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MD Research News

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Drug treatment

Retina. 2015 Sep 21. [Epub ahead of print]

VISUAL AND MORPHOLOGIC OUTCOMES OF INTRAVITREAL RANIBIZUMAB FOR DIABETIC MACULAR EDEMA BASED ON OPTICAL COHERENCE TOMOGRAPHY PATTERNS.

Seo KH, Yu SY, Kim M, Kwak HW.

PURPOSE: To evaluate the visual and morphologic outcomes of intravitreal ranibizumab (IVR) in eyes with diabetic macular edema (DME) based on the morphologic pattern on optical coherence tomography.

METHODS: A prospective and consecutive series of 55 eyes with DME was classified according to OCT features: diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD). Patients received three consecutive monthly injections of IVR and as needed thereafter. The primary outcome was the number of treatments undertaken by DME type over 12 months. Best-corrected visual acuity, retinal thickness, and microstructural changes were also evaluated.

RESULTS: The eyes were classified as DRT (n = 23), CME (16), or SRD (16). The mean number of injections over 12 months was significantly different among the groups: DRT (3.69), CME (5.33), and SRD (5.09; P = 0.028). Best-corrected visual acuity of SRD (20/60) was significantly worse than that of the other types (DRT = 20/38; CME = 20/43; P = 0.015) after 12 months.

CONCLUSION: Vision gains and retinal anatomy improvement were maintained in all three types during the first year of IVR administration. Especially, DRT maintained a good response to ranibizumab in a fewer number of injections. Disruption of the photoreceptor integrity at the baseline was correlated with poorer visual outcome and occurred more frequently in SRD.

PMID: 26398695 [PubMed - as supplied by publisher]

Retina. 2015 Sep 21. [Epub ahead of print]

AFLIBERCEPT FOR THE TREATMENT OF RETINAL PIGMENT EPITHELIAL DETACHMENTS.

He L, Silva RA, Moshfeghi DM, Blumenkranz MS, Leng T.

PURPOSE: To compare anatomical and visual acuity outcomes of eyes with persistent pigment epithelial detachments (PEDs) secondary to exudative age-related macular degeneration despite ranibizumab or bevacizumab treatment.

METHODS: After institutional review board approval, 40 eyes with PEDs switched from ranibizumab or bevacizumab to intravitreal aflibercept were compared for logMAR visual acuity, central subfield thickness on spectral domain optical coherence tomography, and PED height. Using paired t-tests, these parameters at baseline, after 3 consecutive injections, and 1 year after the switch were compared.

RESULTS: Baseline visions of 20/61 ± 3.99 lines declined after 3 injections with aflibercept by 0.39 ± 2.43 lines (P = 0.32) and continued to fall after 1 year by 1.27 ± 3.48 lines (P = 0.03). Central subfield thickness was reduced after 3 injections (9.1 ± 52.0 μm, P = 0.27) and after 1 year (24.4 ± 55.3 μm, P = 0.01). The height of PEDs decreased by 31.7 ± 71.53 μm (P = 0.008) after 3 injections and by 47.81 ± 77.94 μm (P < 0.001) after 1 year.

CONCLUSION: Switching to aflibercept from ranibizumab or bevacizumab resulted in a reduction in the height of PED and central subfield thickness, but a trend toward worse visual acuity 1 year after the switch.

PMID: 26398694 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Sep 18. [Epub ahead of print]

Prospective Trial of Treat-and-Extend versus Monthly Dosing for Neovascular Age-Related Macular Degeneration: TREX-AMD 1-Year Results.

Wykoff CC, Croft DE, Brown DM, Wang R, Payne JF, Clark L, Abdelfattah NS, Sadda SR; TREX-AMD Study Group*.

PURPOSE: To assess prospectively a treat-and-extend (TREX) management strategy compared with monthly dosing of intravitreal ranibizumab in treatment-naïve neovascular age-related macular degeneration (AMD) patients.

DESIGN: Phase IIIb, multicenter, randomized, controlled clinical trial.

PARTICIPANTS: Sixty patients with treatment-naïve neovascular AMD randomized 1:2 to monthly or TREX management.

METHODS: Patients with Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) from 20/32 to 20/500 (Snellen equivalent) were randomized to receive intravitreal 0.5 mg ranibizumab monthly or according to a TREX protocol. The TREX patients were treated monthly for at least 3 doses, until resolution of clinical and spectral-domain optical coherence tomography evidence of exudative disease activity; the interval between visits then was individualized according to a strict prospective protocol.

MAIN OUTCOME MEASURES: Mean ETDRS BCVA change from baseline.

RESULTS: At baseline, mean age was 77 years (range, 59-96 years), mean BCVA was 20/60 (Snellen equivalent), and mean central retinal thickness (CRT) was 511 μm. Fifty-seven eyes (95%) completed month 12, at which point mean BCVA improved by 9.2 and 10.5 letters in the monthly and TREX cohorts, respectively (P = 0.60). The mean number of injections administered through month 12 was 13.0 and 10.1 (range, 7-13) in the monthly and TREX cohorts, respectively (P < 0.0001). Among TREX patients, 7 (18%) were maximally extended, 4 (10%) demonstrated fluid at every visit, and at month 12, 18 (45%) had achieved an extension interval of 8 weeks or more; the mean maximum extension interval between injections after the first 3 monthly doses was 8.4 weeks (range, 4-12 weeks). Most TREX patients who demonstrated recurrent exudative disease activity (17/24 [71%]) were unable to extend beyond their initial maximum extension interval.

CONCLUSIONS: The TREX neovascular AMD management strategy used in this prospective, randomized, controlled trial resulted in visual and anatomic gains comparable with those obtained with monthly dosing.

PMID: 26391465 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2015 Sep 19:0. [Epub ahead of print]

Intravitreal anti-VEGF therapy for macular radiation retinopathy: a 10-year study.

Finger PT, Chin KJ, Semenova EA.

PURPOSE: To report long-term experience with intravitreal anti-vascular endothelial growth factor treatment for radiation maculopathy.

METHODS: From 2005-2015, 120 consecutive patients underwent intravitreal anti-VEGF therapy for radiation maculopathy. Inclusion criteria included a diagnosis of uveal melanoma treated with plaque radiotherapy and subsequent macular radiation vasculopathy (exudate, retinal hemorrhage, intraretinal microangiopathy, neovascularization, edema). Anti-VEGF therapy involved continuous injections in 4- to 12 -week intervals with doses of 1.25 mg/0.05 mL, 2.0 mg/0.08 mL, 2.5 mg/0.1 mL, or 3.0 mg/0.12 mL of bevacizumab as well as 0.5 mg/0.05 mL or 2.0 mg/0.05 mL of ranibizumab. Goals were maintenance of visual acuity and normative macular anatomy. Safety and tolerability (retinal detachment, hemorrhage, infection), visual acuity, central foveal thickness on optical coherence tomography imaging, and clinical features of radiation maculopathy were analyzed.

RESULTS: Progressive reductions in macular edema, hemorrhages, exudates, cotton-wool spots, and microangiopathy were noted. At last follow-up, 80% remained within 2 lines of their initial visual acuity or better, with a mean treatment interval of 38 months (range 6-108 months). Kaplan-Meier analysis of the probability of remaining within 2 lines of initial visual acuity was 69% at 5 years and 38% at 8 years of anti-VEGF therapy. Discontinuation of therapy was rare. Relatively few acute or long-term side effects were noted, allowing for good long-term patient accrual.

CONCLUSIONS: Continuous intravitreal anti-VEGF therapy in patients with radiation maculopathy was well -tolerated and preserved vision. In most cases, reductions or resolution of retinal hemorrhages, cotton-wool spots, and retinal edema were noted for up to 10 years.

PMID: 26391167 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Sep 16;9:1715-8. eCollection 2015.

Conversion to aflibercept for diabetic macular edema unresponsive to ranibizumab or bevacizumab.

Lim LS, Ng WY, Mathur R, Wong D, Wong EY, Yeo I, Cheung CM, Lee SY, Wong TY, Papakostas TD, Kim LA.

BACKGROUND: The purpose of this study was to determine if eyes with diabetic macular edema (DME) unresponsive to ranibizumab or bevacizumab would benefit from conversion to aflibercept.

METHODS: This study was conducted as a retrospective chart review of subjects with DME unresponsive to ranibizumab and/or bevacizumab and subsequently converted to aflibercept.

RESULTS: In total, 21 eyes from 19 subjects of mean age 62±15 years were included. The majority of subjects were male (63%). The median number of ranibizumab or bevacizumab injections before switching to aflibercept was six, and the median number of aflibercept injections after switching was three. Median follow-up was 5 months after the switch. Mean central foveal thickness (CFT) was 453.52±143.39 mm immediately prior to the switch. Morphologically, intraretinal cysts were present in all cases. Mean CFT after the first injection decreased significantly to 362.57±92.82 mm (Wilcoxon signed-rank test; $P<0.001$). At the end of follow-up, the mean CFT was 324.17±98.76 mm ($P<0.001$). Mean visual acuity was 0.42±0.23 logMAR just prior to the switch, 0.39±0.31 logMAR after one aflibercept injection, and 0.37±0.22 log-MAR at the end of follow-up. The final visual acuity was significantly better than visual acuity before the switch ($P=0.04$).

CONCLUSION: Eyes with DME unresponsive to multiple ranibizumab/bevacizumab injections demonstrate anatomical and visual improvement on conversion to aflibercept.

PMID: 26396494 [PubMed] PMCID: PMC4577250

Retina. 2015 Sep 21. [Epub ahead of print]

INTRAVITREAL AFLIBERCEPT FOR CHOROIDAL NEOVASCULARIZATION DUE TO AGE-RELATED

MACULAR DEGENERATION UNRESPONSIVE TO RANIBIZUMAB THERAPY.

Sarao V, Parravano M, Veritti D, Arias L, Varano M, Lanzetta P.

PURPOSE: To assess the efficacy of intravitreal injection of aflibercept for treating choroidal neovascularization due to age-related macular degeneration unresponsive to ranibizumab.

METHODS: Prospective noncomparative study. Indication for conversion to aflibercept (2.0 mg) was a failed response to ranibizumab, defined as persistent or recurrent subretinal and/or intraretinal fluid on spectral domain optical coherence tomography. Best-corrected visual acuity (Early Treatment Diabetic Retinopathy Study letter score), fluorescein angiography, indocyanine green angiography, and spectral domain optical coherence tomography were performed at baseline. Patients were followed up monthly, and retreatment was considered at physician discretion based on functional and morphological patterns.

RESULTS: Ninety-two eyes were included in the study. At 12 months, mean best-corrected visual acuity (±SD) change was +1.8 (±10.3), Early Treatment Diabetic Retinopathy Study letters and central retinal thickness (±SD) decreased on average by 112 (±173) μm. Patients received a mean of 3.5 ± 1.8 injections. No significant adverse event was observed during the follow-up.

CONCLUSION: A low number of intravitreal aflibercept injections reversed the preswitching trend toward losing vision and produced stable visual acuity and morphological improvements for up to 12 months in patients with neovascular age-related macular degeneration, not responding to ranibizumab.

PMID: 26398691 [PubMed - as supplied by publisher]

Curr Eye Res. 2015 Sep 23:1-5. [Epub ahead of print]

Association of Apolipoprotein E Polymorphism with Intravitreal Ranibizumab Treatment Outcomes in Age-Related Macular Degeneration.

Bakbak B, Ozturk BT, Zamani AG, Gonul S, Iyit N, Gedik S, Yıldırım MS.

PURPOSE: Genetic factors are known to influence the response to anti-vascular endothelial growth factor (VEGF) treatment in exudative age-related macular degeneration (AMD). The current study was conducted to investigate the association of Apolipoprotein E (ApoE) polymorphism with the treatment response to ranibizumab for exudative AMD.

METHODS: One hundred nine eyes (109 patients, 59.6% male, mean age 63.84 ± 7.22 years) treated with intravitreal ranibizumab injections were included in the analysis. Smoking status and lesion type were recorded. Patients were categorized into three groups according to visual acuity (VA) change at 6 months after the first injection: VA loss >5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (Group 1); VA change between five ETDRS letters gain and loss (Group 2); VA improvement >5 ETDRS letters (Group 3). The association of ApoE gene polymorphisms with the three groups was evaluated.

RESULTS: Both smoking status and lesion type showed no significant association with VA change ($p = 0.12$ and $p = 0.64$, respectively). A lower frequency of ε2 and a higher frequency of ε4 were observed in Group 3 (2.9 and 25.7%, respectively). VA improvement with more than five ETDRS letters was significantly associated with the presence of the ε4 genotype ($p = 0.01$).

CONCLUSIONS: This study demonstrated that carriers of the ApoE ε4 polymorphism genotype show demonstrable improvement in VA after treatment with ranibizumab in exudative AMD. ApoE polymorphism identification may be used as a genetic screening to tailor individualized therapeutic approach for optimal treatment in neovascular AMD.

PMID: 26398858 [PubMed - as supplied by publisher]

Open Ophthalmol J. 2015 Jul 31;9:121-5. eCollection 2015.

Surgically Induced Corneal Astigmatism Following Intravitreal Ranibizumab Injection.

Kocatürk T, Erkan E, Eğrilmez S, Çakmak H, Dündar SO, Dayanir V.

PURPOSE: To evaluate surgically induced astigmatism (SIA) after an intravitreal ranibizumab (IVR) injection.

METHODS: Fifty eight eyes of 58 patients who underwent IVR injection due to age-related macular degeneration (wet form) or macular edema were included in this study. Patients' pre- and postoperative detailed ophthalmologic examinations were done and topographic keratometric values (K1, K2) were noted. Pre- and postoperative measurements were compared.

RESULTS: The mean preoperative astigmatism of 0.87 Diopters (D) was found to be 0.95 D, 0.75 D, 0.82 D and 0.78 D on the 1st day, 3rd day, 1st week and 1st month, respectively. After injection, absolute change in astigmatism was found to be 0.08 D, 0.12 D, 0.05 D and 0.09 D on the 1st day, 3rd day, 1st week and 1st month, respectively. The absolute change in astigmatism seemed to be insignificant in terms of refractive analysis, however; when we performed a vectorial analysis, which takes into account changes in the axis of astigmatism, the mean value of induced astigmatism were found to be 0.33±0.22 D, 0.32±0.29 D, 0.41±0.37 D, 0.46±0.32 D on the 1st day, 3rd day, 1st week and on 1st month, respectively.

CONCLUSION: Intravitreal injection is a minimally invasive ophthalmologic procedure, however; it may still cause statistically significant induced astigmatism when evaluated from a vectorial point of view.

PMID: 26401170 [PubMed] PMCID: PMC4578144

Clin Ophthalmol. 2015 Sep 8;9:1651-3. eCollection 2015.

Visual outcomes of age-related macular degeneration patients undergoing intravitreal ranibizumab monotherapy in an urban population: letter to the editor.

Stewart MW.

PMID: 26392745 [PubMed] PMCID: PMC4574815

Acta Ophthalmol. 2015 Sep 24. [Epub ahead of print]

Aflibercept anti-vascular endothelial growth factor therapy in vitrectomized eyes with neovascular age-related macular degeneration.

Jung JJ, Hoang QV, Arain MZ, Chang S.

PMID: 26401896 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2015 Sep 21. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY VERSUS TRADITIONAL MULTIMODAL IMAGING IN ASSESSING THE ACTIVITY OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION: A New Diagnostic Challenge.

Coscas GJ, Lupidi M, Coscas F, Cagini C, Souied EH.

PURPOSE: To compare optical coherence tomography angiography (OCTA) with traditional multimodal imaging in patients with exudative age-related macular degeneration in terms of guiding the treatment decision.

METHODS: Prospective case series of 80 eyes of 73 consecutive patients with exudative age-related macular degeneration (39 women, mean age: 79.4 ± 5.3 years) diagnosed with different types of choroidal neovascularization (CNV) (58 Type I, 2 Type II, 6 mixed Type I and II, 3 retinal angiomatous proliferation, and 11 age-related macular degeneration-related polyps). The data obtained from traditional multimodal imaging, based on fluorescein angiography, indocyanine green angiography, and OCT were used to assess the need for treatment, those obtained from OCTA to identify two different patterns of CNV. Traditional multimodal imaging and OCTA findings were then compared with evaluate possible correspondence between treatment decision and CNV aspect on OCTA.

RESULTS: A CNV lesion was identified as Group A (requiring treatment) in 58 eyes (72.5%) in traditional multimodal imaging. On OCTA in 59 eyes (73.7%), the lesion was defined as Pattern I and the remaining 21 (26.3%) as Pattern II. There was 94.9% correspondence between the Pattern I CNV on OCTA and the cases Group A on conventional multimodal imaging. It was also computed 90.5% correspondence between Pattern II CNV on OCTA and the Group B (not requiring treatment) cases on conventional multimodal imaging. There was high ($P < 0.05$) interobserver agreement both for treatment decision in conventional multimodal and for Patterns (I or II) defining on OCTA imaging analysis.

CONCLUSION: This study demonstrates a high level of correspondence, in patients with exudative age-related macular degeneration, between different CNV patterns identified on OCTA and treatment decisions established on conventional multimodal imaging. Although fluorescein angiography remains the gold standard for determining the presence of leakage, and OCT shows fluid accumulation and its variations, OCTA may now offer noninvasive monitoring of the CNV, aiding for each treatment decision during the follow-up.

PMID: 26398697 [PubMed - as supplied by publisher]

J Funct Biomater. 2015 Sep 16;6(3):946-62.

Incorporation of Human Recombinant Tropoelastin into Silk Fibroin Membranes with the View to Repairing Bruch's Membrane.

Shadforth AM, Suzuki S, Alzonne R, Edwards GA, Richardson NA, Chirila TV1, Harkin DG.

Abstract: Bombyx mori silk fibroin membranes provide a potential delivery vehicle for both cells and extracellular matrix (ECM) components into diseased or injured tissues. We have previously demonstrated the feasibility of growing retinal pigment epithelial cells (RPE) on fibroin membranes with the view to repairing the retina of patients afflicted with age-related macular degeneration (AMD). The goal of the present study was to investigate the feasibility of incorporating the ECM component elastin, in the form of human recombinant tropoelastin, into these same membranes. Two basic strategies were explored: (1) membranes prepared from blended solutions of fibroin and tropoelastin; and (2) layered constructs prepared from sequentially cast solutions of fibroin, tropoelastin, and fibroin. Optimal conditions for RPE attachment were achieved using a tropoelastin-fibroin blend ratio of 10 to 90 parts by weight. Retention of tropoelastin within the blend and layered constructs was confirmed by immunolabelling and Fourier-transform infrared spectroscopy (FTIR). In the layered constructs, the bulk of tropoelastin was apparently absorbed into the initially cast fibroin layer. Blend membranes displayed higher elastic modulus, percentage elongation, and tensile strength ($p < 0.01$) when compared to the layered constructs. RPE cell response to fibroin membranes was not affected by the presence of tropoelastin. These findings support the potential use of fibroin membranes for the co-delivery of RPE cells and tropoelastin.

PMID: 26389960 [PubMed]

Ophthalmologica. 2015 Sep 23. [Epub ahead of print]

Long-Term Follow-Up of Fundus Autofluorescence Imaging Using Wide-Field Scanning Laser Ophthalmoscopy.

Duisdieker V, Fleckenstein M, Zilkens KM, Steinberg JS, Holz FG, Schmitz-Valckenberg S.

AIM: To evaluate the variation of peripheral alterations in different retinal diseases over a period of >3 years by using wide-field fundus autofluorescence (FAF) scanning laser ophthalmoscopy (SLO).

METHODS: A total of 26 eyes from 13 patients (median age 66 years, range 19-80) with age-related macular degeneration and other retinal degenerations were examined. In 2009, the Optos P200CAF prototype and from 2012 onwards, the Optos 200Tx (Optos plc, Scotland) were used for wide-field FAF SLO (excitation 532 nm).

RESULTS: The area involvement in outer retinal pathological alterations, such as atrophy and mottling of the retinal pigment epithelium far beyond the vascular arcades, was readily and better visualized within one image frame using wide-field FAF as compared to pseudocolor SLO of the same device. Over time, progression of existing and the development of de novo peripheral lesions were recorded with a concomitant enlargement of central lesions. In two cases (unilateral paravenous pigmented choroidal atrophy and suspected phenocopy of retinal dystrophy), no longitudinal changes of the topographic distribution of peripheral FAF intensities were noted.

CONCLUSIONS: Wide-field FAF SLO allows the mapping of dynamic changes at the outer retina far beyond the vascular arcades. While its ability to detect and monitor these changes appears to be better than that of pseudocolor imaging, wide-field FAF SLO may not only be helpful to assess more widespread retinal dysfunction, but may also be useful for longitudinal assessments in natural history studies and interventional clinical trials.

PMID: 26394020 [PubMed - as supplied by publisher]

Lasers Med Sci. 2015 Sep 24. [Epub ahead of print]

Effects of low-level laser irradiation on proliferation and functional protein expression in human RPE cells.

Dang Y, Wu W, Xu Y, Mu Y, Xu K, Wu H, Zhu Y, Zhang C.

Abstract: Low-level laser irradiation (LLLI) modulates a set of biological effects in many cell types such as fibroblasts, keratinocytes, and stem cells. However, no study to date has reported the effects of LLLI on retinal pigment epithelia (RPE) cells. The aim of this study was to investigate whether LLLI could enhance the proliferation of RPE cells and increase the expression of RPE functional genes/proteins. Human ARPE-19 cells were seeded overnight and treated with 8 J/cm2 of LLLI. Cell proliferation was measured by CCK8 assay and cell cycle distribution was evaluated by FACS. The transcription of cell cycle-specific genes and RPE functional genes was quantified by RT-PCR. Moreover, the expression of ZO-1 and CRALBP were evaluated by immunostaining. A dose of 8 J/cm2 of LLLI significantly increased proliferation and promoted cell cycle progression while upregulating the transcription of CDK4 and CCND1 and decreasing the transcription of CDKN2A, CDKN2C, and CDKN1B in human ARPE-19 cells. Additionally, LLLI enhanced the expression of ZO-1 and CRALBP in human ARPE-19 cells. In conclusion, LLLI could enhance the proliferative ability of human ARPE-19 cells by modulating cyclin D1, CDK4, and a group of cyclin-dependent kinase inhibitors. It also could increase the expression of RPE-specific proteins. Thus, LLLI may be a potential approach for the treatment of RPE degenerative diseases.

PMID: 26404781 [PubMed - as supplied by publisher]

Pathogenesis

Adv Gerontol. 2015;28(1):42-7.

[IS AGE-RELATED MACULAR DEGENERATION A MANIFESTATION OF ALZHEIMER'S DISEASE?]. [Article in Russian]

Nesterova AA, Ermilov VV.

The review conducts clinical morphological and pathogenetic parallels between Alzheimer's disease and

age-related macular degeneration. The common embryology, anatomy and physiology of the brain and eye create the preconditions for the emergence of the friendly processes, including pathological aggregation of β-amyloid and neurodegeneration. Based upon the data the authors justify the need for a thorough ophthalmic status study in the daily practice of an ophthalmologist. According to the authors this is promising for the early diagnosis and monitoring of Alzheimer's disease.

PMID: 26390609 [PubMed - in process]

J Biol Chem. 2015 Sep 22. [Epub ahead of print]

Correlations between photodegradation of bisretinoid constituents of retina and dicarbonyl-adduct deposition.

Zhou J, Ueda K, Zhao J, Sparrow JR.

Abstract: Non-enzymatic collagen cross-linking and carbonyl-adduct deposition are features of Bruch's membrane aging in the eye and disturbances in extracellular matrix turnover are considered to contribute to Bruch's membrane thickening. Since bisretinoid constitutents of the lipofuscin of retinal pigment epithelial cells (RPE) are known to photodegrade to mixtures of aldehyde-bearing fragments and small dicarbonyls (glyoxal, GO and methylglyoxal, MG) we investigated RPE lipofuscin as a source of the reactive species that covalently modify protein side-chains. Abca4-/- and Rdh8-/-/Abca4-/- mice that are models of accelerated bisretinoid formation were studied and pre-exposure of mice to 430 nm light enriched for dicarbonyl release by bisretinoid photodegradation. MG protein adducts were elevated in posterior eyecups of mutant mice while carbonylation of an RPE specific protein was observed in Abca4-/- but not in wild-type mice under the same conditions. Immunolabeling of cryostat sectioned eyes harvested from Abca4-/- mice revealed that carbonyl adduct deposition in Bruch's membrane was accentuated. Cell-based assays corroborated these findings in mice. Moreover, receptor for advanced glycation end-products (RAGE) that recognizes MG and GO adducts and glyoxylase 1 that metabolizes MG and GO, were upregulated in Abca4-/- mice. Additionally, in acellular assays, peptides were cross-linked in the presence of A2E photodegradation products and in a zymography assay, reaction of collagen IV with products of A2E photodegradation resulted in reduced cleavage by the matrix metalloproteinases MMP2 and MMP9. In conclusion, these mechanistic studies demonstrate a link between the photodegradation of RPE bisretinoid fluorophores and aging changes in underlying Bruch's membrane that can confer risk of age-related macular degeneration.

PMID: 26400086 [PubMed - as supplied by publisher]

Dis Model Mech. 2015 Sep 22. pii: dmm.021998. [Epub ahead of print]

Polarization of the epithelial layer and apical localization of integrins are required for engulfment of apoptotic cells.

Meehan TL, Kleinsorge SE, Timmons AK, Taylor JD, McCall K.

Abstract: Inefficient clearance of dead cells or debris by epithelial cells can lead to or exacerbate debilitating conditions such as retinitis pigmentosa, macular degeneration, chronic obstructive pulmonary disease, and asthma. Despite the importance of engulfment by epithelial cells, little is known about the molecular changes that are required within these cells. The misregulation of integrins has previously been associated with disease states, suggesting that a better understanding of the regulation of receptor trafficking may be key to treating diseases caused by defects in phagocytosis. Here, we demonstrate that the integrin heterodimer αPS3/βPS becomes apically enriched and is required for engulfment by the epithelial follicle cells of the Drosophila ovary. We found that integrin heterodimer localization and function is largely directed by the α subunit. Moreover, proper cell polarity promotes asymmetric integrin enrichment, suggesting that αPS3/βPS trafficking occurs in a polarized fashion. We show that several genes previously known for their roles in trafficking and cell migration are also required for engulfment. Moreover, as in mammals, the same α integrin subunit is required by professional and non-professional phagocytes and migrating cells in Drosophila. Our findings suggest that migrating and engulfing cells may use common

machinery and demonstrate a critical role for integrin function and polarized trafficking of integrin subunits during engulfment. This study also establishes the epithelial follicle cells of the Drosophila ovary as a powerful model for understanding the molecular changes required for engulfment by a polarized epithelium.

PMID: 26398951 [PubMed - as supplied by publisher]

Curr Eye Res. 2015 Sep 23:1-6. [Epub ahead of print]

Toll-Like Receptors 2 and 4 Polymorphisms in Age-Related Macular Degeneration.

Güven M, Batar B, Mutlu T, Bostancı M, Mete M, Aras C, Ünal M.

PURPOSE: Age-related macular degeneration (AMD) is a complex disorder with multifactorial etiology, caused by a combination of genetic and environmental factors. Innate immunity appears to play a key role in the pathogenesis of AMD. The purpose of this study was to determine whether common variation in the human toll-like receptors (TLRs) 2 and 4 alters the risk of AMD.

PATIENTS AND METHODS: A total of 183 patients with AMD and 200 disease-free control subjects were enrolled. The genotyping of polymorphisms TLR2 (TLR2-Arg753Gln: rs5743708) and TLR4 (TLR4-Asp299Gly: rs4986790; TLR4-Thr399Ile: rs4986791) were done using real-time PCR.

RESULTS: TLR2 Arg753Gln genotype had approximately four times greater risk of AMD compared with TLR2 Arg753Arg genotype (OR = 3.88; 95% CI: 1.76-8.75, p = 0.001). TLR2 Arg753Gln genotype was significantly higher in the patients with dry-type AMD (16%) and wet-type AMD (18%) than in the control (5%) subjects (p = 0.005 and p = 0.0008, respectively). There were no significant differences in the distribution of TLR4-Asp299Gly and TLR4-Thr399Ile genotypes between AMD patients and controls (p > 0.05).

CONCLUSION: Our results suggest that TLR2 polymorphism may contribute to the pathogenesis of AMD.

PMID: 26398587 [PubMed - as supplied by publisher]

Int J Mol Sci. 2015 Sep 3;16(9):21087-21108.

Exploring the Molecular Interactions of 7,8-Dihydroxyflavone and Its Derivatives with TrkB and VEGFR2 Proteins.

Chitranshi N, Gupta V, Kumar S, Graham SL.

Abstract: 7,8-dihydroxyflavone (7,8-DHF) is a TrkB receptor agonist, and treatment with this flavonoid derivative brings about an enhanced TrkB phosphorylation and promotes downstream cellular signalling. Flavonoids are also known to exert an inhibitory effect on the vascular endothelial growth factor receptor (VEGFR) family of tyrosine kinase receptors. VEGFR2 is one of the important receptors involved in the regulation of vasculogenesis and angiogenesis and has also been implicated to exhibit various neuroprotective roles. Its upregulation and uncontrolled activity is associated with a range of pathological conditions such as age-related macular degeneration and various proliferative disorders. In this study, we investigated molecular interactions of 7,8-DHF and its derivatives with both the TrkB receptor as well as VEGFR2. Using a combination of molecular docking and computational mapping tools involving molecular dynamics approaches we have elucidated additional residues and binding energies involved in 7,8-DHF interactions with the TrkB Ig2 domain and VEGFR2. Our investigations have revealed for the first time that 7,8-DHF has dual biochemical action and its treatment may have divergent effects on the TrkB via its extracellular Ig2 domain and on the VEGFR2 receptor through the intracellular kinase domain. Contrary to its agonistic effects on the TrkB receptor, 7,8-DHF was found to downregulate VEGFR2 phosphorylation both in 661W photoreceptor cells and in retinal tissue.

PMID: 26404256 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmic Epidemiol. 2015 Oct;22(5):308-20.

Neighborhood Deprivation and Risk of Age-Related Eye Diseases: A Follow-up Study in Sweden.

Hamano T, Li X, Tanito M, Nabika T, Shiwaku K, Sundquist J, Sundquist K.

PURPOSE: To examine whether there is an association between neighborhood deprivation and age-related eye diseases, particularly macular degeneration, cataract, diabetes-related eye complications, and glaucoma.

METHODS: The study population comprised a nationwide sample of 2,060,887 men and 2,250,851 women aged 40 years or older living in Sweden who were followed from 1 January 2000 until the first hospitalization/outpatient registration for age-related eye disease during the study period, death, emigration, or the end of the study period on 31 December 2010. Multilevel logistic regression was used to estimate the association between neighborhood deprivation and age-related eye diseases.

RESULTS: In men, the odds ratio (OR) for age-related eye diseases for those living in high-deprivation neighborhoods compared to those living in low-deprivation neighborhoods remained significant after adjustment for potential confounding factors (macular degeneration, OR 1.08, 95% confidence interval [CI] 1.03-1.12; cataract, OR 1.31, 95% CI 1.26-1.35; diabetes-related eye complications, OR 1.36, 95% CI 1.30-1.43; glaucoma, OR 1.11, 95% CI 1.06-1.15). In women, similar patterns were observed (macular degeneration, OR 1.11, 95% CI 1.07-1.15; cataract, OR 1.36, 95% CI 1.31-1.40; diabetes-related eye complications, OR 1.50, 95% CI 1.42-1.59; glaucoma, OR 1.12, 95% CI 1.08-1.17).

CONCLUSION: Our results suggest that neighborhood deprivation is associated with age-related eye diseases in both men and women. These results implicate that individual- as well as neighborhood-level factors are important for preventing age-related eye diseases.

PMID: 26395658 [PubMed - in process]

Ophthalmologica. 2015 Sep 23. [Epub ahead of print]

Characteristics of Neovascular Age-Related Macular Degeneration in Brazilian Patients.

Pereira FB, Veloso CE, Kokame GT, Nehemy MB.

PURPOSE: To report features of neovascular age-related macular degeneration (AMD) in Brazilian patients.

PROCEDURES: Data were prospectively collected from patients diagnosed with neovascular AMD. Eyes were classified as having typical neovascular AMD, polypoidal choroidal vasculopathy (PCV), or retinal angiomatous proliferation (RAP).

RESULTS: In total, 265 eyes of 207 patients of predominantly Caucasian ancestry were included; 166 (62.6%) eyes had typical neovascular AMD, 65 (24.5%) eyes had PCV, and 34 (12.8%) eyes had RAP. RAP demonstrated a higher percentage of bilateral cases ($p = 0.015$). The mean foveal subfield thickness was significantly lower in eyes with PCV ($p < 0.001$). Cases with typical neovascular AMD had a higher percentage of predominantly classic and minimally classic lesions on fluorescein angiography (FA; $p = 0.005$).

CONCLUSIONS: In Brazilian patients, PCV and RAP represented 24.5 and 12.8% of neovascular AMD cases. Neovascular AMD subtypes differ in relation to clinical features, mean foveal subfield thickness and FA presentation.

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PLoS One. 2015 Sep 21;10(9):e0138701. eCollection 2015.

Optic Disc - Fovea Distance, Axial Length and Parapapillary Zones. The Beijing Eye Study 2011.

Jonas RA, Wang YX, Yang H, Li JJ, Xu L, Panda-Jonas S, Jonas JB.

PURPOSE: To measure the distance between the optic disc center and the fovea (DFD) and to assess its associations.

METHODS: The population-based cross-sectional Beijing Eye Study 2011 included 3468 individuals aged 50+ years. The DFD was measured on fundus photographs.

RESULTS: Readable fundus photographs were available for 2836 (81.8%) individuals. Mean DFD was 4.76 ± 0.34mm (median: 4.74 mm; range: 3.76-6.53mm). In multivariate analysis, longer DFD was associated with longer axial length (P<0.001; standardized correlation coefficient beta: 0.62), higher prevalence of axially high myopia (P<0.001; beta:0.06), shallower anterior chamber depth (P<0.001; beta:-0.18), thinner lens thickness (P = 0.004; beta: -0.06), smaller optic disc-fovea angle (P = 0.02; beta: -0.04), larger parapapillary alpha zone (P = 0.008; beta: 0.05), larger parapapillary beta/gamma zone (P<0.001; beta: 0.11), larger optic disc area (P<0.001; beta: 0.08), lower degree of cortical cataract (P = 0.002; beta: -0.08), and lower prevalence of age-related macular degeneration (P = 0.001; beta: -0.06). Bruch´s membrane opening-fovea distance (DFD minus disc radius minus parapapillary beta/gamma zone width) in non-glaucomatous eyes was not significantly (P = 0.60) related with axial length in emmetropic or axially myopic eyes (axial length ≥23.5 mm), while it increased significantly (P<0.001; r: 0.32) with longer axial length in eyes with an axial length of <23.5mm. Ratio of mean DFD to disc diameter was 2.65 ± 0.30. If the ratio of disc-fovea distance to disc diameter was considered constant and if the individual disc diameter was calculated as the individual disc-fovea distance divided by the constant factor of 2.65, the resulting calculated disc diameter differed from the directly measured disc diameter by 0.16 ±0.13 mm (median: 0.13 mm, range: 0.00-0.89 mm) or 8.9 ± 7.3% (median: 7.4%; range: 0.00-70%) of the measured disc diameter.

CONCLUSIONS: DFD (mean: 4.76mm) increases with longer axial length, larger parapapillary alpha zone and parapapillary beta/gamma zone, and larger disc area. The axial elongation associated increase in DFD was due to an enlargement of parapapillary beta/gamma zone while the Bruch's membrane opening-fovea distance did not enlarge with longer axial length. This finding may be of interest for the process of emmetropization and myopization. Due to its variability, the disc-fovea distance has only limited clinical value as a relative size unit for structures at the posterior pole.

PMID: 26390438 [PubMed - in process] PMCID: PMC4577126

Genetics

Mol Ther. 2015 Sep 21. [Epub ahead of print]

BEST1: the best target for gene and cell therapies.

Yang T, Justus S, Li Y, Tsang SH.

Abstract: A retinal pigmented epithelial (RPE) disorder, bestrophinopathy has recently been proven to be amenable to gene and cell-based therapies in preclinical models. RPE disorders and allied retinal degenerations exhibit significant genetic heterogeneity, and diverse mutations can result in similar disease phenotypes. Several RPE disorders have recently become targets for gene therapies in humans. The year 2011 brought a new advance in cell-based therapies, with the FDA approving clinical trials using embryonic stem cells for an RPE disorder known as age-related macular degeneration. Recent studies on induced pluripotent stem (iPS)-RPE generation indicate strong potential for developing patient-specific disease models in vitro, which could eventually enable personalized treatment. This mini-review will briefly highlight the suitability of the retina for gene and cell therapies, the pathophysiology of bestrophinopathy, and the research and treatment opportunities afforded by stem cell and genetic therapies.Molecular Therapy (2015); doi:10.1038/mt.2015.177.

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Annu Rev Genet. 2015 Sep 25. [Epub ahead of print]

From Genomics to Gene Therapy: Induced Pluripotent Stem Cells Meet Genome Editing.

Hotta A, Yamanaka S.

Abstract: The advent of induced pluripotent stem (iPS) cells has opened up numerous avenues of opportunity for cell therapy, including the initiation in September 2014 of the first human clinical trial to treat dry age-related macular degeneration. In parallel, advances in genome-editing technologies by site-specific nucleases have dramatically improved our ability to edit endogenous genomic sequences at targeted sites of interest. In fact, clinical trials have already begun to implement this technology to control HIV infection. Genome editing in iPS cells is a powerful tool and enables researchers to investigate the intricacies of the human genome in a dish. In the near future, the groundwork laid by such an approach may expand the possibilities of gene therapy for treating congenital disorders. In this review, we summarize the exciting progress being made in the utilization of genomic editing technologies in pluripotent stem cells and discuss remaining challenges toward gene therapy applications. Expected final online publication date for the Annual Review of Genetics Volume 49 is November 23, 2015. Please see http://www.annualreviews.org/catalog/pubdates.aspx for revised estimates.

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Diet, lifestyle & low vision

J Clin Med. 2015 Sep 22;4(9):1841-52.

Quality of Life with Macular Degeneration Is Not as Dark as It May Seem: Patients' Perceptions of the MacDQoL Questionnaire.

Ord LM, Wright J, DeAngelis MM, Feehan M.

Abstract: To determine the perceived relevance and value of an individualized measure of the impact of macular degeneration on quality of life (QoL) for elderly people with Age-Related Macular Degeneration (AMD) in the USA, through the assessment of the suitability of the measure's domains and by gaining a deeper insight into the impact of AMD on patients' QoL vis-á-vis these domains, community-dwelling older adults in the metropolitan Salt Lake City, Utah area were interviewed using the macular degeneration on quality of life (MacDQoL) instrument. Participants felt that the MacDQoL was a relevant instrument for use in this US study population, though it could be improved by adding items pertaining to transportation, and independent driving, in particular, as an important QoL indicator. The emerging theme from analysis of the respondent's commentary was that, in spite of AMD, these respondents were committed to engage in, and enjoy life. This is an important concept for clinicians and those who offer support programs to integrate into their care planning and reinforce in messaging to patients with the condition.

PMID: 26402711 [PubMed]

Optom Vis Sci. 2015 Oct;92(10):986-94.

Categorization Task over a Touch Screen in Age-Related Macular Degeneration.

Lenoble Q, Tran TH, Szaffarczyk S, Boucart M.

PURPOSE: In our modern society, many touch screen applications require hand-eye coordination to associate an icon with its specific contextual unit on phones, on computers, or in public transport. We assessed the ability of patients with age-related macular degeneration (AMD) to explore scenes and to associate a target (animal or object) with a unique congruent scene (e.g., to match a fish with the sea) presented between three other distractors on a touch screen computer.

METHODS: Twenty-four patients with AMD (64 to 90 years) with best-corrected visual acuity between

20/40 and 20/400 as well as 17 age-matched (60 to 94 years) and 15 young (22 to 34 years) participants with normal visual acuity had to match a target with a congruent scene by moving their index finger on a 22-in touch screen.

RESULTS: Patients were as accurate (98.7% correct responses) as the age-matched control (98.9% correct responses) and young participants (99.3% correct responses) at performing the task. The duration of exploration was significantly longer for the AMD patients (mean, 4.13 seconds) compared with the age-matched group (mean, 2.96 seconds). The young participants were also significantly faster than the old group (mean, 0.93 seconds). The movement parameters of the older participants (patients and old control subjects) were affected compared with the young; the peak speed decreased (-8 cm/s) and the movement duration increased (+0.9 seconds) with age compared with the young group.

CONCLUSIONS: People with AMD are able to perform a contextual association task on a touch screen with high accuracy. The AMD patients were specifically affected in the "exploration" phase; their accuracy and movement parameters did not differ from the old control group. Our study suggests that the decline associated with AMD is more focused on the duration of exploration than on movement parameters in touch screen use.

PMID: 26398350 [PubMed - in process]

J Alzheimers Dis. 2015 Aug 28;48(1):261-77.

Cognitive Function and Its Relationship with Macular Pigment Optical Density and Serum Concentrations of its Constituent Carotenoids.

Kelly D, Coen RF, Akuffo KO, Beatty S, Dennison J, Moran R, Stack J, Howard AN, Mulcahy R, Nolan JM.

BACKGROUND: Macular pigment (MP) levels correlate with brain concentrations of lutein (L) and zeaxanthin (Z), and have also been shown to correlate with cognitive performance in the young and elderly.

OBJECTIVE: To investigate the relationship between MP, serum concentrations of L and Z, and cognitive function in subjects free of retinal disease with low MP (Group 1, n=105) and in subjects with AMD (Group 2, n=121).

METHODS: MP was measured using customized heterochromatic flicker photometry and dual-wavelength autofluorescence; cognitive function was assessed using a battery of validated cognition tests; serum L and Z concentrations were determined by HPLC.

RESULTS: Significant correlations were evident between MP and various measures of cognitive function in both groups (r=-0.273 to 0.261, p≤0.05, for all). Both serum L and Z concentrations correlated significantly (r=0.187, p≤0.05 and r=0.197, p≤0.05, respectively) with semantic (animal) fluency cognitive scores in Group 2 (the AMD study group), while serum L concentrations also correlated significantly with Verbal Recognition Memory learning slope scores in the AMD study group (r=0.200, p=0.031). Most of the correlations with MP, but not serum L or Z, remained significant after controlling for age, gender, diet, and education level.

CONCLUSION: MP offers potential as a non-invasive clinical biomarker of cognitive health, and appears more successful in this role than serum concentrations of L or Z.

PMID: 26401946 [PubMed - in process]

Int J Mol Sci. 2015 Sep 2;16(9):21008-21020.

Treadmill Exercise Attenuates Retinal Oxidative Stress in Naturally-Aged Mice: An Immunohistochemical Study.

Kim CS, Park S, Chun Y, Song W, Kim HJ, Kim J.

Abstract: In the retina, a number of degenerative diseases, including glaucoma, diabetic retinopathy, and age-related macular degeneration, may occur as a result of aging. Oxidative damage is believed to contribute to the pathogenesis of aging as well as to age-related retinal disease. Although physiological exercise has been shown to reduce oxidative stress in rats and mice, it is not known whether it has a similar effect in retinal tissues. The aim of this study was to evaluate retinal oxidative stress in naturally-aged mice. In addition, we evaluated the effects of aerobic training on retinal oxidative stress by immunohistochemically evaluating oxidative stress markers. A group of twelve-week-old male mice were not exercised (young control). Two groups of twenty-two-month-old male mice were created: an old control group and a treadmill exercise group. The old control group mice were not exercised. The treadmill exercise group mice ran on a treadmill (5 to 12 m/min, 30 to 60 min/day, 3 days/week for 12 weeks). The retinal thickness and number of cells in the ganglion cell layer of the naturally-aged mice were reduced compared to those in the young control mice. However, treadmill exercise reversed these morphological changes in the retinas. We evaluated retinal expression of carboxymethyllysine (CML), 8-hydroxy-2'-deoxyguanosine (8-OHdG) and nitrotyrosine. The retinas from the aged mice showed increased CML, 8-OHdG, and nitrotyrosine immunostaining intensities compared to young control mice. The exercise group exhibited significantly lower CML levels and nitro-oxidative stress than the old control group. These results suggest that regular exercise can reduce retinal oxidative stress and that physiological exercise may be distinctly advantageous in reducing retinal oxidative stress.

PMID: 26404251 [PubMed - as supplied by publisher]

Ophthalmology. 2015 Oct;122(10):e62-3.

Re: Chew et al.: Genetic testing in persons with age-related macular degeneration and the use of AREDS supplements: to test or not to test? (Ophthalmology 2015;122:212-5).

Awh CC, Zanke B.

PMID: 26398061 [PubMed - in process]

Ophthalmology. 2015 Oct;122(10):e60-1. doi: 10.1016/j.ophtha.2015.01.031.

Re: Chew et al.: Genetic testing in persons with age-related macular degeneration and the use of the AREDS supplements: to test or not to test? (Ophthalmology 2015;122:212-5).

Pearlman J.

PMID: 26398058 [PubMed - in process]