Drug treatment

Eur J Ophthalmol. 2017 Oct 14:0. [Epub ahead of print]

Aflibercept in the treatment of diabetic macular edema: a review and consensus paper.


PURPOSE: To reach a consensus, among experts, on the role of aflibercept in diabetic macular edema (DME) through literature review.

METHODS: Two round tables, involving 12 Italian experts, were organized: in the first one, 6 pharmacologic and clinical questions were selected and analyzed by a systematic literature review, using a population, intervention, control, and outcomes framework; in the second one, the nominal group technique was used to discuss relevant evidence related to each question. The consensus was assessed using the 5-point Delphi score.

RESULTS: Agreement on statements was reached on 6/6 questions. The final statements were as follows: 1) High levels of both vascular endothelial growth factor (VEGF) and placental growth factor play an important role in the pathogenesis of DME. 2) The aflibercept pharmacologic profile is notably different from that of other anti-VEGF. 3) Aflibercept significantly improves functional and anatomical outcomes, and rapidly improves best-corrected visual acuity up to its peak; these results remain stable over time. 4) Diabetic macular edema aflibercept treatment requires a 5-monthly injection loading phase. Alternatively, a personalized pro re nata (PRN) regimen based on monthly monitoring and strict retreatment criteria can be used. 5) As an alternative to the bimonthly fixed regimen, in the maintenance phase the treatment schedule may be a PRN regimen with strict retreatment criteria or a treat and extend regimen. 6) No concerns on aflibercept ocular and systemic safety emerged from the literature.

CONCLUSIONS: Consensus was reached among experts on how to best treat patients with DME with aflibercept.

PMID: 29077188


Outcome of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration in real-life setting.

AIMS: To evaluate outcome of anti-vascular endothelial growth factor (VEGF) therapy for the treatment of neovascular age-related macular degeneration (nAMD) in the real-life setting and to compare incidence of ocular serious adverse events (SAE) after injections administered by nurses and physicians.

METHODS: Retrospective, single-centre study. Medical records of patients receiving anti-VEGF treatment for nAMD between 2008 and 2013 with three-loading-dose regimen were evaluated. Outcome measures were baseline visual acuity (VA), change in VA, number of intravitreal injections, incidence of ocular SAE and patients’ baseline characteristics affecting VA change. In addition, the number of injections per 1000 citizens living in the serving area and per individuals over 65 years old were estimated.

RESULTS: 1349 eyes in 1117 patients received a total of 11 562 intravitreal anti-VEGF injections. Twenty-one per cent of patients received treatment for both eyes. The mean baseline Snellen VA was 0.32. The mean change of VA from baseline was +2, +2 and ±0 Early Treatment Diabetic Retinopathy Study letters and the mean numbers of injections were 5.7, 4.7 and 4.9 at years 1, 2 and 3, respectively. There was a negative correlation between baseline VA and change of VA. Incidence of endophthalmitis was 0.086%. No difference in the incidence of ocular SAE was identified between injections given by nurses or by physicians. The number of intravitreal injections per all citizens was 9 per 1000 inhabitants and 45 per 1000 inhabitants over 65 years.

CONCLUSION: The VA was maintained at the baseline level (±0 letters) with the mean of 15.3 anti-VEGF injections in real-world clinical practice during 3-year follow-up.

PMID: 29074495

[The Impact of Multiple Intravitreal Anti-VEGF Injections on Intraocular Pressure]. [Article in German]

Lamprakis I, Todorova MG, Grüb M, Schlote T.

Background: To evaluate the possible effects of multiple intravitreal anti-vascular endothelial growth factor (VEGF) injections on intraocular pressure (IOP).

Methods: This study included 50 eyes of 50 patients who underwent multiple (≥ 10 injections) intravitreal anti-VEGF injections in one eye with age-related macular degeneration, diabetic macular edema or retinal vein occlusion. IOP was recorded after every injection on the first postoperative day. IOP > 21 mmHg was regarded as abnormal. For statistical analysis, the IOP was correlated with the number of injections.

Results: A total of 669 IOP-measurements (mean 13.4 treatment/eye) were analyzed. No IOP-elevation was recorded in 43 eyes (86%). Transient elevated IOP > 21 mmHg was measured after 19 intravitreal injections (2.8%, one patients with 8 IOP elevations). In general, there was no increasing risk of IOP elevation with time, no case of sustained IOP elevation and no additional long term glaucoma treatment necessary. Eyes with pre-existing glaucoma were significantly more affected from transient IOP-elevation than non-glaucoma eyes (5.5 vs. 2.2%).

Conclusions: Multiple anti-VEGF injections are not associated with an increased risk of sustained IOP-elevation. On the other hand, individual risk factors exist and predispose to IOP-elevation (e.g., pre-existing glaucoma).

PMID: 29069705

The ARMOUR Study: Anti-VEGF in Neovascular AMD- Our Understanding in a Real-World Indian
Setting.

Jain N, Yadav NK, Jayadev C, Srinivasan P, Mohan A, Shetty BK.

PURPOSE: The aim of our study was to share our experience with anti–vascular endothelial growth factor (anti-VEGF) injections in the treatment of neovascular age-related macular degeneration (nAMD) in a real-world setting.

DESIGN: A retrospective, observational study.

METHODS: Patients of Indian origin with nAMD receiving anti-VEGF with a minimum follow-up of 12 months were enrolled in this study. In group 1, patients were treated on a pro re nata (PRN) basis; in group 2, patients received a loading dose (3 injections) and were then treated on a PRN basis. Main outcome measures were mean change in corrected distance visual acuity (CDVA) and central subfield thickness (CSFT) from baseline to months 3 and 12.

RESULTS: Overall, we observed that 77.31% (92/119 eyes) of patients either maintained or had improved visual acuity at 12 months' follow-up. Similar visual outcome was observed in both groups. The average number of injections given in group 1 was 4.98 and in group 2 was 3.7. CDVA at 12 months was significantly correlated with type of drug molecule, CSFT at 3 and 12 months, baseline visual acuity, and CDVA at 3 months.

CONCLUSIONS: PRN treatment with significantly fewer injections achieved similar anatomical and functional outcomes when compared with the loading dose group. The results of this study need to be validated with a larger study group and a longer follow-up. This real-world observation shows that an individualized PRN approach without loading dose can be considered in the treatment of nAMD.

PMID: 29057640


A longitudinal study to assess the frequency and cost of antivascular endothelial therapy, and inequalities in access, in England between 2005 and 2015.

Hollingworth W, Jones T, Reeves BC, Peto T.

OBJECTIVES: High-cost antivascular endothelial growth factor (anti-VEGF) medicines for eye disorders challenge ophthalmologists and policymakers to provide fair access for patients while minimising costs. We describe the growth in the use and costs of these medicines and measure inequalities in access.


POPULATION: Patients receiving anti-VEGF injections for age-related macular degeneration, diabetic macular oedema and other eye disorders.

INTERVENTIONS: Higher-cost drugs (ranibizumab or aflibercept) recommended by the National Institute for Health and Care Excellence or lower-cost drug (bevacizumab) not licensed for eye disorders.

MAIN OUTCOME MEASURES: National procedure rates and variation between and within clinical commissioning groups (CCGs). Cost of ranibizumab and aflibercept prescribing.

RESULTS: Injection procedures increased by 215% between 2010/2011 and 2014/2015. In 2014/2015 there were 388 031 procedures (714 per 100 000). There is no evidence that the dramatic growth in rates is
slowing down. Since 2010/2011 the estimated cost of ranibizumab and aflibercept increased by 247% to £447 million in 2015/2016, equivalent to the entire annual budget of a CCG. There are large inequalities in access; in 2014/2015 procedure rates in a 'high use' CCG were 9.08 times higher than in a 'low use' CCG. In the South-West of England there was twofold variation in injections per patient per year (range 2.9 to 5.9).

CONCLUSIONS: The high and rising cost of anti-VEGF therapy affects the ability of the NHS to provide care for other patients. Current regulations encourage the increasing use of ranibizumab and aflibercept rather than bevacizumab, which evidence suggests is more cost-effective. NHS patients in England do not have equal access to the most cost-effective care.

PMID: 29061629

Retina. 2017 Oct 24. [Epub ahead of print]

COMPLIANCE AND ADHERENCE OF PATIENTS WITH DIABETIC MACULAR EDEMA TO INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY IN DAILY PRACTICE.


PURPOSE: We assessed differences in compliance and adherence (lateness of patients, visual acuity, reasons for abstaining) between patients with diabetic macular edema (DME) and patients with age-related macular degeneration (AMD), both under anti-vascular endothelial growth factor therapy.

METHODS: We included 136 patients with DME (36% women, 65 years, 22 visits, 13.9 injections, and 29.9 months of follow-up) and 109 patients with AMD (59% women, 76 years, 20 visits, 14.7 injections, and 22.3 months of follow-up) (minimum follow-up of 12 months and at least 5 injections). We assessed missed appointments (lateness >14 days) and therapy break-offs (lateness >100 days). All delayed patients were called and interviewed for abstaining reasons.

RESULTS: Forty-six percent of patients with DME and 22% of patients with AMD had at least one break-off. Thirty-five percent of patients with DME and 50% of patients with AMD were always on schedule. In patients with DME, there was significant correlation (P = 0.017) between the number of break-offs and change of visual acuity. In 60% DME and 38% AMD of break-off cases, visual acuity was worse than the before break-off. The most common reason for abstaining was comorbidities (33% AMD and 20% DME).

CONCLUSION: There are significant differences between patients with AMD and DME regarding compliance and adherence, which also affects outcome. Strategies to tie patients with DME to costly intravitreal therapy need to be developed to improve outcomes and efficacy.

PMID: 29068914


Anti-Vascular Endothelial Growth Factor Therapy for Myopic Choroidal Neovascularization.

Ng DSC, Lai TYY, Cheung CMG, Ohno-Matsui K.

Abstract: Myopic choroidal neovascularization (CNV) is one of the most vision-impairing complications in patients with pathologic myopia. It is also one of the most frequently encountered non–age-related macular degeneration causes of CNV and affects young patients in the working age group. Fluorescein angiography (FA) and spectral domain optical coherence tomography (OCT) are generally indicated to confirm the diagnosis of active myopic CNV before initiation of treatment. Without treatment, natural history studies
have shown that the vision outcome can be very poor. More recently, a number of retrospective, prospective and phase 3, multicenter, randomized controlled trials have established the safety and efficacy of intravitreal anti-vascular endothelial growth factor (VEGF) agents for the treatment of myopic CNV. Long-term follow-up studies have found that some of the initial vision gained after intravitreal anti-VEGF therapy may not be maintained, owing to the presence and progression of chorioretinal atrophy (CRA) adjacent to the CNV. Further research on clinical and imaging characteristics may elucidate the prognostic factors that are crucial to optimizing the treatment and prevention of visual impairment associated with myopic CNV.

PMID: 29057641


Analysis of retinal layer thickness in diabetic macular oedema treated with ranibizumab or triamcinolone.


PURPOSE: To evaluate detailed changes in retinal layer thickness in spectral-domain optical coherence tomography (SD-OCT) images during a 1-year follow-up of patients treated for diabetic macula oedema (DME).

METHODS: Post hoc analysis of retinal layer thickness changes applying the automated layer segmentation of SD-OCT images in eyes with DME that were randomly assigned to receive pro re nata (PRN) treatment with either 0.5 mg ranibizumab or 8 mg triamcinolone. In each patient, seven retinal layers were segmented in 49 scans covering a 20° × 20° area of the macula at baseline and after 1 year of treatment. Changes in individual layer thickness were correlated with visual acuity (VA) and compared between treatment arms.

RESULTS: Twenty-five patients (seven female, 60.2 ± 15.1 years) were evaluated. Thickness decrease of retinal nerve fibre layer (RNFL) was associated with a gain in VA over 12 months (r > 0.54; p < 0.05). Decrease in ganglion cell layer (GCL) and GCL+IPL thickness pooled for nasal Early Treatment of Diabetic Retinopathy Study (ETDRS) subfields correlated with VA as follows: ranibizumab r = 0.74 (GCL) and r = 0.63 (GCL+IPL); and triamcinolone r = 0.45 (GCL) and r = 0.46 (GCL+IPL).

CONCLUSION: In DME therapy, reduction in RNFL thickness may have a considerable impact on retinal function, unrelated to the type of pharmacological treatment. Precise morphologic quantification of neurosensory layers by SD OCT offers new insight into disease pathology and therapeutic targets.

PMID: 29063703

J Fr Ophtalmol. 2017 Oct 18. [Epub ahead of print]

[Management of wet AMD in France in 2015]. [Article in French]


PURPOSE AND CONTEXT: Intravitreal administration of anti-VEGF agents, available in France since 2007, allows stabilization and improvement in visual acuity in wet age-related macular degeneration (AMD). In the past few years, the management of this disease has evolved in terms of both diagnostic methods and treatment schedules, which have been adapted to the pathophysiology of AMD. The goal of this survey, performed in a representative sample of French ophthalmologists, was to describe the evolution of medical practices one year after a similar survey (Massé et al., J Fr Ophtalmol 2016; 39: 40-7).
METHOD: The survey was performed from December, 2014 to March, 2015 in 191 ophthalmologists (53 general ophthalmologists and 98 retina specialists) with an on-line questionnaire. This questionnaire was designed by a committee of ophthalmologists to describe practices concerning screening, diagnosis, treatment and follow-up of wet AMD.

RESULTS: An initial intravitreal injection of an anti-VEGF agent was usually performed within 10 days after the diagnosis of wet AMD by 98% of ophthalmologists and within 5 days by 63%. The treatment protocols favored by retina specialists were pro re nata (PRN) for 58%, Observe and Plan for 25% and Treat and Extend for 17%. Bilateral intravitreal injections were performed on the same day by 46% of retina specialists, mostly for the convenience of the patient and because of the low infectious risk. The initial protocol was maintained by one third of retina specialists throughout the course of treatment, while two thirds of them reported that they reassessed the protocol on average after 5 months.

CONCLUSION: This survey on the practices of the ophthalmologists in wet AMD highlights an improvement in the time course of patient management and an evolution of treatment schedules toward individualized protocols.

PMID: 29055730

Other treatment & diagnosis

Retina. 2017 Oct 26. [Epub ahead of print]

MEASUREMENTS OF RETINAL FLUID BY OCT LEAKAGE IN DIABETIC MACULAR EDEMA: A Biomarker of Visual Acuity Response to Treatment.

Santos AR, Alves D, Santos T, Figueira J, Silva R, Cunha-Vaz JG.

PURPOSE: To evaluate the effects of anti-vascular endothelial growth factor treatment on retinal fluid in patients with diabetic macular edema by using optical coherence tomography leakage (OCT-L), a new method of quantifying sites of lower than normal optical reflectivity (LOR) in OCT, and to correlate these findings with best-corrected visual acuity (BCVA) response.

METHODS: Prospective analysis of 21 eyes with diabetic macular edema, naive to anti-vascular endothelial growth factor treatment. Macular cube 512 × 128 and OCT angiography 6 × 6-mm scans (CIRRUS AngioPlex; ZEISS, Dublin, CA) were acquired in all eyes before the first ranibizumab injection (V1) and 1 week after treatment (V2). Optical coherence tomography leakage analysis was performed with Angioplex raw scan data used to calculate LOR map ratios. Lower optical reflectivity ratios at baseline and differences from V1 to V2 and other OCT morphological features such as central retinal thickness measurements, disorganization of the inner retinal layers, and disruption of ellipsoid zone were compared with BCVA response 1 month after the first intravitreal injection.

RESULTS: After the first intravitreal injection of ranibizumab, eight patients (38%) were identified as good responders, 5 (24%) as moderate, and 8 (38%) as poor. There were no significant BCVA differences at baseline. Significant differences were found in LOR ratio changes between the different treatment response groups after 1 week of treatment, especially in outer segment and outer plexiform layer (outer segment-good responders: -53%, responders: -12%, and poor responders: 7% [P = 0.026]; outer plexiform layer-good responders: -49%, responders: 18%, and poor responders: 5% [P = 0.010]). Lower optical reflectivity ratios differences after 1 week of treatment predict better the BCVA treatment response at 1 month than changes of central retinal thickness, disorganization of the inner retinal layer, and ellipsoid zone disruption, especially in the outer segment and outer plexiform layer (area under the curve = 0.82 and 0.73, respectively).

CONCLUSION: Optical coherence tomography leakage changes after anti-vascular endothelial growth factor treatment of diabetic macular edema, identifying the degree of decrease in retinal fluid in the outer layers of the retina is a more robust biomarker of BCVA recovery than central retinal thickness,
Sensitivity and Specificity of OCT Angiography to Detect Choroidal Neovascularization.

PURPOSE: To determine the sensitivity and specificity of optical coherence tomography angiography (OCTA) in the detection of choroidal neovascularization (CNV) in age-related macular degeneration (AMD).

DESIGN: Prospective case series.

SUBJECTS: Prospective series of seventy-two eyes were studied, which included eyes with treatment-naive CNV due to AMD, non-neovascular AMD, and normal controls.

METHODS: All eyes underwent OCTA with a spectral domain (SD) OCT (Optovue, Inc.). The 3D angiogram was segmented into separate en face views including the inner retinal angiogram, outer retinal angiogram, and choriocapillaris angiogram. Detection of abnormal flow in the outer retina served as candidate CNV with OCTA. Masked graders reviewed structural OCT alone, en face OCTA alone, and en face OCTA combined with cross-sectional OCTA for the presence of CNV.

MAIN OUTCOME MEASURE: The sensitivity and specificity of CNV detection compared to the gold standard of fluorescein angiography (FA) and OCT was determined for structural SD-OCT alone, en face OCTA alone, and with en face OCTA combined with cross-sectional OCTA.

RESULTS: Of 32 eyes with CNV, both graders identified 26 true positives with en face OCTA alone, resulting in a sensitivity of 81.3%. Four of the 6 false negatives had large subretinal hemorrhage (SRH) and sensitivity improved to 94% for both graders if eyes with SRH were excluded. The addition of cross-sectional OCTA along with en face OCTA improved the sensitivity to 100% for both graders. Structural OCT alone also had a sensitivity of 100%. The specificity of en face OCTA alone was 92.5% for grader A and 97.5% for grader B. The specificity of structural OCT alone was 97.5% for grader A and 85% for grader B. Cross-sectional OCTA combined with en face OCTA had a specificity of 97.5% for grader A and 100% for grader B.

CONCLUSIONS: Sensitivity and specificity for CNV detection with en face OCTA combined with cross-sectional OCTA approaches that of the gold standard of FA with OCT, and it is better than en face OCTA alone. Structural OCT alone has excellent sensitivity for CNV detection. False positives from structural OCT can be mitigated with the addition of flow information with OCTA.

PMID: 29057386 PMCID: PMC5648075 [Available on 2018-07-01]
features of CNVs presenting as the first sign of IOTB initially misdiagnosed as exudative age-related macular degeneration (AMD).

METHODS: A retrospective review of clinical and imaging data of patients initially misdiagnosed with neovascular AMD later diagnosed with inflammatory CNV secondary to IOTB at tertiary referral centers was conducted. Features of fundus photography, fluorescein angiography, indocyanine green angiography, and enhanced depth imaging optical coherence tomography were analyzed. Distinguishing features between neovascular AMD and IOTB-associated CNV were evaluated.

RESULTS: Five patients over 55 years of age, erroneously diagnosed with exudative AMD, were included in the study. Multimodal imaging analysis allowed identification of peculiar choroidal alterations such as choroidal granulomas or choroiditis suggestive for posterior uveitis. Systemic workup for granulomatous uveitis including immunologic investigations such as tuberculin skin test or QuantiFERON TB Gold® and radiologic investigations revealed tubercular etiology in all the cases, allowing correct diagnosis and management of the uveitis and related CNV.

CONCLUSIONS: Choroidal neovascularization represents a rare and unusual presenting sign of IOTB that can be misleading especially when it occurs in the elderly living in countries with low prevalence of the disease. Multimodal imaging can be helpful and should be employed, especially in atypical cases of CNV, in order to avoid misdiagnosis and/or diagnostic delays.

PMID: 29077184

Macromol Biosci. 2017 Oct 27. [Epub ahead of print]

A Novel 3D Cultured Model for Studying Early Changes in Age-Related Macular Degeneration.

Shokoohmand A, Jeon JE, Theodoropoulos C, Baldwin JG, Hutmacher DW, Feigl B.

Abstract: Various in vitro culture systems have been used to investigate the pathogenesis of age-related macular degeneration (AMD). However, many still rely on oversimplified monolayer culture models. AMD is a complex disease, associated with the pathological changes to multiple structural components such as the Bruch's membrane, retinal pigment epithelium (RPE), and choroidal endothelial cells. This study aims to construct a novel 3D coculture model using the polycaprolactone (PCL)-gelatin electrospun scaffold, with human RPE cells (hRPE) and primate choroidal cells (RF-6A). Results from this study show that PCL-gelatin scaffolds have a highly porous ultrastructure that supports the attachment, proliferation, differentiation, and migration of the hRPEs and choroidal endothelial cells. It is also demonstrated that the PCL-gelatin 3D coculture model may be useful in exploring the molecular interplay between the hPRE and the choroidal endothelial cells, and their effects on growth factor modulation, which may be important in the pathogenesis of AMD.

PMID: 29076662


The Nine-Step Minnesota Grading System for Eyebank Eyes With Age Related Macular Degeneration: A Systematic Approach to Study Disease Stages.

Olsen TW, Liao A, Robinson HS, Palejwala NV, Sprehe N.

PURPOSE: To refine the Minnesota Grading System (MGS) using definitions from the Age-Related Eye Disease Studies (AREDS) into a nine-step grading scale (MGS-9).

METHODS: A nine-step grading scale descriptive analysis using three key phenotypic features (total drusen area, increased, and decreased pigmentation) of human eyebank eyes that were graded according
to definitions from the AREDS criteria in order to harmonize studies of disease progression for research involving human tissue. From 2005 through February 2017, we have analyzed 1159 human eyes, procured from two eye banks. Each macula was imaged using high-resolution, stereoscopic color fundus photography with both direct- and transillumination. Fundus images were digitally overlaid with a grading template and triangulated for foveal centration.

RESULTS: We documented and stratified risk for each globe by applying the AREDS nine-step grading scale to the key clinical features from the MGS-9. We found a good distribution within the MGS categories (1-9) with few level eight globes. Eyes were processed within 12.1 ± 6.3, hours from the time of death through imaging, dissection, and freezing or fixation. Applying the MGS-9 to 331 pairs (662 eyes were simultaneously graded), 84% were within one-grading step and 93% within two steps of the fellow eye. We also document reticular pseudodrusen, basal laminar drusen, and pattern dystrophy.

CONCLUSIONS: The MGS nine-step grading scale enables researchers using human tissue to refine the risk assessment of donor tissue. This analysis will harmonize results among researchers when grading human tissue using MGS criteria. Most importantly, the MGS-9 links directly to the known risk for progression from the AREDS.

PMID: 29075760


The Expanded Spectrum of Perifoveal Exudative Vascular Anomalous Complex.

Sacconi R, Freund KB, Yannuzzi LA, Et al

PURPOSE: To expand our understanding of the uncommon entity, referred to as perifoveal exudative vascular anomalous complex (PEVAC) by describing multimodal imaging findings, including optical coherence tomography-angiography (OCT-A).

DESIGN: Retrospective cohort study.

METHODS: Patients diagnosed with PEVAC were identified at 4 retina referral centers worldwide and underwent complete ophthalmologic examination including structural OCT, OCT-A, fluorescein angiography (FA) and indocyanine green angiography (ICGA). Demographics and clinical findings were analyzed at baseline and at available follow-ups.

RESULTS: Fifteen eyes (15 patients, mean age 73±13 years) were included. 6/15 eyes were diagnosed with coincident age-related macular degeneration (AMD) and 2 with myopic macular degeneration. On fundus examination PEVAC presented as a large perifoveal isolated aneurysm, unifocal in 12/15 eyes, associated with small retinal hemorrhages and intraretinal exudation. On structural OCT, PEVAC appeared as a round hyperreflective lesion with hyporeflective lumen, typically surrounded by intraretinal cystic spaces. Dye angiography demonstrated a well-defined hyperfluorescent lesion with variable leakage on FA and without leakage on ICGA. OCT-A showed flow signal correlating with the aneurysmal lesion connecting to retinal capillary plexuses. Seven patients were followed for 13.0±10.5 months with no evidence of functional/anatomical changes. Three patients underwent anti-vascular endothelial growth factor (VEGF) intravitreal injections without improvement. Two eyes were associated with a type 3 neovascularization eccentric to PEVAC.

CONCLUSIONS: PEVAC is an isolated, perifoveal, aneurysmal abnormality, occurring in otherwise healthy patients who may manifest other macular disease including AMD and myopic macular degeneration. PEVAC did not typically respond to anti-VEGF therapy, and may be associated with type 3 neovascularization.

PMID: 29079450
Epiretinal membrane in a subject after transvitreal delivery of palucorcel (CNTO 2476).


BACKGROUND: A 70-year-old woman with retinitis pigmentosa experienced an epiretinal membrane (ERM) formation and a tractional retinal detachment (RD) following subretinal administration of palucorcel (CNTO 2476), a novel human umbilical tissue-derived cell-based therapy, as part of a Phase I study. The clinical course and results of a histologic examination of the ERM, which was peeled during surgery to repair the RD, are described here.

METHODS: In this open-label, first-in-human, Phase I study (NCT00458575), two of seven subjects developed RD, with an ERM formation reported in a woman receiving a targeted dose of $3.0 \times 10^5$ palucorcel administered via a transvitreal route. A sample of the ERM was retained for analysis following the ERM peeling procedure. Clinical outcomes and ERM histology, based on immunocytochemistry analyses and fluorescence in situ hybridization (FISH) staining, were evaluated.

RESULTS: We first noted the RD and formation of the ERM at 26 days after palucorcel administration. The ERM was cellular and contained multiple cell types, including Müller glial cells, immune cells, neurites, retinal pigment epithelial cells, and palucorcel. The majority of cells were not actively dividing. FISH staining showed a subset of Y chromosome-positive cells in the ERM from this woman, supporting the presence of palucorcel (derived from umbilical cord tissue of male neonate). Palucorcel did not differentiate into Müller glia, immune cells, neurites, or retinal pigment epithelial cells.

DISCUSSION: The development of an ERM containing both subject (self) cells and palucorcel suggests that palucorcel egress in the vitreal cavity after retinotomy may contribute to ERM formation and RD and that an alternative delivery method will be required before further studies are conducted. Subsequent clinical research using alternative subretinal delivery methods for palucorcel in other indications suggests that membrane development does not occur when palucorcel is delivered without retinal perforation.

PMID: 29070939 PMCID: PMC5640410


PURPOSE: To describe causes, visual outcomes, and prognostic factors in patients with submacular hemorrhage (SMH).

DESIGN: Retrospective case review.

METHODS: We performed a retrospective review of SMH with a size of at least 1 disc diameter. SMH causes were classified into 3 groups: 1) neovascular age-related macular degeneration (nAMD), 2) polypoidal choroidal vasculopathy (PCV), and 3) other miscellaneous causes.

RESULTS: Ninety-eight eyes of 98 patients were included. Based on clinical presentation and indocyanine green angiography (ICGA), the diagnoses of PCV (59%), nAMD (31%), and miscellaneous other causes (10%) were made. PCV patients were younger ($P = 0.005$) and had larger SMH size than nAMD patients ($P = 0.008$). Poor visual outcome ($>1.0 \text{logMAR}$) at 6 months was associated with low initial visual acuity (VA; $>1.0 \logMAR$; $P = 0.002$) and with the diagnosis of nAMD ($P = 0.02$). In addition, limited visual outcomes were noted for patients older than 65 years and those with persistent SMH for at least 2 months.
CONCLUSIONS: PCV was the most common cause of SMH in Thailand. ICGA represented a valuable tool for the diagnosis. Visual outcomes were limited for patients with nAMD and for patients who presented with poor initial VA.

PMID: 29063740

Ophthalmic Res. 2017 Oct 25. [Epub ahead of print]

Multimodal Evaluation of the Fellow Eye of Patients with Retinal Angiomatous Proliferation.


INTRODUCTION: We conducted a multimodal, cross-sectional evaluation.

METHODS: Eyes were divided into 4 study groups: controls, early/intermediate age-related macular degeneration (AMD), fellow eyes of retinal angiomatous proliferation (RAP), and RAP eyes. Patients were evaluated with spectral-domain optical coherence tomography (OCT), enhanced depth imaging-OCT, and OCT angiography (OCTA). OCTA images were processed to generate maps of the vessel density and perfusion density of the superficial and deep retinal layers (SRL and DRL) and the choriocapillaris level (CL). The thickness of the outer nuclear layer and choroid was manually assessed.

RESULTS: We included 135 eyes of 100 patients (51 controls, 30 AMD, 42 RAP, and 12 fellow eyes). The fellow eyes showed a significantly lower vascular perfusion of the SRL, DRL, and CL (p < 0.02) than the early/intermediate AMD and control eyes did. Similarly, RAP eyes presented a lower vascular perfusion of the DRL and CL (p < 0.05). Besides, structural analyses of the fellow eyes and RAP eyes revealed a significantly higher prevalence of macular pigmentary changes, atrophy of the retinal pigment epithelium, hyperreflective "clumps" above flat drusen, amongst others, than early/intermediate AMD and control eyes (p < 0.05).

CONCLUSION: We present the first report on the OCTA analysis of the fellow eye of patients with RAP. The reduced perfusion density and vessel density observed contributes, in association with clearly defined structural changes, to a wider characterization of RAP as a distinctive phenotype.

PMID: 29065425

Retina. 2017 Oct 20. [Epub ahead of print]

RESIDUAL CHOROIDAL VESSELS IN ATROPHY CAN MASQUERADE AS CHOROIDAL NEOVASCULARIZATION ON OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY: Introducing a Clinical and Software Approach.

Nesper PL, Lutty GA, Fawzi AA.

PURPOSE: To present a postprocessing approach in optical coherence tomography angiography (OCTA) to facilitate the visualization and interpretation of lesions in age-related macular degeneration with coexisting atrophy and choroidal neovascularization (CNV).

METHODS: This retrospective study included 32 eyes of 26 patients with atrophy and treated CNV and 8 eyes with treatment-naive geographic atrophy. En face optical coherence tomography slabs highlighting atrophy were pseudocolored and merged with the corresponding OCTA. Cross-sectional optical coherence tomography and postprocessed OCTA were analyzed to identify CNV and normal choroidal vessels in relationship to the atrophy. We correlate the OCTA findings with those in a donor eye with treatment-naive geographic atrophy studied with transmission electronic microscopy.
RESULTS: Medium-sized choroidal vessels were displaced anteriorly in areas of atrophy in all 40 eyes (100%), visualized in the choriocapillaris slab in all eyes, and in the outer retinal slab in 30 of 40 eyes (75.0%). Cross-sectional OCTA was used to confirm the presence of CNV. Postprocessing successfully highlighted the CNV and distinguished it from choroidal vessels in atrophy. Donor eye transmission electronic microscopy confirmed the anterior displacement of medium-sized choroidal vessels in geographic atrophy.

CONCLUSION: The anterior displacement of larger choroidal vessels in atrophy requires clinician vigilance to avoid misinterpreting these vessels as CNV on en face OCTA. Our proposed postprocessing approach offers a potential solution to facilitate the interpretation of en face OCTA in these cases. In the absence of other tools, clinicians are encouraged to rely on the location of flow relative to Bruch membrane on cross-sectional OCTA flow images.

PMID: 29059100

Ophthalmologe. 2017 Oct 20. [Epub ahead of print]

[Volumetric analysis of vascularized pigment epithelium detachment in AMD: post hoc analysis of the RECOVER study]. [Article in German]


BACKGROUND: The ratio of choroidal neovascularization (CNV) and pigment epithelium detachment (PED) represents an important parameter regarding the risk of developing a tear of the retinal pigment epithelium (RPE) in patients with vascularized PED due to age-related macular degeneration (AMD).

METHODS: Within the framework of the RECOVER study a total of 29 treatment-naive patients with vascularized PED underwent fluorescein angiography (FA), indocyanine green angiography (ICGA) and optical coherence tomography (OCT) volume scans. The CNV-PED ratio was evaluated retrospectively by two independent graders in three ways: 1) manually based on the en face image of the FA late phase and 2) manually based on the en face image of the ICGA late phase. 3) In every OCT scan encompassing the PED, the area between the RPE and Bruch's membrane and the CNV area was measured and multiplied by the distance between OCT scans in order to determine volumetric data of CNV, PED and the serous cavity.

RESULTS: The FA and ICGA showed a mean serous area of 6.14 ± 4.21 mm² (ICGA 5.94 ± 4.13 mm²), a mean CNV area of 3.25 ± 1.79 mm² (ICGA 2.84 ± 1.68 mm²) and a mean PED area of 9.39 ± 4.27 mm² (ICGA 8.79 ± 4.23 mm²) resulting in a mean two-dimensional morphological ratio of 0.35 ± 0.21 (ICGA 0.32 ± 0.22). The volumetric measurement revealed a mean CNV volume of 0.63 ± 0.67 mm³, a mean serous volume of 3.61 ± 3.83 mm³ and a mean total PED volume of 4.25 ± 3.68 mm³. The mean three-dimensional morphological ratio was 0.15 ± 0.29. The difference between the two-dimensional ratios of FA (p < 0.0001) and ICGA (p = 0.0004) was significant compared to the three-dimensional OCT ratio.

CONCLUSION: Assessment of the CNV-PED ratio using volumetric OCT measurements is an additional tool to the en face modalities FA and ICGA. This seems to be clinically relevant regarding the risk stratification of RPE tear development in PED patients and for the planning of the treatment regimen.

PMID: 29058071


A Comparison of En Face Optical Coherence Tomography and Fundus Autofluorescence in Stargardt Disease.

PURPOSE: To compare morphologic changes on en face images derived from wide-field swept-source optical coherence tomography (ssOCT) to hypo- and hyperautofluorescent (hypoAF, hyperAF) areas on short-wavelength autofluorescence (SW-AF), and near-infrared (NIR)-AF in recessive Stargardt disease (STGD1).

METHODS: Wide-field ssOCT cube scans were obtained from 16 patients (16 eyes). Averaged B-scans and SW-AF images were obtained using Spectralis HRA+OCT. NIR-AF images were obtained from 6 eyes. The inner/outer segment (IS/OS), OS/RPE, and RPE/Bruch's membrane boundaries were segmented, and en face slab images generated. A subRPE slab image was used to measure the abnormal RPE area, and an IS/OS slab image, the IS/OS junction loss area. These were compared to hypo- and abnormal SW-AF areas, and hypoNIR-AF areas. A preRPE(OS) slab image was used to evaluate the spatial and intraretinal locations of flecks.

RESULTS: For all eyes, RPE atrophy was visualized as a central hyperreflective area on the subRPE slab, and IS/OS junction loss as an abnormal reflective area on the IS/OS slab; the latter was significantly larger (P = 0.04). There was good agreement between the hyperreflective area on the subRPE slab image and hypoSW-AF area, and between the abnormal reflective area on the IS/OS slab and hypo-hyperSW-AF area; the hypoNIR-AF area indicated that the hyperreflective area on the subRPE slab underestimated RPE atrophy. The spatial locations of hyperreflective flecks on the en face preRPE(OS) slab image corresponded to those on the SW-AF images.

CONCLUSIONS: Wide-field en face OCT imaging has the potential to be a clinically useful tool for the management of STGD1.

PMID: 29049723 PMCID: PMC5642378


Automated Age-related Macular Degeneration screening system using fundus images.
Kunumpol P, Umpaipant W, Kanchanaranya N, Charoenpong T, Vongkittirux S, Kupakanjana T, Tantibundhit C.

Abstract: This work proposed an automated screening system for Age-related Macular Degeneration (AMD), and distinguishing between wet or dry types of AMD using fundus images to assist ophthalmologists in eye disease screening and management. The algorithm employs contrast-limited adaptive histogram equalization (CLAHE) in image enhancement. Subsequently, discrete wavelet transform (DWT) and locality sensitivity discrimination analysis (LSDA) were used to extract features for a neural network model to classify the results. The results showed that the proposed algorithm was able to distinguish between normal eyes, dry AMD, or wet AMD with 98.63% sensitivity, 99.15% specificity, and 98.94% accuracy, suggesting promising potential as a medical support system for faster eye disease screening at lower costs.

PMID: 29060156


Fully-automated segmentation of fluid regions in exudative age-related macular degeneration subjects: Kernel graph cut in neutrosophic domain.
Rashno A, Nazari B, Koozekanani DD, Drayna PM, Sadri S, Rabbani H, Parhi KK.

Abstract: A fully-automated method based on graph shortest path, graph cut and neutrosophic (NS) sets is
presented for fluid segmentation in OCT volumes for exudative age related macular degeneration (EAMD) subjects. The proposed method includes three main steps: 1) The inner limiting membrane (ILM) and the retinal pigment epithelium (RPE) layers are segmented using proposed methods based on graph shortest path in NS domain. A flattened RPE boundary is calculated such that all three types of fluid regions, intra-retinal, sub-retinal and sub-RPE, are located above it. 2) Seed points for fluid (object) and tissue (background) are initialized for graph cut by the proposed automated method. 3) A new cost function is proposed in kernel space, and is minimized with max-flow/min-cut algorithms, leading to a binary segmentation. Important properties of the proposed steps are proven and quantitative performance of each step is analyzed separately. The proposed method is evaluated using a publicly available dataset referred as Optima and a local dataset from the UMN clinic. For fluid segmentation in 2D individual slices, the proposed method outperforms the previously proposed methods by 18%, 21% with respect to the dice coefficient and sensitivity, respectively, on the Optima dataset, and by 16%, 11% and 12% with respect to the dice coefficient, sensitivity and precision, respectively, on the local UMN dataset. Finally, for 3D fluid volume segmentation, the proposed method achieves true positive rate (TPR) and false positive rate (FPR) of 90% and 0.74%, respectively, with a correlation of 95% between automated and expert manual segmentations using linear regression analysis.

PMID: 29059257


Injectable hydrogels for ophthalmic applications.

Wang K, Han Z.

Abstract: The demand for effective eye therapies is driving the development of injectable hydrogels as new medical devices for controlled delivery and filling purposes. This article introduces the properties of injectable hydrogels and summarizes their versatile application in the treatment of ophthalmic diseases, including age-related macular degeneration, cataracts, diabetic retinopathy, glaucoma, and intraocular cancers. A number of injectable hydrogels are approved by FDA as surgery sealants, tissue adhesives, and are now being investigated as a vitreous humor substitute. Research on hydrogels for drug, factor, nanoparticle, and stem cell delivery is still under pre-clinical investigation or in clinical trials. Although substantial progress has been achieved using injectable hydrogels, some challenging issues must still be overcome before they can be effectively used in medical practice.

PMID: 29061512


A targeted drug delivery platform for assisting retinal surgeons for treating Age-related Macular Degeneration (AMD).

Nasseri MA, Maier M, Lohmann CP.

Abstract: In this paper we present our latest robotic setup, which has been modified for sub-retinal interventions. The setup consists of: 1) sub-retinal micro cannula with automatic pump; 2) Micromanipulator; 3) patient fixation mechanism and 4) clinically compatible workstation. The primary objective of this work is to allow ophthalmologists to improve administration of substances such as drugs, stem-cells and gene cargos to their desired targets in the sub-retinal microstructures. Such a delivery method will enable effective treatment of Age-related Macular Degeneration (AMD). AMD is the leading cause of blindness in developed countries and as yet there is no efficient treatment. To validate the precision of the system a successful targeted delivery scenario with the proposed setup and using an intra-operative OCT integrated microscope in a clinical environment is presented in this paper.

PMID: 29060856

Reply to a letter to the editor: inner nuclear layer cystoid spaces are a poor prognostic factor in typical age-related macular degeneration and polypoidal choroidal vasculopathy.

Kang EC, Choi S, Koh HJ.
PMID: 29067530


Inner nuclear layer cystoid spaces are a poor prognostic factor in typical age-related macular degeneration and polypoidal choroidal vasculopathy.

Călugăru D, Călugăru M.
PMID: 29075861

Pathogenesis


PDGF-C and PDGF-D in ocular diseases.

Kumar A, Li X.

Abstract: PDGFs and their receptors are critical regulators of numerous tissues and organs, including the eye. Extensive studies have shown that PDGFs and their receptors play critical roles in many ocular neovascular diseases, such as neovascular age-related macular degeneration, retinopathy of prematurity, and proliferative vitreoretinopathy. In addition, PDGFs and PDGFRs are also important players in ocular diseases involving the degeneration of retinal neuronal and vascular cells, such as glaucoma and retinitis pigmentosa. Due to their critical roles in the pathogenesis of many blinding ocular diseases, the PDGFs and PDGFRs have been considered as important target molecules for the treatment of eye diseases. PDGF-C and PDGF-D are relatively new members of the PDGF family and are potent angiogenic and survival factors. Recent studies have demonstrated their important roles in different types of eye diseases. Thus, modulating PDGF-C and PDGF-D activities may have therapeutic values for the treatment of ocular neovascular and degenerative diseases. This review mainly summarizes the recent advances on PDGF-C and PDGF-D biology in relationship to some major ocular diseases.
PMID: 29079201


Network-mediated responses of ON ganglion cells to electric stimulation become less consistent across trials during retinal degeneration.

Jae-Ik Lee, Fried SI, Maesoon Im.

Abstract: Microelectronic retinal prostheses are being developed to restore sight in individuals blinded by outer retinal degenerative diseases such as retinitis pigmentosa and age-related macular degeneration. Unfortunately, the quality of vision restored by these devices is still limited. To improve the quality of elicited vision, our group studies the responses of retinal neurons to electric stimulation. Our previous work showed that responses mediated through the retinal network are reproducible with high temporal precision, even for spikes that occur >100 ms after stimulus onset. Because they arise through the network, it is important to
understand whether such reliability changes in the degenerate retina. Here, we examined response variability at several different stages of degeneration: postnatal day 14 (P14), P18, P31 and P60 in a well-established mouse model of degeneration (rd10). Spiking responses of ON alpha RGCs were recorded multiple times to an identical electric stimulus. We found that the trial-to-trial variability increased over the course of retinal degeneration. This finding may help to explain the reported variability in the quality of elicited vision across subjects using these devices.

PMID: 29060314


Saposin B Binds the Lipofuscin Bisretinoid A2E and Prevents its Enzymatic and Photooxidation.

Tinklepaugh J, Smith BM, Nie Y, Moody K, Grohn K, Bou-Abdallah F, Doyle RP.

Abstract: Vitamin A based bisretinoid accumulation is a major focus in the study of macular degeneration. Whether specific endogenous lysosomal proteins can bind A2E, a pronounced bisretinoid in lipofuscin granules in retinal pigment epithelial cells, and interfere with enzymatic or photoinduced oxidation of such, has not been explored. Herein, using fluorescence and electronic absorption spectroscopy and mass spectrometry, we demonstrate that Saposin B, a critical protein in the degradation of sulfatides and "flushing" of lipids, can bind A2E, preventing its H2O2-dependent enzymatic oxidation by horseradish peroxidase and photooxidation by blue light (λ=450-460 nm).

PMID: 29057298 PMCID: PMC5646234 [Available on 2018-03-01]


Development of copolymeric nanoparticles of hypocrellin B: Enhanced phototoxic effect and ocular distribution.


Abstract: In the present work, we have developed a photosensitizer hypocrellin B (HB) and nano silver loaded PLGA-TPGS nanoparticles with improved singlet oxygen production for enhanced photodynamic effect for the efficient treatment of age related macular degeneration. Random copolymer (PLGA-TPGS) synthesized by ring opening and bulk polymerization was characterized by IR, 1H NMR and TGA analysis. HBS-CP-NPs prepared by nanoprecipitation techniques were spherical shaped 89.6-753.6nm size particles with negative zeta potential. The average encapsulation efficiency was 84.06±11.43% and HB release from the HBS-CP-NPs was found to be biphasic with a slow release of 1.41% in the first 8h and 48.91% during 3days as measured by RP-HPLC. DSC thermograms indicate that HB was dispersed as amorphous form in HBS-CP-NPs. The ROS generation level of HBS-CP-NPs was significantly higher than that of HB/HB-CP-NPs. The production of 1O2 of HBS-CP-NPs has been assessed using EPR spectrometer. The 1O2 generating efficiency follows the order of nano silver>HB-CP-NPs>HBS-CP-NPs>pure HB drug solution. The superior phototoxic effect of HBS-CP-NPs (85.5% at 50μM) was attained at 2h irradiation in A549 cells. Significant anti angiogenic effect of HBS-CP-NPs was observed in treated CAM embryos. Following intravenous injection of HBS-CP-NPs to rabbits, the maximum amount of HB was found in retina (3h), iris (9h), aqueous humour (9h) and vitreous humour (9h).

PMID: 29055734
Epidemiology

Retina. 2017 Oct 20. [Epub ahead of print]

PREVALENCE OF POLYPOIDAL CHOROIDAL VASCULOPATHY IN WHITE PATIENTS WITH EXUDATIVE AGE-RELATED MACULAR DEGENERATION: Systematic Review and Meta-Analysis.

Lorentzen TD, Subhi Y, Sørensen TL.

PURPOSE: Polypoidal choroidal vasculopathy (PCV) is a disease with significant inter-ethnic differences. In this study, we systematically review the literature on the prevalence of PCV in whites referred with a diagnosis of exudative age-related macular degeneration (AMD).

METHODS: We searched PubMed, Embase, the Cochrane Library, and the Web of Science on 24 March, 2017 for studies evaluating the prevalence of PCV in white patients with exudative AMD. Data extraction and risk of bias assessments were performed in duplicate. Studies were included for a qualitative review and a meta-analysis, including subgroup analysis for differences in age and sex.

RESULTS: We included data from 11 studies (>2,200 participants). For diagnosis, indocyanine green angiography was used together with a set of supporting criteria on fundus examination and optical coherence tomography. Extramacular location was more prevalent in eyes with PCV. Drusen was present in the fellow eye in 17% to 27%. Pooled prevalence of PCV in white patients with exudative AMD was 8.7% (confidence interval 95%: 7.2%-10.3%). Patients with PCV were 3.7 years (confidence interval 95%: 2.1 years-5.3 years) younger than those with other exudative AMD. Sex did not differ significantly.

CONCLUSION: Polypoidal choroidal vasculopathy is not a rare subtype of exudative AMD in whites—it is present in approximately one in 11 patients.

PMID: 29059101


CD11b and CD200 on Circulating Monocytes Differentiate Two Angiographic Subtypes of Polypoidal Choroidal Vasculopathy.


PURPOSE: To investigate surface expression of CD11b and CD200 on circulating monocytes in patients with polypoidal choroidal vasculopathy (PCV).

METHODS: This was a prospective case-control study of patients with PCV (n = 27), age-matched healthy controls (n = 27), and patients with neovascular AMD (n = 49). All participants underwent a comprehensive ocular examination. Fluorescein and indocyanine green angiography were performed in patients suspected of neovascular AMD or PCV. Polypoidal choroidal vasculopathy was angiographically categorized into those with a strong presence of a branching vascular network (BVN) (type 1) or with a faint/no clear presence of a BVN (type 2). Fresh venous blood was stained with fluorescent antibodies for flow cytometric analyses. We compared the percentages of CD11b+, CD200+, and CD11b+CD200+ monocytes between groups of diagnosis and between different angiographic subtypes of PCV.

RESULTS: Overall, CD11b+ monocytes were both increased in patients with PCV and neovascular AMD. CD200+ and CD11b+CD200+ monocytes were increased in patients with neovascular AMD. An age-related increase in CD11b+CD200+ monocytes was absent in patients with PCV and neovascular AMD. Patients with PCV type 1 had significantly higher CD11b+, CD200+, and CD11b+CD200+ monocytes, whereas patients with PCV type 2 had levels similar to that in healthy controls.

CONCLUSIONS: We found that PCV is immunologically heterogeneous with significant differences
between angiographic subtypes. Increased CD11b+ and CD200+ monocytes in those with a strong
presence of BVN indicate that BVN development may be associated with retinal injury and a VEGF-
mediated process that is either reflected or propelled by systemic changes in monocytes.

PMID: 29049725

Genetics & gene therapy

Dec.

Data analysis in the post-genome-wide association study era.

Wang QL, Tan WL, Zhao YJ, Shao MM, Chu JH, Huang XD, Li J, Luo YY, Peng LN, Cui QH, Feng T, Yang
J, Han YL.

Abstract: Since the first report of a genome-wide association study (GWAS) on human age-related macular
degeneration, GWAS has successfully been used to discover genetic variants for a variety of complex
human diseases and/or traits, and thousands of associated loci have been identified. However, the
underlying mechanisms for these loci remain largely unknown. To make these GWAS findings more useful,
it is necessary to perform in-depth data mining. The data analysis in the post-GWAS era will include the
following aspects: fine-mapping of susceptibility regions to identify susceptibility genes for elucidating the
biological mechanism of action; joint analysis of susceptibility genes in different diseases; integration of
GWAS, transcriptome, and epigenetic data to analyze expression and methylation quantitative trait loci at
the whole-genome level, and find single-nucleotide polymorphisms that influence gene expression and
DNA methylation; genome-wide association analysis of disease-related DNA copy number variations.
Applying these strategies and methods will serve to strengthen GWAS data to enhance the utility and
significance of GWAS in improving understanding of the genetics of complex diseases or traits and
translate these findings for clinical applications.

PMID: 29063047 PMCID: PMC5643765

Stem cells


Evaluating role of bone marrow-derived stem cells in dry age-related macular degeneration using
multifocal electroretinogram and fundus autofluorescence imaging.

Kumar A, Midha N, Mohanty S, Chohan A, Seth T, Gogia V, Gupta S.

AIM: To evaluate the role of bone marrow-derived stem cells in the treatment of advanced dry age-related
macular degeneration (AMD) using multifocal electroretinogram (mf-ERG) and fundus autofluorescence
imaging.

METHODS: Thirty patients (60 eyes) with bilateral central geographic atrophy (GA) were recruited. Worse
eye of each patient received autologous bone marrow-derived hematopoietic stem cells (BM-HSCs) (group
1) and the fellow eye with better visual acuity served as control (group 2). The effect of stem cell therapy
was determined in terms of visual acuity, amplitude and implicit time in mf-ERG and size of GA on fundus
autofluorescence imaging. These tests were performed at presentation and first, third and sixth month
follow up. Adverse events (if any) were also monitored.

RESULTS: At 6mo follow-up there was no statistically significant improvement in median logMAR best
corrected visual acuity (BCVA) in either group. MF-ERG revealed significant improvement in amplitude and
implicit time in the intervention group. A significant decrease was also noted in greatest linear dimension (GLD) of GA in the eyes receiving stem cells [6.78±2.60 mm at baseline to 6.56±2.59 mm at 6mo (P=0.021)]. However, no such improvement was noted in the control group.

CONCLUSION: Electrophysiological and anatomical improvement in the intervention group sheds light on the therapeutic role of BM-HSCs. Further studies are required to determine the stage of disease at which the maximal benefit can be achieved and to standardize the dose and frequency of stem cell injection.

PMID: 29062775 PMCID: PMC5638977


Nicotinamide, iRPE-in-a dish, and age-related macular degeneration therapy development.

Bergen AA.

Comment on: Nicotinamide Ameliorates Disease Phenotypes in a Human iPSC Model of Age-Related Macular Degeneration. [Cell Stem Cell. 2017]

PMID: 29057253 PMCID: PMC5639030

**Diet, Lifestyle & low vision**


Enhancing the efficacy of AREDS antioxidants in light-induced retinal degeneration.

Wong P, Markey M, Rapp CM, Darrow RM, Ziesel A, Organisciak DT.

PURPOSE: Light-induced photoreceptor cell degeneration and disease progression in age-related macular degeneration (AMD) involve oxidative stress and visual cell loss, which can be prevented, or slowed, by antioxidants. Our goal was to test the protective efficacy of a traditional Age-related Eye Disease Study antioxidant formulation (AREDS) and AREDS combined with non-traditional antioxidants in a preclinical animal model of photooxidative retinal damage.

METHODS: Male Sprague-Dawley rats were reared in a low-intensity (20 lux) or high-intensity (200 lux) cyclic light environment for 6 weeks. Some animals received a daily dietary supplement consisting of a small cracker infused with an AREDS antioxidant mineral mixture, AREDS antioxidants minus zinc, or zinc oxide alone. Other rats received AREDS combined with a detergent extract of the common herb rosemary, AREDS plus carnosic acid, zinc oxide plus rosemary, or rosemary alone. Antioxidant efficacy was determined by measuring retinal DNA levels 2 weeks after 6 h of intense exposure to white light (9,000 lux). Western blotting was used to determine visual cell opsin and arrestin levels following intense light treatment. Rhodopsin regeneration was determined after 1 h of exposure to light. Gene array analysis was used to determine changes in the expression of retinal genes resulting from light rearing environment or from antioxidant supplementation.

RESULTS: Chronic high-intensity cyclic light rearing resulted in lower levels of rod and cone opsins, retinal S-antigen (S-ag), and medium wavelength cone arrestin (mCAR) than found for rats maintained in low cyclic light. However, as determined by retinal DNA, and by residual opsin and arrestin levels, 2 weeks after acute photooxidative damage, visual cell loss was greater in rats reared in low cyclic light. Retinal damage decreased with AREDS plus rosemary, or with zinc oxide plus rosemary whereas AREDS alone and zinc oxide alone (at their daily recommended levels) were both ineffective. One week of supplemental AREDS plus carnosic acid resulted in higher levels of rod and cone cell proteins, and higher levels of retinal DNA than for AREDS alone. Rhodopsin regeneration was unaffected by the rosemary treatment. Retinal gene
array analysis showed reduced expression of medium-wavelength opsin 1 and arrestin C in the high-light reared rats versus the low-light rats. The transition of rats from low cyclic light to a high cyclic light environment resulted in the differential expression of 280 gene markers, enriched for genes related to inflammation, apoptosis, cytokine, innate immune response, and receptors. Rosemary, zinc oxide plus rosemary, and AREDS plus rosemary suppressed 131, 241, and 266 of these genes (respectively) in high-light versus low-light animals and induced a small subset of changes in gene expression that were independent of light rearing conditions.

CONCLUSIONS:

Long-term environmental light intensity is a major determinant of retinal gene and protein expression, and of visual cell survival following acute photooxidative insult. Rats preconditioned by high-light rearing exhibit lower levels of cone opsin mRNA and protein, and lower mCAR protein, than low-light reared animals, but greater retention of retinal DNA and proteins following photooxidative damage. Rosemary enhanced the protective efficacy of AREDS and led to the greatest effect on the retinal genome in animals reared in high environmental light. Chronic administration of rosemary antioxidants may be a useful adjunct to the therapeutic benefit of AREDS in slowing disease progression in AMD.

PMID: 29062223 PMCID: PMC5640517

Retina. 2017 Oct 23. [Epub ahead of print]

PREFERRED RETINAL LOCUS LOCATIONS IN AGE-RELATED MACULAR DEGENERATION.

Erbezci M, Ozturk T.

PURPOSE: An evaluation of the preferred retinal locus (PRL) in patients with age-related macular degeneration and a central scotoma is becoming a standard of care in the practice of low-vision rehabilitation. This is a retrospective study of PRL specifications and whether they have a correlation with the best-corrected visual acuities of patients with age-related macular degeneration.

METHODS: Seventy-two patients with macular degeneration (144 eyes) were included in the study. The PRLs were evaluated monocularly with a scanning laser ophthalmoscope. Each PRL's location, the fovea-PRL distance, the PRL edge of the lesion distance, and PRL stability were measured with the built-in caliper of the ophthalmoscope.

RESULTS: The most frequent location of a PRL was nasal (29.2%). The PRL was located in the left visual field of 34.0% of the patients. The best-corrected visual acuity values were positively correlated with the lesion's vertical and horizontal dimensions, as well as its surface area, the PRL-fovea distance, the PRL border of the lesion distance, and PRL stability.

CONCLUSION: The clinical PRL evaluation methodology that we describe can be used to facilitate making decisions on how to provide best visual rehabilitation to patients with a central scotoma.

PMID: 29065012


SCORE2 Report 5: Vision-Related Function in Patients with Macular Edema Secondary to Central Retinal or Hemiretinal Vein Occlusion.

Scott IU, Figueroa MJ, Oden NL, Ip MS, Blodi BA, VanVeldhuisen PC; SCORE2 Investigator Group.

PURPOSE: To describe baseline vision-related function, measured with the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), in patients with macular edema secondary to central retinal vein
occlusion (CRVO) or hemiretinal vein occlusion (HRVO) in the Study of COMparative Treatments for REtinal Vein Occlusion 2 (SCORE2); evaluate the baseline relationship between NEI-VFQ-25 scores with visual acuity letter score (VALS) and central retinal thickness; and compare baseline NEI-VFQ-25 scores in SCORE2 participants with those in normal vision reference populations and patients in other retinal vein occlusion trials.

DESIGN: Multicenter, non-inferiority randomized controlled trial.

METHODS: SCORE2 was designed to assess whether intravitreal bevacizumab is non-inferior to intravitreal aflibercept for treatment of decreased vision attributable to macular edema due to CRVO or HRVO. SCORE2 enrolled 362 participants, including 305 with CRVO and 57 with HRVO. Analyses were of cross-sectional baseline data. The main outcome measures were baseline NEI-VFQ-25 composite and subscale scores.

RESULTS: SCORE2 participants' baseline NEI-VFQ-25 composite and subscale scores are significantly lower compared with three normal vision reference populations (p<0.01; except for ocular pain score) and similar to patients in other retinal vein occlusion clinical trials. Baseline VALS in the better eye was correlated with baseline NEI-VFQ-25 composite and subscale scores of general vision, near activities, role difficulties, dependency, and color vision, with correlations ranging from 0.19 to 0.26 (p<0.05 for each score).

CONCLUSIONS: CRVO and HRVO patients in SCORE2 had significantly worse baseline patient-reported vision-related function than normal vision populations, despite the disease being primarily unilateral with typically excellent vision in the fellow eye.

PMID: 29074161


Motion-generated optical information allows event perception despite blurry vision in AMD and amblyopic patients.

Pan JS, Li J, Chen Z, Mangiaracina EA, Connell CS, Wu H, Wang XM, Bingham GP, Hassan SE.

Abstract: Events consist of objects in motion. When objects move, their opaque surfaces reflect light and produce both static image structure and dynamic optic flow. The static and dynamic optical information co-specified events. Patients with age-related macular degeneration (AMD) and amblyopia cannot identify static objects because of weakened image structure. However, optic flow is detectable despite blurry vision because visual motion measurement uses low spatial frequencies. When motion ceases, image structure persists and might preserve properties specified by optic flow. We tested whether optic flow and image structure interact to allow event perception with poor static vision. AMD (Experiment 1), amblyopic (Experiments 2 and 3), and normally sighted observers identified common events from either blurry (Experiments 1 and 2) or clear images (Experiment 3), when either single image frames were presented, a sequence of frames was presented with motion masks, or a sequence of frames was presented with detectable motion. Results showed that with static images, but no motion, events were not perceived well by participants other than controls in Experiment 3. However, with detectable motion, events were perceived. Immediately following this and again after five days, participants were able to identify events from the original static images. So, when image structure information is weak, optic flow compensates for it and enables event perception. Furthermore, weakened static image structure information nevertheless preserves information that was once available in optic flow. The combination is powerful and allows events to be perceived accurately and stably despite blurry vision.

PMID: 29067401
Detecting impaired vision caused by AMD from gaze data.

Huiying Liu, Yanwu Xu, Damon Wong, Ai Ping Yow, Laude A, Tock Han Lim.

Abstract: Age Related Macular Degeneration (AMD) is the third leading cause of blindness and the first one in the elderly. AMD usually causes central blindness due to loss of photoreceptor cell. In this paper, we propose to detect AMD caused vision impairment from gaze data. Compared with the current methods, e.g., Amsler grid, Microperimetry and Preferential Hyperacuity Perimetry, to detect vision impairments, the proposed method has several advantages. 1) It does not require the patient to stare at a fixed position throughout the test. 2) It does not require the patient to orally or manually report / mark out the vision impairment. 3) It is easy to operate thus a trained nurse is capable of operating the test. We collect gaze data while the patient is performing fixation and smooth pursuit. Features describing the gaze properties are extracted and SVM with linear kernel is trained to detect AMD impaired vision. To implement the proposed method, we collected gaze data of 74 eyes of 57 patients, who are diagnosed as AMD patient by clinicians. Nidek Microperimetry is adopted as gold standard. 57 eyes with normal vision and 17 eyes with impaired vision (blind at more than half test points in Nidek test) are used for test. The result verifies the effectiveness of detecting vision impairment from gaze data.

PMID: 29060564

Automatic visual impairment detection system for age-related eye diseases through gaze analysis.

Ai Ping Yow, Damon Wong, Huiying Liu, Hongyuan Zhu, Ivy Jing-Wen Ong, Laude A, Tock Han Lim.

Abstract: Visual impairment associated with Age-related Macular Degeneration (AMD) often results in a central scotoma which is an alteration in the central vision, leading to distortion or loss of vision. Current methods for assessing visual performance such as Amsler grid and Microperimetry are typically manual and have limitations as an indicator of visual field. In this paper, we present an automated system for detecting visual impairment through gaze tracking (AVIGA). Two types of assessments namely, Impulse Stimuli Response (ISR) test and Pursuit Stimuli Response (PSR) test were implemented in AVIGA system. A Support Vector Regression (SVR)-based approach is applied on the assessment results to differentiate the severity of visual impairment. The results show that AVIGA system is well-correlated to visual acuity test (VA) and performs better in identifying presence of visual impairments in eyes, compared to Microperimetry.

PMID: 29060394

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