Drug treatment

Retina. 2017 Nov 10. [Epub ahead of print]

PANRETINAL PHOTOCOAGULATION VERSUS RANIBIZUMAB FOR PROLIFERATIVE DIABETIC RETINOPATHY: COMPARISON OF PERIPAPILLARY RETINAL NERVE FIBER LAYER THICKNESS IN A RANDOMIZED CLINICAL TRIAL.


PURPOSE: Compare changes in retinal nerve fiber layer (RNFL) thickness between eyes assigned to intravitreous ranibizumab or panretinal photocoagulation and assess correlations between changes in RNFL and visual field sensitivity and central subfield thickness.

METHODS: Eyes with proliferative diabetic retinopathy were randomly assigned to ranibizumab or panretinal photocoagulation. Baseline and annual follow-up spectral domain optical coherence tomography RNFL imaging, optical coherence tomography macular imaging, and automated static perimetry (Humphrey visual field 60-4 algorithm) were performed.

RESULTS: One hundred forty-six eyes from 120 participants were analyzed. At 2 years, for the ranibizumab (N = 74) and panretinal photocoagulation (N = 66) groups, respectively, mean change in average RNFL thickness was -10.9 ± 11.7 μm and -4.3 ± 11.6 μm (difference, -4.9 μm; 95% confidence interval [-7.2 μm to -2.6 μm]; P < 0.001); the correlation between change in RNFL thickness and 60-4 Humphrey visual field mean deviation was -0.27 (P = 0.07) and +0.33 (P = 0.035); the correlation between change in RNFL thickness and central subfield thickness was +0.63 (P < 0.001) and +0.34 (P = 0.005), respectively.

CONCLUSION: At 2 years, eyes treated with ranibizumab had greater RNFL thinning than eyes treated with panretinal photocoagulation. Correlations between changes in RNFL thickness, visual field, and central subfield thickness suggest that the decrease in RNFL thickness with ranibizumab is likely due to decreased edema rather than loss of axons.

PMID: 29135802

Ophthalmologe. 2017 Nov 14. [Epub ahead of print]

[Reasons for delayed and discontinued therapy in age-related macular degeneration]. [Article in German]

Wintergerst MWM, Bouws J, Loss J, Heimes B, Pauleikhoff D, Holz FG, Finger RP.
BACKGROUND: Critical prerequisites for successful therapy of neovascular age-related macular degeneration (nvAMD) are an early initiation and continuous monitoring; however, delays in starting therapy and non-medically indicated discontinuation of therapy are frequent, which limits therapy efficacy and, thus, visual outcomes.

OBJECTIVE: To identify the reasons for delay in therapy and non-medically indicated termination of therapy.

MATERIAL AND METHODS: Patients who had started a new therapy (starters) and those who independently terminated therapy (dropouts) were interviewed by telephone with a specific, standardized questionnaire. Results were summarized descriptively.

RESULTS: A total of 100 starters and 55 dropouts were interviewed. The mean therapy delay was 22 (±28 SD) days. This was mainly due to the time until the decision to see an ophthalmologist was made. Main reasons for dropping out were: transportation issues (27%), poor general health (25%) and the assumption that there is no benefit from therapy (11%). Of the patients who dropped out 63% would have liked to continue therapy.

CONCLUSION: There is potential for improvement in nvAMD management regarding therapy start as well as therapy maintenance. Sensitizing for initial nvAMD symptoms is important as is reduction of barriers to therapy maintenance, since most therapy dropouts would like to continue the therapy.

PMID: 29138977


The VEGF paradox: Does diabetic retinopathy protect from age related macular degeneration?

Saravia M, Zeman L, Ingolotti M, Schlaen A.

Abstract: Age-related macular disease (AMD) and diabetic retinopathy (DR) are prevalent diseases. Vascular endothelial growth factor (VEGF) related retinal neovascularization is a common feature in both. Consequently, both pathologies are treated with anti-VEGF therapy. We have previously reported a lower incidence of AMD in patients with DR compared to controls. The present study hypothesizes that DR in stages in which the concentration of intravitreal VEGF is increased, might have a protective role for both the onset and development of AMD.

PMID: 29150277

Retina. 2017 Nov 17. [Epub ahead of print]

EXIT STRATEGY IN A TREAT-AND-EXTEND REGIMEN FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.


PURPOSE: To evaluate the outcome of an exit strategy in a treat-and-extend regimen for neovascular age-related macular degeneration.

METHODS: Five hundred and ninety-eight eyes of 488 patients with neovascular age-related macular degeneration receiving intravitreal anti-vascular endothelial growth factor injections according to a treat-and-extend regimen were included in this retrospective study. A treat-and-extend regimen with either interval extension by 2 weeks or shortening by 1 week was used. "Exit criteria" were defined as 3 consecutive injections 16 weeks apart with stable findings after which the patient was exited from treatment and followed up at 3 to 4 monthly intervals without therapy. Best-corrected visual acuity, central retinal thickness
at treatment initiation and termination, incidence of recurrence after treatment termination, presence of characteristics in the optical coherence tomography, duration of therapy, number and intervals of injections were analyzed.

RESULTS: Seventeen percent of all included eyes met the exit criteria. The mean number of anti-vascular endothelial growth factor injections was 23.7 ± 14.7 with a mean treatment duration of 4.5 ± 2.5 years. Twelve percent reached exit with the minimal number of injections. Thirteen percent had recurrent disease after a mean of 37 ± 16 weeks. In the subgroup with recurrent disease, rate of pigment epithelial detachment at treatment termination was significantly higher than without recurrence (77% vs. 30%, P = 0.0018) with a significant higher proportion of serous pigment epithelial detachment (31% vs. 7%, P = 0.0247).

CONCLUSION: The high percentage of patients meeting the exit criteria and the relatively low incidence of recurrences underline the usefulness of a predefined exit strategy. However, in a subgroup of patients, continuation of therapy may be advisable. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PMID: 29135888


Location of submacular hemorrhage as a predictor of visual outcome after intravitreal ranibizumab for age-related macular degeneration.

Karagiannis D, Chatziralli I, Kaprinis K, Georgalas I, Parikakis E, Mitropoulos P.

PURPOSE: To evaluate the anatomical and functional outcomes in patients with submacular hemorrhage (SMH) due to age-related macular degeneration (AMD) treated with ranibizumab, and to evaluate the potential role of the SMH location in the final outcome after treatment.

METHODS: Participants in this study were 12 treatment-naïve patients with SMH due to neovascular AMD who were treated with intravitreal ranibizumab and had at least 12 months' follow-up. All patients underwent best-corrected visual acuity measurement and optical coherence tomography at baseline and at every visit posttreatment, while fluorescein angiography was done at baseline and at the discretion of the physician thereafter.

RESULTS: Of the patients, 83.4% showed improvement or stabilization in best-corrected visual acuity after treatment at the 12-month follow-up, with a mean number of 7.3±2.9 injections. Patients with SMH surrounding the foveal area in 360° presented worse anatomical and functional outcomes compared to those with SMH adjacent to the fovea.

CONCLUSION: Intravitreal ranibizumab seems to be safe and effective, either improving or stabilizing visual acuity, in patients with SMH due to wet AMD. The location of the SMH may predict the final outcome after treatment.

PMID: 29138543 PMCID: PMC5679569


Refractive changes after intravitreal ranibizumab injections for diabetic macular oedema.

Chatziralli I, Chatzipantelis A, Dimitriou E, Mpourouki E, Theodossiadis G, Theodossiadis P.
PURPOSE: The purpose of this study was to evaluate refractive changes after intravitreal ranibizumab injections for the treatment of diabetic macular oedema.

METHODS: Participants in this retrospective study were 35 patients (35 eyes) with diabetic macular oedema, who received intravitreal ranibizumab injections. Spherical equivalent refractive power was evaluated before treatment and at least one month after the last injection where no fluid existed. Demographic characteristics, visual acuity, central retinal thickness and the number of injections were recorded and analysed.

RESULTS: The spherical equivalent refractive power did not differ significantly pre- or post-injections. Changes in visual acuity and central retinal thickness were statistically significant before and after injections.

CONCLUSIONS: Intravitreal ranibizumab injections did not seem to affect the refractive power of patients with diabetic macular oedema. Therefore, appropriate spectacle correction can be prescribed any time during ongoing treatment with ranibizumab injections.

PMID: 29134696


Real-World Vision in Age-Related Macular Degeneration Patients Treated with Single Anti-VEGF Drug Type for 1 Year in the IRIS Registry.


PURPOSE: The purpose of this study is to compare real-world visual acuity (VA) in patients with neovascular age-related macular degeneration (nAMD) treated with a single anti-vascular endothelial growth factor (VEGF) drug monotherapy for 1 year from the American Academy of Ophthalmology (AAO) Intelligent Research in Sight (iIRIS) Registry.

DESIGN: Retrospective, nonrandomized, comparative study.

PARTICIPANTS: IRIS Registry patients with nAMD who received bevacizumab, ranibizumab, or aflibercept only for 1 year between 2013-2016.

METHODS: Participants were divided into 3 groups based on monotherapy type. Multivariate analysis of covariance models (ANCOVA) was constructed in a stepwise fashion.

MAIN OUTCOME MEASURES: The logarithm of the minimum angle of resolution (logMAR) VA at 1 year and mean change in logMAR VA between baseline and 1 year were compared between drug types.

RESULTS: Of 13 859 patients, 6723 received bevacizumab, 2749 received ranibizumab, and 4387 received aflibercept only for 1 year. A total of 84 828 injections were performed. The mean number of injections (standard deviation) at 1 year was higher in the ranibizumab (6.4 ±2.4) and aflibercept groups (6.2 ±2.4) compared to bevacizumab group (5.9 ±2.4; P < 0.0001). In the age-adjusted model, both ranibizumab and aflibercept achieved better logMAR VA at 1 year compared with bevacizumab (0.50 ±0.49, 0.49 ±0.44, 0.55 ±0.57; P < 0.0001). However, this difference was not significant after multivariate adjustment (age, baseline VA, diabetes, posterior vitreous detachment, number of injections, race, insurance). There was no statistical difference in the age-adjusted or multivariate-adjusted mean logMAR VA change (standard deviation) at 1 year among treatment groups (-0.048 [0.44] bevacizumab, -0.053 [0.46] ranibizumab, -0.040 [0.39] aflibercept; P = 0.46). A higher percentage of patients achieved a ≥3-line VA improvement at 1 year in the bevacizumab group (22.7%) compared with ranibizumab (20.1%; P = 0.0093) and aflibercept (17.8%; P < 0.0001). However, after multivariate adjustment, aflibercept exhibited a greater log odds of a ≥3-line VA loss compared with bevacizumab only (1.25 log odds ratio; P < 0.0016).
CONCLUSIONS: This study suggests that all 3 drugs improve VA similarly over 1 year of monotherapy.

PMID: 29146306

Eur J Ophthalmol. 2017 Nov 4:0. [Epub ahead of print]

Sequential tissue plasminogen activator, pneumatic displacement, and anti-VEGF treatment for submacular hemorrhage.

Bardak H, Bardak Y, Erçalık Y, Erdem B, Arslan G, Timlioglu S.

PURPOSE: To report the results of our sequential intravitreal (IV) tissue plasminogen activator (tPA), pneumatic displacement (PD), and IV anti-vascular endothelial growth factor (VEGF) treatment in patients with neovascular age-related macular degeneration (nAMD)-related submacular hemorrhage (SMH).

METHODS: A total of 16 eyes of 16 patients with SMH of less than 15 days duration were included in this retrospective pilot study. The tPA was applied on the day of diagnosis, and PD was performed the following day. Patients received 3 consecutive monthly IV injections of ranibizumab starting from 15 days after PD. During the follow-ups, additional ranibizumab treatment was performed if persistent macular or recurrent subretinal or intraretinal fluid hemorrhage was observed.

RESULTS: The mean central retinal thickness was 489 ± 92 μm (311-621 μm) at the time of diagnosis, 324 ± 56 μm (209-409 μm) at the first month, 262 ± 48 μm (197-364 μm) at 3 months, 248 ± 40 μm (190-334 μm) at 6 months, and 253 ± 41 μm (192-356 μm) at the last control (p<0.01). The mean best-corrected visual acuity was 2.08 ± 0.79 logMAR (0.7-3.0 logMAR) at baseline, 1.41 ± 0.70 logMAR (0.56-2.50 logMAR) at the first month, 1.21 ± 0.66 logMAR (0.3-2.0 logMAR) at 3 months, 1.14 ± 0.77 logMAR (0.2-2.50 logMAR) at 6 months, and 1.09 ± 0.73 logMAR (0.3-2.50 logMAR) at the last follow-up (p<0.01).

CONCLUSIONS: Sequential IV tPA, PD, and IV anti-VEGF treatments for SMH in patients with nAMD is effective. However, further studies are needed to establish the best treatment algorithm for SMH in patients with nAMD.

PMID: 29148027


Risk Factors for Discontinuation of Treatment for Neovascular Age-Related Macular Degeneration.

Westborg I, Rosso A.

PURPOSE: To investigate risk factors for treatment discontinuation for neovascular age-related macular degeneration (nAMD).

METHODS: Data from the Swedish Macula Register and the Skåne Healthcare Register are reported on the treatment received by 932 nAMD patients diagnosed 2013-2015. Treatment discontinuation is defined as having a termination visit or lacking a control or treatment visit during the period of 10-14 months after the diagnostic visit. The risk of treatment discontinuation during the first year is estimated using a Poisson model and a classification tree.

RESULTS: 503 eyes (50.9%) discontinued the treatment within the first year. Patients with visual acuity below 60 ETDRS letters (20/60 Snellen) at baseline, serious comorbidities, or treated at the university hospital have a 42% (95% CI 25-61%, P < 0.001), 27% (95% CI 13-43%, P = 0.001) and 30% (95% CI 15-46%, P < 0.001) increased risk to discontinue treatment compared with similar patients. Patients on ranibizumab therapy have a 45% (95% CI 28-63%, P < 0.001) increased risk for treatment discontinuation during year 1 compared with patients on aflibercept therapy. The classification tree also shows that patients...
on ranibizumab therapy and those with low VA at baseline are at a higher risk of terminating treatment.

CONCLUSIONS: Almost half of the patients starting anti-VEGF therapy discontinue treatment during the first year. Patients with risk factors may require additional support to continue with the treatment. Aflibercept therapy could be an alternative to patients at risk of treatment discontinuation.

PMID: 29131696


Advances in Age-related Macular Degeneration Understanding and Therapy.

Miller JW, Bagheri S, Vavvas DG.

Abstract: While the development of anti-vascular endothelial growth factor (anti-VEGF) as a therapy for neovascular age-related macular degeneration (AMD) was a great success, the pathologic processes underlying dry AMD that eventually leads to photoreceptor dysfunction, death, and vision loss remain elusive to date, with a lack of effective therapies and increasing prevalence of the disease. There is an overwhelming need to improve the classification system of AMD, to increase our understanding of cell death mechanisms involved in both neovascular and non-neovascular AMD, and to develop better biomarkers and clinical endpoints to eventually be able to identify better therapeutic targets—especially early in the disease process. There is no doubt that it is a matter of time before progress will be made and better therapies will be developed for non-neovascular AMD.

PMID: 29142592 PMCID: PMC5683729


Age-related macular degeneration: using morphological predictors to modify current treatment protocols.

Ashraf M, Souka A, Adelman RA.

Abstract: To assess predictors of treatment response in neovascular age-related macular degeneration (AMD) in an attempt to develop a patient-centric treatment algorithm. We conducted a systematic search using PubMed, EMBASE and Web of Science for prognostic indicators/predictive factors with the key words: 'age related macular degeneration', 'neovascular AMD', 'choroidal neovascular membrane (CNV)', 'anti-vascular endothelial growth factor (anti-VEGF)', 'aflibercept', 'ranibizumab', 'bevacizumab', 'randomized clinical trials', 'post-hoc', 'prognostic', 'predictive', 'response' 'injection frequency, 'treat and extend (TAE), 'pro re nata (PRN)', 'bi-monthly' and 'quarterly'. We only included studies that had an adequate period of follow-up (>1 year), a single predefined treatment regimen with a predetermined re-injection criteria, an adequate number of patients, specific morphological [optical coherence tomography (OCT)] criteria that predicted final visual outcomes and injection frequency and did not include switching from one drug to the other. We were able to identify seven prospective studies and 16 retrospective studies meeting our inclusion criteria. There are several morphological and demographic prognostic indicators that can predict response to therapy in wet AMD. Smaller CNV size, subretinal fluid (SRF), retinal angiomatous proliferation (RAP) and response to therapy at 12 weeks (visual, angiographic or OCT) can all predict good visual outcomes in patients receiving anti-VEGF therapy. Patients with larger CNV, older age, pigment epithelial detachment (PED), intraretinal cysts (IRC) and vitreomacular adhesion (VMA) achieved less visual gains. Patients having VMA/VMT required more intensive treatment with increased treatment frequency. Patients with both posterior vitreous detachment (PVD) and SRF required infrequent injections. Patients with PED are prone to recurrences of fluid activity with a reduction in visual acuity (VA). A regimen that involves less intensive therapy and extended follow-up intervals (4 weekly) can be suggested for patients who show adequate visual response and have both SRF and PVD at baseline. In addition, patients with poor
prognostic indicators such as IRC, VMA, large CNV size, older age and poor response at 12 weeks should be extended very cautiously with the possibility of fixed monthly/bimonthly (every 2 months) treatments if they fail to achieve dryness. Patients with PED at baseline should receive monthly/bimonthly injections of anti-VEGF therapy or can be extended very cautiously (two weekly intervals) using a TAE protocol.

PMID: 29130626

J Fr Ophtalmol. 2017 Nov 10. [Epub ahead of print]

Relationship between visual outcomes and retinal fluid resorption in patients with diabetic macular edema treated with ranibizumab.


PURPOSE: We assessed the relationship between visual acuity (VA) recovery and a qualitative criterion - complete retinal fluid resorption (CRFR) - among patients treated with ranibizumab for diabetic macular edema (DME)

METHODS: All consecutive diabetic patients with central DME received a loading dose of 3 monthly injections of ranibizumab 0.5mg, followed by retreatments on an as-needed basis as determined by monthly follow-up. Patients were divided into 3 groups: CRFR (defined as a CRT <300μm and restoration of the foveolar pit) with BCVA≤70 letters (group 1: G1), CRFR with BCVA>70 letters (20/40) (G2), and persistent retinal fluid throughout the follow-up (G3).

RESULTS: Forty eyes were included. Mean baseline VA was 48.7 letters and no patient had VA>70 letters. Twenty-four (60%) eyes achieved CRFR: 12 (30%) in G1 and 12 (30%) in G2. In 16 patients (40%), the efficacy of the treatment was partial without CRFR (G3). At the time of the initial CRFR, VA was 57.4 letters in G1 (min-max: 30-65) and 77.5 letters in G2 (71-85). In G3, maximal VA during follow-up was 55 letters (25-70) and no patient achieved a VA >70 letters.

CONCLUSIONS: In this study, CRFR was required but not sufficient to achieve a VA>70 letters.

PMID: 29132693

J Ocul Pharmacol Ther. 2017 Nov 17. [Epub ahead of print]

Nonclinical Safety Assessment of Anti-Factor D: Key Strategies and Challenges for the Nonclinical Development of Intravitreal Biologics.

Bantseev V, Erickson R, Leipold D, Amaya C, Miller PE, Booler H, Thackaberry EA.

PURPOSE: The nonclinical toxicology program described here was designed to characterize the safety profile of anti-factor D (AFD; FCFD4514S, lampalizumab) to support intravitreal (ITV) administration in patients with geographic atrophy (GA).

METHODS: The toxicity of AFD was assessed in a single-dose and 6-month repeat-dose study in monkeys at doses up to 10 mg/eye. Toxicity was assessed by clinical ophthalmic examinations, intraocular pressure measurements, ocular photography, electroretinography, fluorescein angiography, optical coherence tomography, and anatomic pathology.

RESULTS: Systemic exposure to AFD generally increased with the increase in dose level. The increases in mean maximal concentration and area under the curve values were roughly dose proportional. No accumulation of AFD was observed following 10 doses, and drug exposures were not affected by anti-drug antibodies. AFD was locally and systemically well tolerated in monkeys following ITV doses of up to 10 mg/eye. Ocular effects associated with AFD were limited to transient, reversible, dose-related, aqueous cell
responses and injection-related, mild, vitreal cell responses. In the 6-month repeat-dose study, 2 monkeys had a nonspecific immune response to AFD that resulted in severe ocular inflammation, attributed to administration of a heterologous (humanized) protein.

CONCLUSIONS: The comprehensive toxicology program in monkeys described here was designed to evaluate the safety profile of AFD and to support multiple ITV injections in the clinic. Administration of a heterologous (humanized) protein presents a challenge, and immunogenicity in nonclinical species is not predictive of immunogenicity in humans. Taken together, the results of the nonclinical program described here support the use of AFD in patients with GA.

PMID: 29148965


Severe Gemella haemolysans endophthalmitis following ranibizumab intravitreal injection.

Salceanu SO, Levy S, Cunningham R, Frimpong-Ansah K.

Abstract: Gemella haemolysans is a commensal of the upper respiratory tract that is rarely involved in ocular pathology. We present a unique case of endophthalmitis with negative cultures and positive 16s ribosomal ribonucleic acid gene sequencing showing G. haemolysans infection after an intravitreal ranibizumab injection for wet age-related macular degeneration.

PMID: 29133669

Eye (Lond). 2017 Nov 17. [Epub ahead of print]

A novel record for patients with neovascular age-related macular degeneration: providing information and a personal treatment record.

Shah M, Haque AM, Downes SM.

PMID: 29148527

Other treatment & diagnosis

J Clin Apher. 2017 Nov 18. [Epub ahead of print]

Seeing is believing: A review of apheresis therapy in the treatment of ophthalmologic disease.

Graham BC, Pulido JS, Winters JL.

Abstract: Apheresis procedures have a role in treatment of disparate diseases involving many different organ systems. Often the disease processes where apheresis plays a role in treatment are considered "orphan diseases"-relatively rare disease processes that lack specific pharmaceutical agents or established treatment protocols. Many of these disease processes can affect the eye with devastating results for the eyesight of these patients. The unique ability of apheresis to affect disease by modifying blood plasma and modulating disease-causing agents therein renders apheresis procedures valuable tools in the treatment of certain ophthalmologic diseases. This review comprehensively evaluates the role of apheresis in the treatment of ophthalmologic diseases of the eye and surrounding orbit including age-related macular degeneration, bilateral diffuse uveal melanocytic proliferation, paraneoplastic retinopathy, atopic keratoconjunctivitis, sympathetic ophthalmasia, and endocrine-associated ophthalmopathy. Apheresis procedure parameters are provided for the apheresis practitioner based on review of the relevant literature.

PMID: 29150864

Developing prognostic biomarkers in intermediate age-related macular degeneration: their clinical use in predicting progression.

Ly A, Yapp M, Nivison-Smith L, Assaad N, Hennessy M, Kalloniatis M.

Abstract: Age-related macular degeneration is a common, complex and blinding eye disease. When early and intermediate levels of severity are detected in one or both eyes, there is a wide-ranging 0.4 to 53 per cent risk of progression to advanced disease in five years. In order to maximise visual outcomes for their patients, practising eye-care professionals must be able to stratify patients according to their risk of progression, intervene (for example by recommending smoking cessation or nutritional supplements and Amsler grid self-monitoring in intermediate disease) and monitor accordingly. With the aid of ocular imaging, a range of under-recognised yet meaningful risk factors have been identified. The purpose of this review is to assist the eye-care practitioner in stratifying the risk of progression in intermediate age-related macular degeneration using the range of established and emerging precursory signs that herald loss of vision.

PMID: 29136680

J Ocul Pharmacol Ther. 2017 Nov 17. [Epub ahead of print]

Morphologic Criteria of Lesion Activity in Neovascular Age-Related Macular Degeneration: A Consensus Article.


Abstract: Intravitreal antivascular endothelial growth factor drugs represent the current standard of care for neovascular age-related macular degeneration (nAMD). Individualized treatment regimens aim at obtaining the same visual benefits of monthly injections with a reduced number of injections and follow-up visits, and, consequently, of treatment burden. The target of these strategies is to timely recognize lesion recurrence, even before visual deterioration. Early detection of lesion activity is critical to ensure that clinical outcomes are not compromised by inappropriate delays in treatment, but questions remain on how to effectively monitor the choroidal neovascularization (CNV) activity. To assess the persistence/recurrence of lesion activity in patients undergoing treatment for nAMD, an expert panel developed a decision algorithm based on the morphological features of CNV. After evaluating all current retinal imaging techniques, the panel identified optical coherent tomography as the most reliable tool to ascertain lesion activity when funduscopy is not obvious.

PMID: 29148864


[Visual Analysis of Retinal OCT Data]. [Article in German]

Röhlig M, Jünemann A, Fischer DC, Prakasam RK, Stachs O, Schumann H.

Abstract: Optical coherence tomography (OCT) enables noninvasive high-resolution 3D imaging of the human retina, and thus plays a fundamental role in ophthalmology. Via OCT examination, even subtle retinal changes can be captured, which occur in very early stages of different diseases (e.g., glaucoma, diabetes mellitus, or age-related macular degeneration). Yet, analyzing the resulting data is challenging. Conventionally, OCT data are strongly aggregated via automated methods. While this reduces the amount of information to be analyzed, it also makes it difficult, if not impossible, to identify small and localized retinal changes. This might lead to wrong diagnoses, since these methods do not account for patient-
specific characteristics. We address this problem by providing new and efficient visual-interactive methods. Particularly, we introduce dedicated visualizations that show different aspects of the data. In addition, we support patient-specific selections of relevant data regions. Selected regions are emphasized, or separately visualized to inspect retinal substructures in detail. By visually comparing the regions to reference data, even very small retinal changes can be detected. We demonstrate the utility of our approach by applying it to data of a study with pediatric patients suffering from diabetes mellitus type 1. Our results show that visual-interactive methods indeed help to analyze subtle retinal changes and, thus, support the diagnosis of diseases in an early stage.

PMID: 29145690


Moving from Clinic to Home: What the Future Holds for Ophthalmic Telemedicine.

Holekamp NM

PURPOSE: To describe the expanding role of telemedicine in healthcare, the key criteria required for a successful device and program implementation, and the current and future role of home monitoring in ophthalmology.

DESIGN: Expert perspective

METHODS: Analysis with real-world interpretation of home monitoring technologies including current adoption barriers and expanded future demands based on demographic and market forces.

RESULTS: Remote patient monitoring represents a paradigm shift in the way physicians care for patients. Success depends on meeting several criteria among which are a recognized value proposition to the physician, robust device performance validation, ease of use for the patient, reliability of connectivity, safe and secure data transmission, and economic feasibility. Ophthalmic diseases, such as age-related macular degeneration, glaucoma, and diabetic retinopathy, are ideal candidates for home monitoring practice integration. Established home monitoring technology is already facilitating early detection and improved visual outcomes for patients with age-related macular degeneration. Future innovation currently underway or on the horizon will continue to evolve and expand the footprint of telemedicine within ophthalmology.

CONCLUSION: Home monitoring has the potential to enhance the patient-physician relationship and to positively impact visual acuity outcomes in ophthalmic diseases. Advances in technology, demographic shifts, market changes, and patient demand for personalized medicine will require physicians to embrace technology in new and diverse ways, perhaps facilitating widespread adoption of home monitoring technology platforms.

PMID: 29137959


Optical coherence tomography angiography in patients with diabetic retinopathy treated with anti-VEGF intravitreal injections: Case report.

Michalska-Małecka K, Heinke Knudsen A.

PURPOSE: To present optical coherence tomography angiography (OCTA) features in patients with diabetic retinopathy (DR) at the baseline and in response to treatment with anti-VEGF intravitreal injections. To investigate the role of OCTA in management of patients with DR.

METHODS: Retrospective case series showing primary outcomes of 3 patients with DR and diabetic macular edema. Patients were injected intravitreally a loading phase of 3 monthly 2.0mg aflibercept,
followed by 2 injections bimonthly (5 injections in total). Before each injection OCTA was performed using 3 mm × 3mm scans (Optovue, XR Avanti). The obtained scans of the macula were analyzed and compared to the image at the baseline. Best-corrected visual acuity (BCVA) was examined at the baseline and before each injection.

RESULTS: In the superficial plexus, a rarefaction of capillaries with capillary dropout and nonperfusion areas were present in all eyes. The microaneurysms were good to visualize in 3mm × 3mm scans. In deep vascular network, evident microvascular alterations around the small cystoid edema cells were to detect. There were no differences in perfusion density level for the whole macular area in 3mm × 3mm scans shown in density maps between injections in all presented cases. After a series of aflibercept intravitreal injections decreased cystic changes were observed. Moreover in all presented cases, the decrease in central retinal thickness that correlated clinically with improvement of visual acuity (BCVA) was observed. All patients achieved a goal of well-controlled diabetes by having a HbA1c level (<8.0%) before each injection.

CONCLUSIONS: OCTA is a dyeless, quick, and noninvasive method which allows to detect ischemic changes in DR and might be a useful tool in observing the progress of the disease and the response to anti-VEGF treatment in clinical practice.

PMID: 29137019

Retina. 2017 Nov 10. [Epub ahead of print]

VITRECTOMY WITH SUBRETINAL TISSUE PLASMINOGEN ACTIVATOR AND GAS TAMPOANE FOR SUBFOVEAL HEMORRHAGE: Prognostic Factors and Clinical Outcomes.

Plemel DJA, Lapere SRJ, Rudnisky CJ, Tennant MTS.

PURPOSE: To study the prognostic factors and clinical outcomes of patients who underwent pars plana vitrectomy, subretinal injection of tissue plasminogen activator, and gas tamponade for the treatment of subfoveal hemorrhage (SFH).

METHODS: A retrospective noncomparative interventional case series.

RESULTS: Seventy-eight eyes from 77 patients were included. A total of 84.6% of eyes developed SFH from age-related macular degeneration. Partial or complete displacement of the SFH was achieved in 91.5% of eyes within 2 months of surgery. Visual acuity improved from 20/1,449 preoperatively to 20/390 after a mean follow-up time of 6.3 months, corresponding to approximately 5 lines of Snellen acuity improvement (P < 0.001). Better visual acuity was associated with the absence of age-related macular degeneration (P = 0.02) and less hemorrhage superior to the fovea (P < 0.001). Final visual acuity was not associated with the area of SFH (P = 0.17), use of anticoagulants (P = 0.14), or visibility of the ellipsoid layer by optical coherence tomography (P = 0.64). Nine patients (11.5%) developed a recurrence of SFH within the follow-up period. Recurrence of SFH was not associated with concurrent anticoagulant therapy (P = 0.52).

CONCLUSION: An etiology other than age-related macular degeneration with less hemorrhage superior to the fovea predicts a better outcome in patients with SFH treated with pars plana vitrectomy, subretinal tissue plasminogen activator, and gas tamponade.

PMID: 29135798


Retinal Structure in Pre-Clinical Age-Related Macular Degeneration.

PURPOSE: To determine, if there are identifiable retinal structural changes associated with genetic risk for age-related macular degeneration (AMD).

MATERIALS AND METHODS: Seventy-three subjects (range 51.5 to 68.9 years) participated in this prospective study. Subjects were recruited based on the presence of a family history of AMD in one or both parents. All participants underwent a complete ophthalmic exam and imagery for staging of disease severity and genetic testing to assess genetic risk for AMD development. Optical coherence tomography (OCT) imaging was performed on all participants. Semi-automated retinal layer segmentation was performed to assess retinal structural changes.

RESULTS: Of 73 subjects, 47 subjects had normal appearing retina with no evidence of drusen or other changes consistent with AMD, 16 subjects were classified as early AMD, and 13 were designated as intermediate AMD. Retinal volume measures of total retina, outer retina, outer nuclear layer and the retinal pigment epithelium, were not related to AMD classification, genetic risk scores, or age. The thickness of the outer retina showed statistically significant thickening in the foveal region in only the intermediate AMD group and a statistically significant thickening of the RPE in early and intermediate AMD groups in the central retina.

CONCLUSION: No consistent changes were observed in retinal structure at multiple locations that are associated with pre-clinical AMD, based on AMD genetic risk or with aging within the age range of our cohort.

PMID: 29135322

**Pathogenesis**


Quantitative study of zinc and metallothioneins in the human retina and RPE cells by mass spectrometry-based methodologies.


Abstract: The retina contains the highest concentration of zinc in the human eye and it is primarily associated with the retinal pigment epithelium (RPE). Metallothioneins (MTs) are the main cytosolic zinc-ion-binding proteins, exerting a tight control in the number of atoms of Zn-bound to the MTs related with their antioxidant and neuroprotective functions. In order to study the Zn-MT system in retina and RPE, we have implemented mass spectrometry (MS)-based technologies: two complementary element detection methodologies (HPLC- and laser ablation (LA)-ICP-MS) have been successfully employed to study metal content in the human eye as well as to perform speciation studies of Zn-MTs. First, Zn-elemental distribution was studied on cryogenic ocular sections by LA-ICP-MS. Quantitative images of Zn along RPE cell layer and the retina were obtained with a laser beam diameter of 25µm, showing a preferential distribution in the RPE. We carried out then the quantitative speciation of Zn, Fe, and Cu in the water-soluble protein fractions of RPE and retina to study their protein binding profile using HPLC-ICP-MS, where Zn is mainly associated to low molecular mass proteins (i.e., MTs). Finally, the effect of addition of different inductors, such as metal (i.e., 68ZnSO4), dexamethasone (DEX) and erythropoietin, was investigated in an in vitro cellular model of human RPE cells (HRPEsv), again using HPLC-ICP-MS in combination with stable isotopes and mathematical calculations based on isotope dilution and isotope pattern deconvolution. Exogenous Zn and DEX were found to increase MT proteins synthesis and exerted a stoichiometric transition in MT proteins in HRPEsv cells.

PMID: 29136815
Involvement of cannabinoid receptor type 2 in light-induced degeneration of cells from mouse retinal cell line in vitro and mouse photoreceptors in vivo.

Imamura T, Tsuruma K, Inoue Y, Otsuka T, Ohno Y, Ogami S, Yamane S, Shimazawa M, Hara H.

Abstract: Earlier studies showed that the expressions of the agonists of the cannabinoid receptors are reduced in the vitreous humor of patients with age-related macular degeneration (AMD), and the cannabinoid type 2 receptor is present in the retinas of rats and monkeys. The purpose of this study was to determine whether the cannabinoid type 2 receptor is involved in the light-induced death of cultured 661W cells, an immortalized murine retinal cell line, and in the light-induced retinal degeneration in mice. Time-dependent changes in the expression and location of retinal cannabinoid type 2 receptor were determined by Western blot and immunostaining. The cannabinoid type 2 receptor was down-regulated in murine retinas and cone cells. In the in vitro studies, HU-308, a cannabinoid type 2 receptor agonist, had a protective effect on the light-induced death of 661W cells, and this effect was attenuated by SR144528, a cannabinoid type 2 receptor antagonist. Because the cannabinoid type 2 receptor is a G-protein coupled receptor and is coupled with Gi/o protein, we investigated the effects of the cAMP-dependent protein kinase (PKA). HU-308 and H89, a PKA inhibitor, deactivated PKA in retinal cone cells, and H89 also suppressed light-induced cell death. For the in vivo studies, a cannabinoid type 2 receptor agonist, HU-308, or an antagonist, SR144528, was injected intravitreally into mouse eyes before the light exposure. Electrotoretinography was used to determine the physiological status of the retinas. Injection of HU-308 improved the a- and b-waves of the ERGs and also the thickness of the outer nuclear layer of the murine retina after light exposure. These findings indicate that the cannabinoid type 2 receptor is involved in the light-induced retinal damage through PKA signaling. Thus, activation of cannabinoid type 2 receptor may be a therapeutic approach for light-associated retinal diseases.

PMID: 29133122

Increased Th1/Th17 Responses Contribute to Low-Grade Inflammation in Age-Related Macular Degeneration.

Chen J, Wang W, Li Q.

BACKGROUND/AIMS: Age-related macular degeneration (AMD) is the primary cause of senior blindness in developed countries. Mechanisms underlying initiation and development of AMD remained known.

METHODS: We examined the CD4+ T cell compartments and their functions in AMD patients.

RESULTS: AMD patients presented significantly higher frequencies of interferon (IFN)-γ-expressing and interleukin (IL)-17-expressing CD4+ T cells than healthy controls. The levels of IFN-γ and IL-17 expression by CD4+ T cells were significantly higher in AMD patients. These IFN-γ-expressing Th1 cells and IL-17-expressing Th17 cells could be selectively enriched by surface CCR3+ and CCR4+CCR6+ expression, respectively. Th1 and Th17 cells from AMD patients promoted the differentiation of monocytes toward M1 macrophages, which were previously associated with retinal damage. Th1 and Th17 cells also increased the level of MHC class I expression in human retinal pigment epithelial (RPE)-1 cells, while Th1 cells increased the frequency of MHC class II-expressing RPE-1 cells. These proinflammatory effects were partly, but not entirely, induced by the secretion of IFN-γ and IL-17.

CONCLUSIONS: This study demonstrated an enrichment of Th1 cells and Th17 cells in AMD patients. These Th1 and Th17 cells possessed proinflammatory roles in an IFN-γ- and IL-17-dependent fashion, and could potentially serve as therapeutic targets.

PMID: 29132135
Epidemiology


Generational Differences in the 5-Year Incidence of Age-Related Macular Degeneration.


IMPORTANCE: Whether a reported decline in the risk of developing age-related macular degeneration (AMD) continued for people born during the Baby Boom years (1946-1964) or later is unknown. These data are important to plan for ocular health care needs in the 21st century.

OBJECTIVES: To determine whether the 5-year risk for AMD declined by generation and to identify factors that contributed to improvement in risk.

DESIGN, SETTING, AND PARTICIPANTS: Data came from the longitudinal cohort Beaver Dam Eye Study (March 1, 1988, through September 15, 1990, and March 1, 1993, through June 15, 1995) and the Beaver Dam Offspring Study (June 8, 2005, through August 4, 2008, and July 12, 2010, through March 21, 2013). These population-based studies examined residents of Beaver Dam, Wisconsin, aged 43 to 84 years in 1987 through 1988 and their adult offspring aged 21 to 84 years in 2005 through 2008. A total of 4819 participants were at risk for developing AMD based on fundus images obtained at baseline visits. Data were analyzed from February 18, 2016, through June 22, 2017, with additional analyses ending September 22, 2017.

MAIN OUTCOMES AND MEASURES: Fundus images were graded for AMD using the Wisconsin Age-related Maculopathy Grading System. The incidence of AMD was defined as the presence at the 5-year follow-up examination of pure geographic atrophy or exudative macular degeneration, any type of drusen with pigmentary abnormalities, or soft indistinct drusen without pigmentary abnormalities.

RESULTS: Among the 4819 participants, the mean (SD) baseline age of the cohort was 54 (11) years; 2117 were men (43.9%) and 2702 were women (56.1%). The 5-year age- and sex-adjusted incidence of AMD was 8.8% in the Greatest Generation (born during 1901-1924), 3.0% in the Silent Generation (born during 1925-1945), 1.0% in the Baby Boom Generation (born during 1946-1964), and 0.3% in Generation X (born during 1965-1984). Adjusting for age and sex, each generation was more than 60% less likely to develop AMD than the previous generation (relative risk, 0.34; 95% CI, 0.24-0.46). The generational association (relative risk, 0.40; 95% CI, 0.28 to 0.57) remained significant after adjusting for age, sex, smoking, educational attainment, exercise, levels of non-high-density lipoprotein cholesterol and high-sensitivity C-reactive protein, and use of nonsteroidal anti-inflammatory drugs, statins, and multivitamins.

CONCLUSIONS AND RELEVANCE: The 5-year risk for AMD declined by birth cohorts throughout the 20th century. Factors that explain this decline in risk are not known. However, this pattern is consistent with reported declines in risks for cardiovascular disease and dementia, suggesting that aging Baby Boomers may experience better retinal health at older ages than did previous generations.

PMID: 29145549


Prevalence and factors associated with age-related macular degeneration in a southwestern island population of Japan: the Kumejima Study.


AIMS: To evaluate the prevalence of and factors associated with age-related macular degeneration (AMD) in a rural population of southwestern Japan.
METHODS: This population-based cross-sectional study of all residents aged 40 years or older was conducted on the island of Kumejima, Okinawa, Japan. Of 4632 eligible residents, 3762 completed a comprehensive questionnaire and underwent ocular examination (participant rate, 81.2%). A non-mydriatic fundus photograph was used to grade AMD lesions according to the Wisconsin protocol. Prevalence of AMD was calculated and factors associated with AMD were identified by logistic regression.

RESULTS: Of 3068 subjects with gradable photographs, 469 had early AMD and 4 had late AMD. Age-adjusted prevalence was 13.4% for any AMD, 13.3% for early AMD and 0.09% for late AMD. In multivariate analysis, any AMD was positively associated with age (OR 1.04 per year, 95% CI 1.03 to 1.05), male sex (OR 1.42, 95% CI 1.14 to 1.75) and history of cataract surgery (OR 1.35, 95% CI 1.00 to 1.82) and was negatively associated with longer axial length (OR 0.85 per millimetre, 95% CI 0.74 to 0.96). Early AMD similarly showed significant associations with these same factors.

CONCLUSIONS: Prevalence of early or late AMD in a southwestern island population of Japan was 13.4% or 0.09%. Our data suggest relatively high prevalence for early AMD and low prevalence for late AMD in this sample of rural Japanese population. Significant factors associated with any or early AMD were mostly similar to that of previous studies.

PMID: 29146756

Australas J Ageing. 2017 Nov 15. [Epub ahead of print]

Risk factors for falls among older Aboriginal and Torres Strait Islander people in urban and regional communities.


OBJECTIVE: To examine associations between fall risk factors identified previously in other populations and falls among Aboriginal people aged 60 years and older, living in New South Wales, Australia.

METHODS: Interviews were conducted with older Aboriginal people in five urban and regional communities. Associations between past falls and 22 fall predictor variables were examined using linear and multiple regression analyses.

RESULTS: Of the 336 participants, 80 people (24%) reported at least one fall in the past year, and 34 (10%) reported two or more falls. Participants had an increased fall risk if they were female; used three or more medications; had arthritis, macular degeneration, depression, history of stroke; were unable to do their own housework; or were unable to do their own shopping.

CONCLUSION: Falls were experienced by one-quarter of study participants. Fall risk factors identified for older Aboriginal people appear to be similar to those identified in the general population. Understanding of fall risk factors may assist with the development of appropriate and effective community-led fall prevention programs.

PMID: 29143435

Genetics & gene therapy


The Role Of Gene Therapy In The Treatment Of Retinal Diseases: A Review

Campa C, Gallenga CE, Bolletta E, Perri P.
BACKGROUND: Gene therapy represents the therapeutic delivery of nucleic acid polymers into a patient's cells with the aim of treating an underlying disease. Over the past 2 decades this new therapy has made substantial progress owing to better understanding of the pathobiologic basis of various diseases coupled with growth of gene transfer biotechnologies. The eye, in particular, represents a suitable target for such therapy due to the immune privilege provided by the blood-ocular barrier, the ability to directly visualize, access and locally treat the cells and the minimal amount of vector needed given the size of this organ. It is not surprising therefore that several clinical trials are now ongoing in this field.

OBJECTIVE: The purpose of this review was to provide an update on gene therapy for retinal diseases, discussing differences in treatment strategies, vector designs and surgical techniques.

METHOD: Research was performed on PubMed, ClinicalTrials.gov, and Home Genetic Reference. We additionally utilized the internet database for genetics of retinal diseases, the portal for rare diseases and orphan drugs and the NCBI database Online Mendelian Inheritance in Man. No restriction was applied on the language of publications.

RESULTS: We present the available results of current active clinical trials for inherited retinal disease such Leber’s congenital amaurosis type 2, choroideremia, Stargardt disease, achromatopsia and juvenile X-linked retinoschisis. We also illustrate a new approach of this therapy for the treatment of much more common ocular diseases such as age-related macular degeneration and diabetic retinopathy.

CONCLUSION: Gene therapy represents an emerging and promising therapeutic approach for the treatment not only of rare inherited retinal diseases but also much more common retinal pathologies.

PMID: 29149824


Molday LL, Wahl D, Sarunic M, Molday RS.

Abstract: ABCA4 is a member of the superfamily of ATP-binding cassette (ABC) proteins that transports N-retinylidene-phosphatidylethanolamine (N-Ret-PE) across outer segment disc membranes thereby facilitating the removal of potentially toxic retinoid compounds from photoreceptor cells. Mutations in the gene encoding ABCA4 are responsible for Stargardt disease (STGD1), an autosomal recessive retinal degenerative disease that causes severe vision loss. To define the molecular basis for STGD1 associated with the p.Asn965Ser (N965S) mutation in the Walker A motif of nucleotide binding domain 1 (NBD1), we generated a p.Asn965Ser knockin mouse and compared the subcellular localization and molecular properties of the disease variant with wild-type (WT) ABCA4. Here, we show that the p.Asn965Ser ABCA4 variant expresses at half the level of WT ABCA4, partially mislocalizes to the endoplasmic reticulum (ER) of photoreceptors, is devoid of N-Ret-PE activated ATPase activity, and causes an increase in autofluorescence and the bisretinoid A2E associated with lipofuscin deposits in retinal pigment epithelial cells as found in Stargardt patients and Abca4 knockout mice. We also show for the first time that a significant fraction of WT ABCA4 is retained in the inner segment of photoreceptors. On the basis of these studies we conclude that loss in substrate-dependent ATPase activity and protein misfolding are mechanisms underlying STGD1 associated with the p.Asn965Ser mutation in ABCA4. Functional and molecular modeling studies further suggest that similar pathogenic mechanisms are responsible for Tangiers disease associated with p.Asn935Ser (N935S) mutation in the NBD1 Walker A motif of ABCA1.

PMID: 29145636
Novel Complex ABCA4 Alleles in Brazilian Patients With Stargardt Disease: Genotype-Phenotype Correlation.


PURPOSE: To analyze the presence of complex alleles of the ABCA4 gene in Brazilian patients with Stargardt disease and to assess the correlation with clinical features.

METHODS: This was an observational cross-sectional study. Patients with a diagnosis of Stargardt disease who presented three pathogenic variants of the ABCA4 gene or who had variants previously described as complex alleles were included. The relatives of these probands were evaluated in the segregation analysis. The patients were evaluated based on age at symptom onset and visual acuity, and the clinical characteristics were classified according to the findings observed on autofluorescence examination.

RESULTS: Among the 47 families analyzed, approximately 30% (14/47) presented complex alleles. The segregation analysis in 14 families with cases of Stargardt disease identified three novel complex alleles and one previously described complex allele. The known complex allele p.[Leu541Pro; Ala1038Val] was identified in two families. The novel complex alleles identified were p.[Leu541Pro; Arg1443His] in five families, p.[Ser1642Arg; Val1682_Val1686del] in seven families, and p.[Pro1761Arg; Arg2106Cys] in one family. Furthermore, four new variants (p.Lys22Asn, p.Asp915Asn, p.Glu1447Val, and p.Pro1761Arg) were identified in the second allele of the ABCA4 gene.

CONCLUSIONS: Segregation analysis is important in order to confirm the molecular diagnosis of patients with Stargardt disease, given the frequency of complex alleles in the ABCA4 gene. The various pathogenic variation combinations observed in this study were associated with different phenotypes.

PMID: 29114839

Association of copy number variations in complement factor H-Related genes among age-related macular degenerative subjects.


Abstract: Age-related macular degeneration (AMD) is the most widely recognised cause of irreversible vision loss and previous studies have suggested that the advancement of wet AMD is influenced by both modifiable and non-modifiable elements. Single nucleotide polymorphism (SNPs) and copy number of variations (CNVs) have been associated with AMD in various populations, however the results are conflicting. Our aim is to determine the CNVs of Complement Factor H-Related genes among Malaysian subjects with wet AMD. 130 patients with wet AMD and 120 healthy controls were included in this research. DNA was extracted from all subjects and CNVs of CFH, CFHR1 and CFHR3 genes; determined using quantitative real-time PCR and were compared between the two groups. A consistent association was observed between CFH gene and wet AMD susceptibility (P < 0.05). The age-adjusted data suggests a possible increased risk of AMD disease (P < 0.05). No correlation was detected between CNVs and wet AMD for the remaining genes after we compared the frequencies of mean for that gene. An association was observed between CFH CNVs and wet AMD in the Malaysian population, however, strong evidence of a link with wet AMD was not found. Further investigative studies are needed using larger sample sizes to elucidate the role of CNVs in AMD pathogenesis.

PMID: 29132549
Diet, lifestyle & low vision


Dietary guidance for lutein: consideration for intake recommendations is scientifically supported.


Abstract: Lutein, a yellow xanthophyll carotenoid found in egg yolks and many colorful fruits and vegetables, has gained public health interest for its putative role in visual performance and reducing the risk of age-related macular degeneration. The National Academies of Sciences, Engineering and Medicine’s recommended Dietary Reference Intakes (DRIs) focus on preventing deficiency and toxicity, but there is a budding interest in establishing DRI-like guidelines for non-essential bioactives, like lutein, that promote optimal health and/or prevent chronic diseases. Lupton et al. developed a set of nine criteria to determine whether a bioactive is ready to be considered for DRI-like recommendations. These criteria include: (1) an accepted definition; (2) a reliable analysis method; (3) a food database with known amounts of the bioactive; (4) cohort studies; (5) clinical trials on metabolic processes; (6) clinical trials for dose-response and efficacy; (7) safety data; (8) systematic reviews and/or meta-analyses; (9) a plausible biological rationale. Based on a review of the literature supporting these criteria, lutein is ready to be considered for intake recommendations. Establishing dietary guidance for lutein would encourage the consumption of lutein-containing foods and raise public awareness about its potential health benefits.

PMID: 29149368


The ‘Displacing Foods of Modern Commerce’ Are the Primary and Proximate Cause of Age-Related Macular Degeneration: A Unifying Singular Hypothesis.

Knobbe CA, Stojanoska M.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss and blindness in developed nations. AMD is anticipated to affect 196 million people worldwide, by 2020. However, the etiology of this disease remains unknown. Aging, genetic, and environmental influences have generally been implicated as major etiologic factors. We sought to examine the hypothesis that consumption of the ‘displacing foods of modern commerce,’ which equate to processed, nutrient-deficient and potentially toxic foods, may be the primary and proximate cause of AMD. To evaluate this hypothesis, we ran correlative AMD prevalence data against well-known proxy markers of processed food consumption, namely, sugar and vegetable oils, in 25 nations. In twenty-one nations, published studies provided AMD prevalence data and in four Pacific Island nations, practicing ophthalmologists in the regions completed retrospective chart analyses to estimate AMD prevalence in their respective regions. To estimate AMD prevalence historically, an extensive review of published papers and ophthalmic literature was completed. This review indicates that, between the years 1851 and 1930, AMD was a medical rarity worldwide, which then rose modestly in prevalence in the 1930s in the U.S. and U.K, finally elevating to epidemic proportions by 1975 in the U.S. Numerous developed nations have followed suit in recent decades. Simultaneously, between approximately 1880 and 2009, processed, nutrient-deficient foods gradually supplanted and displaced whole, unprocessed, nutrient-dense foods in developed nations, such that by 2009, 63 percent of the American diet was made up of nutrient-deficient foods in the form of refined white flour, added sugars, vegetable oils, and artificially created trans fats. The correlative data in 25 nations shows that increasing sugar and polyunsaturated vegetable oil consumption is invariably associated with new onset or rising prevalence of AMD, generally within about 30-40 years of the beginning of increasing consumption of these proxy marker processed food components. The correlative data also demonstrates that, when consumption of sugar is moderate, but “harmful vegetable oil” consumption remains extremely low or absent, the prevalence of AMD remains rare. This study supports the hypothesis that the ‘displacing foods of modern
commerce,’ which equate to processed, nutrient-deficient, and potentially toxic foods, are the primary and proximate cause of AMD. This study also supports the conclusion that macular degeneration is entirely preventable, through ancestral dietary strategy and avoidance of processed foods. Finally, this research has implications for patients with existing early and intermediate stages of AMD.

PMID: 29150284

**Biotechnol Bioeng. 2017 Nov 18. [Epub ahead of print]**

**Photoautotrophic production of macular pigment in a Chlamydomonas reinhardtii strain generated by using DNA-free CRISPR-Cas9 RNP-mediated mutagenesis.**

Baek K, Yu J, Jeong J, Sim SJ, Bae S, Jin E.

Abstract: Lutein and zeaxanthin are dietary carotenoids reported to be protective against age-related macular degeneration. Recently, the green alga Chlamydomonas reinhardtii has received attention as a photosynthetic cell factory, but the potential of this alga for carotenoid production has not yet been evaluated. In this study, we selected the C. reinhardtii CC-4349 strain as the best candidate among seven laboratory strains tested for carotenoid production. A knock-out mutant of the zeaxanthin epoxidase gene induced by preassembled DNA-free CRISPR-Cas9 ribonucleoproteins in the CC-4349 strain had a significantly higher zeaxanthin content (56-fold) and productivity (47-fold) than the wild type without the reduction in lutein level. Furthermore, we produced eggs fortified with lutein (2-fold) and zeaxanthin (2.2-fold) by feeding hens a diet containing the mutant. Our results clearly demonstrate the possibility of cost-effective commercial use of microalgal mutants induced by DNA-free CRISPR-Cas9 ribonucleoproteins in algal biotechnology for the production of high-value products.

PMID: 29150930

**Mol Nutr Food Res. 2017 Nov 13. [Epub ahead of print]**

**β-Cryptoxanthin Inhibits Angiogenesis in Human Umbilical-Vein Endothelial Cells (HUVEC) Through Retinoic-Acid Receptor (RAR).**

Quesada-Gómez JM, Santiago-Mora R, Durán-Prado M, Dorado G, Pereira-Caro G, Moreno-Rojas JM, Casado-Díaz A.

SCOPE: β-Cryptoxanthin is an abundant carotenoid in fruits and vegetables that can be quantified in human blood-serum. Yet, contrary to other carotenoids, its effects on endothelial cells and angiogenesis remain unknown.

METHODS AND RESULTS: Human umbilical-vein endothelial cells (HUVEC) were treated with 0.01, 0.1 or 1 μM of β-cryptoxanthin. Antioxidant activity was determined by its free radical scavenging and oxygen-radical absorbance capacity (ABTS and ORAC assays). Effect on migration and formation of tubular structures was studied. Additionally, effect on angiogenesis was also analyzed using an in vivo model. β-Cryptoxanthin exhibited scavenging ability, having antioxidant effect on HUVEC. Interestingly, β-cryptoxanthin reduced their migration and angiogenesis, even in presence of vascular endothelial growth-factor (VEGF). Additionally, such carotenoid inhibited in vivo angiogenesis induced by VEGF. Besides, treatment of HUVEC with LE540 [retinoic-acid receptor (RAR) panantagonist] inhibited β-cryptoxanthin antiangiogenic effect on HUVEC.

CONCLUSION: β-Cryptoxanthin inhibits angiogenesis through RAR. Thus, this carotenoid and food containing it may be useful for prevention and treatment of angiogenic pathologies. That includes tumoral growth and wet macular-degeneration associated to aging. To the best of our knowledge, this is the first report of the antioxidant effect and antiangiogenic activity of such carotenoid on HUVEC, both in vitro and in
Gaming to improve vision: 21st century self-monitoring for patients with age-related macular degeneration.

Razavi H, Baglin E, Sharangan P, Caruso E, Tindill N, Griffin S, Guymer R.

IMPORTANCE: Improved vision self-monitoring tools are required for people at risk of neovascular complications from age related macular degeneration (AMD).

BACKGROUND: To report the self-monitoring habits of participants with intermediate AMD using the Amsler grid chart, and the use of personal electronic devices and gameplay in this over 50 year old cohort.

DESIGN: Single-centre descriptive study carried out at the Centre for Eye Research (CERA), Melbourne, Australia.

PARTICIPANTS: 140 participants over 50 years of age, with a diagnosis of intermediate AMD and best-corrected visual acuity (BCVA) of ≥6/12 in each eye.

METHODS: Structured questionnaire survey of participants who were enrolled in natural history of AMD studies at CERA.

MAIN OUTCOME MEASURES: Frequency of vision self-monitoring using of the Amsler grid chart, and frequency of general use of personal electronic devices and gameplay.

RESULTS: Of 140 participants with mean age of 70.5 years, 83.6% used an Amsler grid chart, but only 39.3% used it once per week. Most participants (91.4%) used one or more personal electronic devices. Of these, over half (54.7%) played games on them, among whom 39% played games once a day. Of participants aged 50-69 years, 92% (95%CI 85.1-98.9) were willing to play a game to monitor their vision, compared to 78% (95%CI 69.0-87.0) of those aged 70 years and older (p<0.05).

CONCLUSIONS AND RELEVANCE: A large proportion of AMD patients already use personal electronic devices. Gamification techniques are likely to increase compliance with self-monitoring, leading to earlier detection in the next generation of patients with neovascular AMD.

PMID: 29131493

Hospital anxiety and depression scale assessment of 100 patients before and after using low vision care: A prospective study in a tertiary eye-care setting.

Rishi P, Rishi E, Maitray A, Agarwal A, Nair S, Gopalakrishnan S.

PURPOSE: Assessment of anxiety and depression in patients attending low vision care (LVC) using Hospital Anxiety and Depression Scale (HADS).

METHODS: In this prospective, observational study, 100 patients with best-corrected visual acuity (BCVA) worse than 6/18 in the better eye or limitation of field of vision to <10° from center of fixation were assessed on the depression and anxiety subscales of HADS questionnaire before and after LVC. HADS is a 14-item scale with seven items each for anxiety and depression subscales. Scoring for each item ranges from zero to three. A subscale score >8 denotes anxiety or depression.

PMID: 29131551
RESULTS: Mean age at presentation was 38.2 years. Mean duration of symptoms was 9.6 years. Underlying etiology of visual impairment included retinal dystrophy/degeneration (n = 35), disorders of the optic nerve (n = 17), glaucoma (n = 10), diabetic retinopathy (n = 9), age-related macular degeneration (n = 5), uncorrected refractive errors (n = 5), and miscellaneous diseases (n = 19). Mean presenting BCVA in the better eye was 0.83 (±0.64) which improved significantly to 0.78 (±0.63) after LVC (P < 0.001). The HADS-Depression subscale score was comparable for severity of visual impairment for both distance (P = 0.57) and near vision (P = 0.61). Similarly, HADS-Anxiety scores were also comparable for severity of distance (P = 0.34) and near-visual impairment (NVI; P = 0.50). At baseline, mean HADS-Depression and HADS-Anxiety scores were 8.4 (±3.7) and 9.6 (±4.3) points, which improved significantly to 6.0 (±3.4) and 6.7 (±3.7), respectively, after low-vision correction (P < 0.001).

CONCLUSION: Low vision correction can significantly improve anxiety and depression indicators in visually impaired patients.

PMID: 29133652


Erratum to "Nutritional and Lifestyle Interventions for Age-Related Macular Degeneration: A Review".

Carneiro Â, Andrade JP.

Abstract

Erratum for

Nutritional and Lifestyle Interventions for Age-Related Macular Degeneration: A Review. [Oxid Med Cell Longev. 2017]

PMID: 29147458 PMCID: PMC5632903


Physical Activity and Age-related Macular Degeneration: A Systematic Literature Review and Meta-analysis.

Liu L, Majithia S, Tham YC.

PMID: 29128098