the two cytokines it is responsible for activating, ie, IL-1β and IL-18.

PMID: 25653548 [PubMed] PMCID: PMC4303395

Cell Tissue Res. 2015 Feb 1. [Epub ahead of print]

PTB-associated splicing factor inhibits IGF-1-induced VEGF upregulation in a mouse model of oxygen-induced retinopathy.

Dong L, Nian H, Shao Y, et al

Abstract: Pathological retinal neovascularization, including retinopathy of prematurity and age-related macular degeneration, is the most common cause of blindness worldwide. Insulin-like growth factor-1 (IGF-1) has a direct mitogenic effect on endothelial cells, which is the basis of angiogenesis. Vascular endothelial growth factor (VEGF) activation in response to IGF-1 is well documented; however, the molecular mechanisms responsible for the termination of IGF-1 signaling are still not completely elucidated. Here, we show that the polypyrimidine tract-binding protein-associated splicing factor (PSF) is a potential negative regulator of VEGF expression induced by IGF stimulation. Functional analysis demonstrated that ectopic expression of PSF inhibits IGF-1-stimulated transcriptional activation and mRNA expression of the VEGF gene, whereas knockdown of PSF increased IGF-1-stimulated responses. PSF recruited Hakai to the VEGF transcription complex, resulting in inhibition of IGF-1-mediated transcription. Transfection with Hakai siRNA reversed the PSF-mediated transcriptional repression of VEGF gene transcription. In summary, these results show that PSF can repress the transcriptional activation of VEGF stimulated by IGF-1 via recruitment of the Hakai complex and delineate a novel regulatory mechanism of IGF-1/VEGF signaling that may have implications in the pathogenesis of neovascularization in ocular diseases.

PMID: 25638408 [PubMed - as supplied by publisher]

Am J Med. 2015 Jan 28. [Epub ahead of print]

Immunoactivation at the Crossroads of Human Diseases.

Margolis L.

Abstract: It is becoming increasingly clear that immunoactivation, which evolved as a system of host defense against pathogens, can become dysregulated and promote the pathogenesis of diverse diseases with both known and unknown etiologies (e.g., AIDS, age-related macular degeneration, cancer) as well as aging. Immunoactivation seems to be a "common denominator" or general mechanism of pathogenesis, and may explain the association and similarities in pathology among otherwise unrelated human diseases. Identification of general mechanisms of immunoactivation may lead to the development of new therapeutic strategies applicable to many diseases even before detailed knowledge of specific etiology and pathogenesis may be available.

PMID: 25637756 [PubMed - as supplied by publisher]

Epidemiology

Invest Ophthalmol Vis Sci. 2015 Feb 5. [Epub ahead of print]

Risk Prediction for Progression of Macular Degeneration: 10 Common and Rare Genetic Variants, Demographic, Environmental, and Macular Covariates.

Seddon JM, Silver RE, Kwong M, Rosner B.

Purpose: To determine the association between genetic variants and transition to advanced age-related macular degeneration (AMD), and to develop a predictive model and online application to assist in clinical decision making.

Methods: Among 2951 subjects in the Age-Related Eye Disease Study, 834 progressed from no AMD, early and intermediate AMD to advanced disease. Survival analysis was used to assess which genetic, demographic, environmental, and macular covariates were independently associated with progression. Attributable risk (AR), area under the curve statistics (AUCs), and reclassification odds ratios (ORs) were calculated. Split-sample validation was performed. An online risk calculator was developed and is available at www.seddonamdriskscore.org.

Results: Ten genetic loci were independently associated with progression, including newly identified rare variant C3 K155Q (hazard ratio: 1.7, 95% confidence interval: 1.2-2.5, p=0.002), 3 variants in CFH, and 6 variants in ARMS2/HTRA1, CFB, C3, C2, COL8A1 and RAD51B. AR calculations revealed that 80% of incident AMD is attributable to genetic factors, adjusting for demographic covariates and baseline macular phenotypes. In a model including 10 genetic loci, age, sex, education, BMI, smoking, and baseline AMD status, the AUC for progression to advanced AMD over 10 years was 91.1%. Split-sample validation showed a similar AUC (90.7%). Reclassification analyses indicated that subjects were categorized into a more accurate risk category if genetic information was included (OR: 3.2, p <0.0001).

Conclusion Rare variant C3 K155Q was independently associated with AMD progression. The comprehensive model may be useful for identifying and monitoring high risk patients, selecting appropriate therapies, and designing clinical trials.

PMID: 25655794 [PubMed - as supplied by publisher]

Genetics

Genomics. 2015 Jan 31. [Epub ahead of print]

Transcriptome of the human retina, retinal pigmented epithelium and choroid.

Tian L, Kazmierkiewicz KL, Bowman AS, et al

Abstract: The retina and its adjacent supporting tissues - retinal pigmented epithelium (RPE) and choroid - are critical structures in human eyes required for normal visual perception. Abnormal changes in these layers have been implicated in diseases such as age-related macular degeneration and glaucoma. With the advent of high-throughput methods, such as serial analysis of gene expression, cDNA microarray, and RNA sequencing, there is unprecedented opportunity to facilitate our understanding of the normal retina, RPE, and choroid. This information can be used to identify dysfunction in age-related macular degeneration and glaucoma. In this review, we describe the current status in our understanding of these transcriptomes through the use of high-throughput techniques.

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Diet, lifestyle & low vision

BMC Ophthalmol. 2015 Jan 30;15(1):9. [Epub ahead of print]

Evaluation of real-world mobility in age-related macular degeneration.

Sengupta S, Nguyen AM, van Landingham SW, et al

BACKGROUND: Previous research has suggested an association between poor vision and decreased mobility, including restricted levels of physical activity and travel away from home. We sought to determine the impact of age-related macular degeneration (AMD) on these measures of mobility.

METHODS: Fifty-seven AMD patients with bilateral, or severe unilateral, visual impairment were compared to 59 controls with normal vision. All study subjects were between the ages of 60 and 80. Subjects wore accelerometers and cellular network-based tracking devices over 7 days of normal activity. Number of steps taken, time spent in moderate-to-vigorous physical activity (MVPA), number of excursions from home, and time spent away from home were the primary outcome measures.

RESULTS: In multivariate negative binomial regression models adjusted for age, gender, race, comorbidities, and education, AMD participants took fewer steps than controls (18% fewer steps per day, $p = 0.01$) and spent significantly less time in MVPA (35% fewer minutes, $p < 0.001$). In multivariate logistic regression models adjusting for age, sex, race, cognition, comorbidities, and grip strength, AMD subjects showed an increased likelihood of not leaving their home on a given day (odds ratio = 1.36, $p = 0.04$), but did not show a significant difference in the magnitude of time spent away from home (9% fewer minutes, $p = 0.11$).

CONCLUSION: AMD patients with poorer vision engage in significantly less physical activity and take fewer excursions away from the home. Further studies identifying the factors mediating the relationship between vision loss and mobility are needed to better understand how to improve mobility among AMD patients.

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Arch Biochem Biophys. 2015 Jan 28. [Epub ahead of print]

Lutein and factor D: Two intriguing players in the field of age-related macular degeneration.

Tian Y, Kijlstra A, Webers CA, Berendschot TT.

Abstract: Age-related macular degeneration (AMD) is a progressive eye disease that impairs central vision among elderly populations in Western, industrialized countries. In this review we will focus on the role of factor D (FD) and lutein in AMD. FD is a rate-limiting enzyme of the alternative complement activation pathway that may play an important role in the development of AMD. Several independent studies have shown a significant increase in the level of a number of complement factors of the alternative pathway, including factor D in the blood of AMD patients as compared to healthy individuals, which suggests a systemic involvement in the pathogenesis of AMD. FD, also called adipsin, is mainly produced by adipose tissue. Besides playing a role in the activation of the alternative pathway, FD is also known to regulate the immune system. Of interest is our preliminary finding that lutein supplementation of early AMD cases was shown to lower the level of systemic FD. If confirmed, these findings provide further support for the application of anti-factor D intervention as a new approach to control the development of this disease.

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Invest Ophthalmol Vis Sci. 2015 Feb 3. [Epub ahead of print]

Age-Related Eye Disease and Cognitive Function.

Harrabi H, Kergoat MJ, Rousseau J, et al

Purpose: To determine whether people with age-related eye disease have lower cognitive scores than people with normal vision.

Methods: A hospital-based cross-sectional study was performed in which 420 people ages 65 and older from the ophthalmology clinics at Maisonneuve-Rosemont Hospital (Montreal, Canada) were recruited who had either age-related macular degeneration (AMD), Fuch's corneal dystrophy, or glaucoma. Patients with AMD and Fuchs had to have visual acuity in the better eye of worse than 20/40 while patients with glaucoma had to have visual field in their worse eye of at least -4dB. Controls, recruited from the same clinics, did not have significant vision loss. Cognitive status was measured using the Mini-Mental State Exam Blind Version (range 0-22) which excludes 8 items that rely on vision. Linear regression with bootstrapped standard errors was used to adjust for demographic and medical factors.

Results: People with AMD, Fuch's corneal dystrophy, and glaucoma had lower cognitive scores, on average, than controls ($P<0.05$). These relationships remained statistically significant after adjusting for factors such as age, gender, race, education, living alone, systemic comorbidities, and lens opacity.

Conclusions: People with vision loss due to three different age-related eye diseases had lower cognitive scores. Reasons for this should be explored using longitudinal studies and a full battery of cognitive tests that do not rely on vision.

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Int J Food Sci Nutr. 2015 Feb 6:1-8. [Epub ahead of print]

Incorporation of lutein and docosahexaenoic acid from dietary microalgae into the retina in quail.

Schnebelen-Berthier C, Acar N, Pouillart P, et al

Abstract: Lutein and docosahexaenoic acid (DHA) are associated with the prevention of age-related macular degeneration (AMD). Since microalgae are potent natural sources of these nutrients, their nutritional value should be evaluated based on the bioavailability of lutein and DHA for the retina via the plasmatic compartment. In this study, quail were fed for 5 months either with a diet supplemented or deprived with microalgae rich in lutein and DHA. In the microalgae-fed group, the retinal concentrations of lutein and zeaxanthin gradually increased whereas in plasma, these compounds started to increase from the first month of supplementation. We also observed a significant increase in retinal and plasmatic levels of DHA in the microalgae-fed group. In conclusion, the plasmatic and retinal contents of lutein and DHA were significantly increased in quail fed with lutein- and DHA-rich microalgae. Food fortification with microalgae may be an innovative way to increase lutein and DHA consumption in humans.

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Perception. 2014;43(11):1214-24.

Does perisaccadic compression require foveal vision?

Matziridi M, Hartendorp MO, Brenner E, Smeets JB.

Abstract: People make systematic errors when localizing a stimulus that is presented briefly near the time of a saccade. These errors have been interpreted as compression towards the position that is fixated after

the saccade. Normally, fixating a position means that its image falls on the fovea. Macular degeneration (MD) damages the central retina, obliterating foveal vision. Many people with MD adopt a new retinal locus for fixation, called the preferred retinal locus (PRL). If the compression of space during the saccade is a special characteristic of the fovea, possibly due to the high density of cones that is found in the fovea, one might expect people lacking central vision to show no compression of space around the time of a saccade. If the compression of space during the saccade is related to the position that is fixated after the saccade, one would expect compression towards the PRL, despite the lack of a high density of cones in this area. We found that a person with MD showed a clear compression towards her PRL. We conclude that perisaccadic compression is related to the position that is fixated after the saccade rather than to the high density of receptors in the fovea.

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