Drug treatment

Eye (Lond). 2017 Jul 21. [Epub ahead of print]

Real-world visual acuity outcomes between ranibizumab and aflibercept in treatment of neovascular AMD in a large US data set.

Lotery A, Griner R, Ferreira A, Milnes F, Dugel P.

Purpose: To examine 12-month real-world visual acuity outcomes and treatment patterns in neovascular age-related macular degeneration (nAMD) eyes, including those with pigment epithelial detachment (PED), receiving ranibizumab or aflibercept.

Patients and methods: Electronic medical records were used to identify ranibizumab or aflibercept-treated nAMD eyes with 12 months follow-up from first prescription. The primary objective was to compare mean change in visual acuity (VA) between index and month 12, in eyes treated with ranibizumab and aflibercept to assess the non-inferiority of ranibizumab vs aflibercept using a -5 letter non-inferiority margin. The number of injections and non-injection visits during follow-up were key secondary objectives.

Results: A total of 3350 ranibizumab and 4300 aflibercept treatment-naive eyes were included. At month 12, mean change from index in VA letter score was -0.30 for ranibizumab and -0.19 for aflibercept (P=0.81). The adjusted difference of mean change was -0.14 (-0.79 to 0.51) (P=0.67) (generalized estimating equations method) confirming the non-inferiority of ranibizumab. Eyes received a similar number of injections during follow-up. The mean (±SD) number of ranibizumab and aflibercept injections were 6.70 (±2.54) and 7.00 (±2.40), respectively (P<0.0001). In PED eyes, the mean (±SD) change between baseline to month 12 was 1.25 (±11.3) for ranibizumab and -0.39 (±13.3) for aflibercept (adjusted between-group difference 1.80 (-0.71 to 4.30; P=0.16)) achieved with a mean (±SD) 7.85 (±2.68) ranibizumab and 7.47 (±2.45) aflibercept injections, (P=0.11).

Conclusions: Ranibizumab and aflibercept treatment yielded comparable VA outcomes in nAMD eyes, including those with PED, with similar treatment patterns over 12 months in real-world clinical practice.

PMID: 28731052


Case report of a secondary macular hole closure after intravitreal bevacizumab therapy in a patient with retinal pigment epithelial detachment.

Storch MW, Hoerauf H.

Abstract: We describe a case of macular hole (MH) closure after intravitreal bevacizumab therapy for an underlying pigment epithelial detachment (PED) due to exudative age-related macular degeneration (AMD). The 73-year-old Caucasian female presented with reduced visual acuity (20/80) of the left eye and
metamorphopsia for approximately 6 months. Spectral domain optical coherence tomography revealed a subfoveal PED due to AMD with an associated MH. To treat the exudative component of the pathology, we started intravitreal bevacizumab therapy, consecutively leading to reduction of the height of PED and allowing closure of the MH. Detachment recurred during further follow-up, but the MH remained closed. MHS and exudative AMD are common diseases, which rarely occur simultaneously. To the best of our knowledge (search via PubMed for “MH,” “PED,” “age-related macular degeneration”), no other case with the persistent closure of an MH associated with PED during intravitreal antivascular endothelial growth factor therapy and despite recurrent PED has been published to date.

PMID: 28724829


Real-world evidence of safety profile of intravitreal bevacizumab (Avastin) in an Indian scenario.

Jain P, Sheth J, Anantharaman G, Gopalakrishnan M.

PURPOSE: The purpose of this study was to evaluate the safety profile of intravitreal bevacizumab (Avastin) as an off-label pharmacotherapeutic agent for various ocular conditions.

METHODS: Retrospective analysis was carried out on 3806 injections of 1761 patients that were administered with intravitreal bevacizumab injection at a tertiary eye care center in India. The injections were administered on a pro re nata basis for various indications such as age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO).

RESULTS: The mean age of the patients was 61.8 ± 11.59 years. A total of 59.2% of the patients were men and 40.8% women. The most common indications for which the injection was administered were DME (27.5%), AMD (26%), and branch RVO (12.3%). Among the ocular side effects, endophthalmitis was seen in three eyes (0.08%), retinal breaks in none of the eyes whereas 35 eyes had a rise in intraocular pressure (IOP) >21 mmHg (0.9%). Preexisting glaucoma was present in four eyes while remaining 31 eyes did not have any history of glaucoma. IOP rise was significantly more in eyes with preexisting glaucoma as compared to nonglaucomatous eyes (P = 0.04). No systemic adverse events were noted in our study population.

CONCLUSION: Our study provides real-world evidence regarding the safety profile of intravitreal bevacizumab (Avastin). These data suggest that bevacizumab is a safe and economical pharmacotherapeutic agent that can be administered for a variety of ocular disorders. Analyzing the safety of bevacizumab is necessary for a developing country like India as the majority of the population cannot afford the costly ranibizumab as compared to bevacizumab for ocular healthcare.

PMID: 28724817


Predictive imaging biomarkers relevant for functional and anatomical outcomes during ranibizumab therapy of diabetic macular edema.

Gerendas BS, Prager S, Deak G, Simader C, Lammer J, Waldstein SM, Guerin T, Kundi M, Schmidt-Erfurth UM.

BACKGROUND/AIMS: The objective is to identify imaging biomarkers in optical coherence tomography predicting functional/anatomical outcomes in diabetic macular edema (DMO).

METHODS: The presented study is a post hoc analysis of the RESTORE/RESTORE-extension studies. Best-corrected visual acuity (BCVA) was analysed using general estimating equation models using treatment group/morphological features as predictor variables. In addition, linear multiple regression models
analysed BCVA gain up to 12 and 36 months with BCVA/morphological baseline characteristics as independent predictor variables. The correlations between central retinal thickness (CRT)/BCVA were calculated as Spearman's/Pearson's correlation coefficients.

RESULTS: A weak negative linear correlation between CRT/BCVA was observed in all study arms at baseline (r=-0.34, p<0.001) and at month 36 (r=-0.26, p<0.001). Patients with baseline height of intraretinal cystoid fluid (IRC) ≤380 µm had better baseline BCVA compared with patients with IRC height >380 µm (64.84±10.63 vs 61.66±9.92 letters; p=0.0071, respectively), which was maintained until the end of month 12 (70.5±12.33 vs 67.0±14.09 letters; p=0.0252, respectively). With laser, there was a trend for patients with subretinal fluid (SRF) at baseline to lose BCVA letters at month 12 (-5.38±16.54 vs 2.49±9.72 letters; p=0.1038), whereas ranibizumab patients trended towards higher BCVA gains (10.28±7.14 vs 6.76±7.67; p=0.0563), compared with those without SRF. With combined therapy, all patients had similar BCVA gains regardless of SRF (p=0.3768).

CONCLUSION: With ranibizumab treatment, the height of IRC spaces at baseline was a better predictor of functional/anatomical improvement than CRT alone. There was also a trend for SRF to show a positive impact on ranibizumab therapy response and a negative impact on laser therapy response.

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PROGRESSION OF MACULAR ATROPHY IN EYES WITH TYPE 1 NEOVASCULARIZATION AND AGE-RELATED MACULAR DEGENERATION RECEIVING LONG-TERM INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY: An Optical Coherence Tomographic Angiography Analysis.

Christenbury JG, Phasukkijwatana N, Gilani F, Freund KB, Sadda S, Sarraf D.

PURPOSE: To evaluate the size and location of macular atrophy in eyes with Type-1 neovascularization (NV) and age-related macular degeneration receiving chronic intravitreal anti-vascular endothelial growth factor therapy.

METHODS: A retrospective review of a case series of 27 eyes with Type-1 NV and retinal pigment epithelial detachment (PED) having a minimum of 12 months follow-up was performed. Demographic information and visual acuity at baseline and the final follow-up were collected. Spectral-domain optical coherence tomography (OCT) and near-infrared reflectance were analyzed at 6-month intervals to detect and measure macular atrophy. Location and area (in square millimeter) of macular atrophy were measured using Heidelberg software tools. Also, OCT angiography was used to colocalize the area of Type-1 NV flow versus the location of atrophy.

RESULTS: Twenty-seven eyes of 27 patients were included in this analysis. The median visual acuity was 20/50, mean age was 82.7 years, and mean number of injections was 29.5. A larger percentage of eyes (59.3%) developed atrophy predominantly eccentric to the PED versus predominantly overlying the PED (11.1%) when measured with spectral-domain OCT and near-infrared imaging. At the final follow-up, there was a larger area of atrophy surrounding the fibrovascular PED (mean, 3.326 mm) than overlying it (mean, 0.542 mm), and this was statistically significant (P = 0.0118). En-face OCT images were overlaid with OCT angiography in 11 eyes, and a predominantly eccentric pattern of atrophy was identified in 9 of 11 eyes. Using this method, the mean area of atrophy predominantly overlying the Type-1 NV was 1.652 mm (range of 0-10.464 mm), whereas the area of atrophy predominantly eccentric to the neovascular complex was 4.345 mm (range of 0.705-13.758 mm), and this was statistically significant (P = 0.0465). The average rate of atrophy progression was 1.04 mm/year (SD 0.938).

CONCLUSION: With long-term anti-vascular endothelial growth factor therapy for eyes with Type-1 NV secondary to age-related macular degeneration, macular atrophy tends to develop predominantly eccentric to the PED and the neovascular flow imaged on OCT angiography. With chronic vascular endothelial growth factor suppression, Type-1 NV may evolve into a multilayered PED that may confer a protective
effect to the overlying retinal pigment epithelium and outer retina.

PMID: 28723848


**Incidence of outer retinal tubulation in eyes with choroidal neovascularization under intravitreal anti-vascular endothelial growth factor therapy in a Japanese population.**


PURPOSE: The purpose of this study was to investigate the occurrence of outer retinal tubulation (ORT) among patients with different types of choroidal neovascularization (CNV) over time.

MATERIALS AND METHODS: In this retrospective chart review, disease type was classified as typical age-related macular degeneration (t-AMD), polypoidal choroidal vasculopathy (PCV), retinal angiomatous proliferation (RAP), or myopic CNV (mCNV). Spectral domain-optical coherence tomography (SD-OCT) images were evaluated for the appearance of ORT and subretinal fibrosis and fluid. Furthermore, the association of the presence of ORT with clinical data and OCT findings was investigated.

RESULTS: Among the 136 eyes studied, the overall rates of occurrence of ORT were 7.8%, 18.8%, and 31.6% after 12, 24, and 36 months from baseline, respectively. Among patients with t-AMD, RAP, and mCNV, the occurrence of ORT increased soon after the initial visit. In contrast, among patients with PCV, the occurrence of ORT increased slowly over time. Patients with and without ORT - ORT (+) and ORT (-) groups, respectively - differed significantly in terms of sex ratio and presence of intraretinal fluid at the initial visit and presence of subretinal fibrosis at 3 years from baseline. The ORT (+) group exhibited lower visual acuity (VA; 0.67±0.43) than that of the ORT (-) group (0.41±0.36; P<0.001).

CONCLUSION: The occurrence of ORT tended to increase more slowly among eyes diagnosed with PCV than among eyes with other types of CNV.

PMID: 28721006 PMCID: PMC5499934


**Intravitreal Bevacizumab: Indications And Complications.**

Jan S, Nazim M, Karim S, Hussain Z.

BACKGROUND: Bevacizmab is still an unlicensed drug for intraocular use in spite of the fact that it has shown comparable efficacy to other anti-vascular endothelial growth factors (anti-VEGF) medications in some large sample randomized control trails. Although repackaged bevacizumab has got safety concerns but its use is growing because of easy availability and low cost. Our study focuses on the diverse and growing indications of intravitreal bevacizumab (IVB) and its ocular complications in our geographical setting.

METHODS: This interventional case series was carried out at my private practice in Said Anwar Medical Complex, Dabgari, Peshawar, from January 2008 to July 2015. Total of 6107 injections were given to 4352 eyes. Intravitreal bevacizumab was injected in proper operating room setting. Bevacizumab injections were prepared from same vial by multiple withdrawals taking care of aseptic precautions. Follow up was done at 1 week and 20 days and adverse effects were noted.

RESULTS: Diabetic macular oedema (36%), central retinal vein occlusion (17.6%) and branched retinal vein occlusion (11%) were the top three indications of IVB. Other common indications were proliferative diabetic retinopathy (9.6%), neo-vascular glaucoma (5.9%), proliferative diabetic retinopathy with vitreous
bleed (4.4%), proliferative diabetic retinopathy with tractional retinal detachment (3.7%), neo-vascular age related macular degeneration (2.9%), central serous retinopathy (1.48%) and Eale’s disease (1.48%). Endophthalmitis occurred in 3 eyes (0.069%) while retinal detachment was found in only 2 eyes (0.046%).

CONCLUSIONS: Common indications of bevacizumab are diabetic macular oedema, central retinal vein occlusion and branched retinal vein occlusion. Complications like endophthalmitis and retinal detachment are rare.

PMID: 28718542

Ophthalmologica. 2017 Jul 18. [Epub ahead of print]

Early Response to Ranibizumab Is Associated with 12-Month Outcome in Diabetic Macular Edema after Prior Macular Laser Therapy.

Sheu SJ, Lee YY.

PURPOSE: To evaluate the efficacy of ranibizumab in persistent or recurrent diabetic macular edema (DME) after previous laser therapy.

METHODS: This prospective, interventional study consisted of a 3-month period of scheduled ranibizumab treatment followed by a 9-month period of pro re nata treatment.

RESULTS: A total of 21 eyes (18 patients) were included. Both best corrected visual acuity and central retinal thickness had statistically significantly improved from baseline at month 12 (p < 0.001). The mean number of injections within these 12 months was 7.8 ± 2.6 (range 3-11). The visual change at month 12 did not vary by more than 5 letters from the response observed at week 12.

CONCLUSIONS: Our study showed a beneficial effect from ranibizumab in DME patients previously treated with macular laser therapy. The response at week 12 was sustained up to 1 year. A suboptimal early visual response may predict a long-term suboptimal response and help identify patients who would benefit from an alternative regimen.

PMID: 28715811


Efficiency and safety of laser photocoagulation with or without intravitreal ranibizumab for treatment of diabetic macular edema: a systematic review and Meta-analysis.

Qian TW, Zhao MY, Li XX, Xu X.

AIM: To compare the therapeutic effect and safety of laser photocoagulation along with intravitreal ranibizumab (IVR) versus laser therapy in treatment of diabetic macular edema (DME).

METHODS: Pertinent publications were identified through comprehensive searches of PubMed, EMBASE, Web of Science, Cochrane Library, and ClinicalTrials.gov to identify randomized clinical trials (RCTs) comparing IVR+laser to laser monotherapy in patients with DME. Therapeutic effect estimates were determined by weighted mean differences (WMD) of change from baseline in best corrected visual acuity (BCVA) and central retinal thickness (CRT) at 6, 12, or 24mo after initial treatment, and the risk ratios (RR) for the proportions of patients with at least 10 letters of improvement or reduction at 12mo. Data regarding major ocular and nonocular adverse events (AEs) were collected and analyzed. The Review Manager 5.3.5 was used.

RESULTS: Six RCTs involving 2069 patients with DME were selected for this Meta-analysis. The results showed that IVR+laser significantly improved BCVA compared with laser at 6mo (WMD: 6.57; 95% CI: 4.37-8.77; P<0.00001), 12mo (WMD: 5.46; 95% CI: 4.35-6.58; P<0.00001), and 24mo (WMD: 3.42; 95% CI:
0.84-5.99; $P=0.009$) in patients with DME. IVR+laser was superior to laser in reducing CRT at 12mo from baseline with statistical significance (WMD: -63.46; 95% CI: -101.19 to -25.73; $P=0.001$). The pooled RR results showed that the proportions of patients with at least 10 letters of improvement or reduction were in favor of IVR+laser arms compared with laser (RR: 2.13; 95% CI: 1.77-2.57; $P<0.00001$ and RR: 0.37; 95% CI: 0.22-0.62; $P=0.0002$, respectively). As for AEs, the pooled results showed that a significantly higher proportion of patients suffering from conjunctival hemorrhage (study eye) and diabetic retinal edema (fellow eye) in IVR+laser group compared to laser group (RR: 3.29; 95% CI: 1.53-7.09; $P=0.002$ and RR: 3.02; 95% CI: 1.24-7.32; $P=0.01$, respectively). The incidence of other ocular and nonocular AEs considered in this Meta-analysis had no statistical difference between IVR+laser and laser alone.

CONCLUSION: The results of our analysis show that IVR+laser has better availability in functional (improving BCVA) and anatomic (reducing CRT) outcomes than laser monotherapy for the treatment of DME. However, the patients who received the treatment of IVR+laser may get a higher risk of suffering from conjunctival hemorrhage (study eye) and diabetic retinal edema (fellow eye).

Eur J Ophthalmol. 2017 Jul 20:0. [Epub ahead of print]

Subthreshold micropulse laser reduces anti-VEGF injection burden in patients with diabetic macular edema.

Moisseiev E, Abbassi S, Thinda S, Yoon J, Yiu G, Morse LS.

PURPOSE: To evaluate the efficacy of micropulse laser in the early treatment of diabetic macular edema (DME) and its associated burden of anti-vascular endothelial growth factor (VEGF) injections.

METHODS: This retrospective comparative study compared a group of 19 eyes with DME treated with micropulse laser to a matched control group of 19 eyes with DME treated with ranibizumab injections without micropulse laser. Recorded parameters included previous medical and ocular history, previous and subsequent ranibizumab injections administered for DME, visual acuity (VA), central macular thickness throughout the follow-up period, and the occurrence of any complications.

RESULTS: The improvement in VA was comparable in both groups, at 12 months and at the final follow-up. Patients treated with micropulse laser required significantly fewer ranibizumab injections than their controls, both at 12 months (1.7 ± 2.3 vs 5.6 ± 2.1) and by the end of the follow-up (2.6 ± 3.3 vs 9.3 ± 5.1) ($p<0.001$ for both). No complications related to the micropulse laser were encountered.

CONCLUSIONS: Micropulse laser is a safe and effective treatment for DME, which may achieve comparable improvement in VA along with a significant reduction in the burden of anti-VEGF injections. We suggest a treatment approach for its inclusion in the early stages of DME.

PMID: 28731494


Letter to the Editor: Aflibercept For Diabetic Macular Edema in Eyes Previously Treated With Ranibizumab And/Or Bevacizumab May Further Improve Macular Thickness.

Călugăru D, Călugăru M.

PMID: 28728178
**Other treatment & diagnosis**


**Optical Coherence Tomography Features Preceding the Onset of Advanced Age-Related Macular Degeneration.**

Ferrara D, Silver RE, Louzada RN, Novais EA, Collins GK, Seddon JM.

PURPOSE: Age-related macular degeneration (AMD) is a progressive disease with multifactorial etiology. There is a need to identify clinical features that are harbingers of advanced disease. We evaluated morphologic features of the retina and choroid on optical coherence tomography (OCT) to determine if they predict progression to advanced disease.

METHODS: Progressors transitioned from early or intermediate AMD to advanced disease (n = 40 eyes), and were matched on baseline AMD grade and follow-up interval to nonprogressors who did not develop advanced AMD (n = 40 eyes). Features of the neurosensory retina, photoreceptors, retinal pigment epithelium (RPE), and choroid were evaluated. Logistic regression was used to evaluate univariate associations between features and progression to overall advanced AMD, geographic atrophy (GA), and neovascular disease (NV). Multivariate associations based on stepwise regression models were also assessed.

RESULTS: Ellipsoid zone disruption was associated with progression to overall advanced AMD and NV (odds ratios [ORs]: 17.9 and 30.6; P < 0.001), with a similar trend observed for GA. Drusenoid RPE detachment, RPE thickening, and retinal pigmentary hyperreflective material were significantly associated with higher risk of progression to advanced AMD (ORs: 5.0-8.5) and NV (ORs: 10.8-17.2). Pigmentary hyperreflective material was associated with progression to GA (OR: 7.5, P = 0.009). Total retinal thickness, pigmentary hyperreflective material, nascent GA features, and choroidal vessel abnormalities were independently associated with progression to advanced AMD in a multivariate stepwise model.

CONCLUSIONS: Abnormalities in the photoreceptors, retinal thickness, RPE, and choroid were associated with higher risk of developing advanced AMD. These findings provide insights into disease progression, and may be helpful to identify earlier endpoints for clinical studies.

PMID: 28715590 PMCID: PMC5512971


**Evaluation of Two Systems for Fundus-Controlled Scotopic and Mesopic Perimetry in Eye with Age-Related Macular Degeneration.**

Steinberg JS, Saßmannshausen M, Pfau M, Fleckenstein M, Finger RP, Holz FG, Schmitz-Valckenberg S.

PURPOSE: The purpose of this study was to evaluate and compare the MP-1S (Nidek Technologies, Padova, Italy) and the S-MAIA (CenterVue, Padova, Italy) for mesopic and scotopic fundus-controlled perimetry (FCP) in age-related macular degeneration (AMD).

METHODS: Eleven eyes from 11 patients underwent mesopic and, after 30 minutes of dark adaptation, scotopic (MP-1S: Goldmann V, 200 ms, background luminance 0.0032 cd/m2; S-MAIA: Goldman III, 200 ms, background luminance <0.0001 cd/m2) FCP. For the S-MAIA device, cyan (505 nm) and red (627 nm) scotopic FCP were performed. For both devices, a grid of 56 stimulus points covering 16° of the central macula was used. Examination time, fixation stability, and threshold values were analyzed.

RESULTS: The upper end of the dynamic range (≤4 dB of lowest threshold) was frequently reached by the MP-1S for mesopic testing (median 34 of 56 stimuli), while threshold values within the lower 4 dB of the dynamic range were occasionally found with the S-MAIA for scotopic testing (median 3 for cyan, median 2 for red). After correction of the stimulus intensity for the S-MAIA results, the median difference for all stimuli between both devices for mesopic testing was -2.0 dB (interquartile range [-4.0], range -14 to 6).
CONCLUSIONS: The results indicate that robust testing of mesopic and scotopic function is feasible with both devices in patients with AMD, although both devices are susceptible to floor and ceiling effects.

TRANSLATIONAL RELEVANCE: The interpretation and particularly the comparison of both scotopic and mesopic FCP results between the MP-1S and the S-MAIA in AMD eyes need to consider variable susceptibility of floor and ceiling effects. Further software updates are desirable as FCP captures visual functional loss that is not noted with best-corrected central visual acuity and is important for clinical trials in AMD.

PMID: 28713647 PMCID: PMC5509379


Indocyanine Green Angiography and Optical Coherence Tomography Angiography of Choroidal Neovascularization in Age-Related Macular Degeneration.


PURPOSE: To compare the capability of indocyanine green angiography (ICGA) and optical coherence tomography angiography (OCTA) in detecting choroidal neovascularization (CNV).

METHODS: In this prospective study, patients with CNV detected with fluorescein angiography (FA) underwent ICGA and OCTA, spectral domain OCT (SD-OCT), and infrared or fundus color photographs. CNV lesions were outlined on ICGA and OCTA images, and the composition and size of the CNV was documented.

RESULTS: One hundred eighty-two eyes were included. With ICGA, well-defined lesions were observed in 37.9%, partly defined in 44.5%, and undefined in 17% of eyes. On OCTA, well-defined, partly defined, and undefined vessels were observed in 53.8%, 27.5%, and 18.7% of eyes, respectively. There was a good correlation between CNV size measured with the two instruments (r = 0.84). However, OCTA underestimated CNV area by about 4.5% (slope coefficient with linear regression: 0.55, 95% confidence interval [CI]: 0.46 to 0.65; intercept: 0.27, 95% CI: -0.2 to 0.56). On ICGA, CNV composition was capillary in 28%, mature in 14.3%, and mixed (capillary and major neovascular complex) in 57.7% of eyes. Similarly, OCTA revealed capillary, mature, and mixed CNV in 28.9%, 15.9%, and 55.5% of eyes, respectively.

CONCLUSIONS: OCTA provides the clinician the ability to perform precise structural and vascular assessment of CNV noninvasively. Our study is, to our knowledge, the largest OCTA analysis to date of CNV secondary to neovascular AMD analyzed simultaneously by ICGA and OCTA.

PMID: 28738134


Age-related macular degeneration in a randomized controlled trial of low-dose aspirin: Rationale and study design of the ASPREE-AMD study.


PURPOSE: Although aspirin therapy is used widely in older adults for prevention of cardiovascular disease, its impact on the incidence, progression and severity of age-related macular degeneration (AMD) is uncertain. The effect of low-dose aspirin on the course of AMD will be evaluated in this clinical trial.

DESIGN: A sub-study of the 'ASPiRin in Reducing Events in the Elderly' (ASPREE) trial, ASPREE-AMD is a
5-year follow-up double-blind, placebo-controlled, randomized trial of the effect of 100 mg daily aspirin on the course of AMD in 5000 subjects aged 70 years or older, with normal cognitive function and without cardiovascular disease at baseline. Non-mydriatic fundus photography will be performed at baseline, 3-year and 5-year follow-up to determine AMD status.

PRIMARY OUTCOME MEASURES: The incidence and progression of AMD. Exploratory analyses will determine whether aspirin affects the risk of retinal hemorrhage in late AMD, and whether other factors, such as genotype, systemic disease, inflammatory biomarkers, influence the effect of aspirin on AMD.

CONCLUSION: The study findings will be of significant clinical and public interest due to a potential to identify a possible low cost therapy for preventing AMD worldwide and to determine risk/benefit balance of the aspirin usage by the AMD-affected elderly. The ASPREE-AMD study provides a unique opportunity to determine the effect of aspirin on AMD incidence and progression, by adding retinal imaging to an ongoing, large-scale primary prevention randomized clinical trial.

PMID: 28736754 PMCID: PMC5518696 [Available on 2018-06-01]


[Multifocal electroretinography for therapeutic effect evaluation of intravitreal injection Lucentis for wet age-related macular degeneration]. [Article in Chinese]

Ju RH, He MS, Hou JT, Li MY, Zhang JL, Wu ZM.

OBJECTIVE: To evaluate the changes in retinal functions using multifocal electroretinography (mfERG) following intravitreal injection of Lucentis for treatment of wet age-related macular degeneration.

METHODS: This prospective study was conducted in 14 patients (9 men and 5 women, 14 eyes) with wet age-related macular degeneration receiving treatment with intravitreal injections of ranibizumab (Lucentis) in our hospital between October, 2014 and January, 2016. All the patients received the treatment following a 1+PRN protocol and after the initial injection, the patients were followed up monthly for 6 months to decide if additional injections were needed. The corrected visual acuity and mfERG findings of the patients were assessed before and at 1, 3 and 6 months after the initial injection.

RESULTS: At the last follow-up, the patients received injections for a mean of 2.86±1.58 times. The best corrected visual acuity (BCVA) at 1 month after the initial treatment was not significantly different from that before treatment (P=0.07), but showed significant improvements at 3 and 6 months (P<0.05). In mfERG, the implicit time of the 6 rings showed no significant decrease after the treatment, but the amplitude density of P1 and N1 in rings 1 and 2 improved significantly at 1, 3, and 6 months after the initial injection (P<0.05).

CONCLUSION: Multifocal electroretinography can serve as a useful modality for evaluating visual function changes in patients receiving intravitreal injection of Lucentis for wet age-related macular degeneration.

PMID: 28736371


Treatment-Naïve quiescent choroidal neovascularization in geographic atrophy secondary to non-exudative age-related macular degeneration.

Capuano V, Miere A, Querques L, Sacconi R, Carnevali A, Amoroso F, Bandello F, Souied EH, Querques G.

PURPOSE: To describe the characteristics and natural history of quiescent choroidal neovascularization (CNV) in geographic atrophy (GA) secondary to non-exudative age-related macular degeneration (AMD) through multimodal imaging.
DESIGN: Retrospective observational case series.

METHODS: Patients diagnosed with quiescent CNV were analyzed in two high-volume referral centers. Imaging features obtained using fluorescein angiography (FA), indocyanine green angiography (ICGA), structural optical-coherence-tomography (OCT), and OCT-Angiography (OCT-A) were noted at first presentation and during the study period.

RESULTS: Nineteen eyes of 19 patients were included. Mean (+SD) follow-up was 45.7±14.7 months. Quiescent CNV appeared as an ill-defined hyperfluorescent lesion without leakage or pooling of dye in the late phase of FA. On ICGA, quiescent CNV appeared as a distinct area of hyperfluorescence (vascular network) in early to intermediate frames, and as a hyperfluorescent plaque in the late frame (late plaque). OCT-A revealed a flow signal beneath the small irregular elevation of the retinal pigment epithelium at the site of the quiescent CNV visualized by structural OCT. During the study period, 5/19 of the CNV developed exudation. The remainder showed specific alterations in both structural OCT and OCT-A imaging. At last follow-up, 92% of the quiescent CNV seemed to cover the area spared from atrophy.

CONCLUSIONS: The characteristics of the quiescent CNVs were very similar to those already described for intermediate AMD, although they had several specific features in the context of GA.

PMID: 28734811


Algorithms for the Automated Analysis of Age-Related Macular Degeneration Biomarkers on Optical Coherence Tomography: A Systematic Review.

Wintergerst MWM, Schultz T, Birtel J, Schuster AK, Pfeiffer N, Schmitz-Valckenberg S, Holz FG, Finger RP.

PURPOSE: To assess the quality of optical coherence tomography (OCT) grading algorithms for retinal biomarkers of age-related macular degeneration (AMD).

METHODS: Following a systematic review of the literature data on detection and quantification of AMD retinal biomarkers by available algorithms were extracted and descriptively synthesized. Algorithm quality was assessed using a modified version of the Quality Assessment of Diagnostic Accuracy Studies 2 checklist with a focus on accuracy against established reference standards and risk of bias.

RESULTS: Thirty five studies reporting computer-aided diagnosis (CAD) tools for qualitative analysis or algorithms for quantitative analysis were identified. Compared with manual assessment in reference standards correlation coefficients ranged from 0.54 to 0.97 for drusen, 0.80 to 0.98 for geographic atrophy (GA), and 0.30 to 0.98 for intra- or subretinal fluid and pigment epithelial detachment (PED) detection by automated algorithms. CAD tools achieved area under the curve (AUC) values of 0.94 to 0.99, sensitivity of 0.90 to 1.00, and specificity of 0.89 to 0.92.

CONCLUSIONS: Automated analysis of AMD biomarkers on OCT is promising. However, most of the algorithm validation was performed in preselected patients, exhibiting the targeted biomarker only. In addition, type and quality of reported algorithm validation varied substantially.

TRANSLATIONAL RELEVANCE:

The development of algorithms for combined, simultaneous analysis of multiple AMD biomarkers including AMD staging and the agreement on standardized validation procedures would be of considerable translational value for the clinician and the clinical researcher.

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OCT angiography documented reperfusion of translocated autologous full thickness RPE-choroid graft for complicated neovascular age-related macular degeneration.

Veckeneer M, Augustinus C, Feron E, Schauwvlieghe PP, Ruys J, Cosemans I, Van Meurs J.

Purpose: The purpose of this study is to investigate the reperfusion of translocated retinal pigment epithelium (RPE)-choroid graft in the treatment of patients with neovascular age-related macular degeneration (nAMD), using OCT angiography (OCTA), a novel non-invasive, high-resolution imaging modality.

Patients and methods: Eighteen eyes of 18 consecutive patients suffering from complicated nAMD underwent RPE-choroid patch graft translocation surgery using a peripheral retinotomy and flap-over technique. We analyzed functional and anatomical outcome using visual acuity, Spectral Domain OCT and OCTA.

Results: With a mean follow-up of 11 months, out of 18 patients, 15 gained vision, 1 remained stable, and 2 lost vision. Overall, the visual acuity improved with a mean of 30 letters. Perfusion of the graft tissue was confirmed in all patients. Two patients developed signs of a recurrent neovascular membrane during follow-up. No cases of proliferative vitreoretinopathy occurred in this series.

Conclusions: OCTA images show signs of perfusion in all grafts. Encouraging functional results and low risk of severe complications suggest that RPE-choroid graft translocation is a valid option in patients with complicated nAMD.

PMID: 28731053


Humanin G (HNG) protects age-related macular degeneration (AMD) transmitochondrial ARPE-19 cybrids from mitochondrial and cellular damage.

Nashine S, Cohen P, Chwa M, Lu S, Nesburn AB, Kuppermann BD, Kenney MC.

Abstract: Age-related macular degeneration (AMD) ranks third among the leading causes of visual impairment with a blindness prevalence rate of 8.7%. Despite several treatment regimens, such as anti-angiogenic drugs, laser therapy, and vitamin supplementation, being available for wet AMD, to date there are no FDA-approved therapies for dry AMD. Substantial evidence implicates mitochondrial damage and retinal pigment epithelium (RPE) cell death in the pathogenesis of AMD. However, the effects of AMD mitochondria and Humanin G (HNG), a more potent variant of the mitochondrial-derived peptide (MDP) Humanin, on retinal cell survival have not been elucidated. In this study, we characterized mitochondrial and cellular damage in transmitochondrial cybrid cell lines that contain identical nuclei but possess mitochondria from either AMD or age-matched normal (Older-normal (NL)) subjects. AMD cybrids showed (1) reduced levels of cell viability, lower mtDNA copy numbers, and downregulation of mitochondrial replication/transcription genes and antioxidant enzyme genes; and (2) elevated levels of genes related to apoptosis, autophagy and ER-stress along with increased mtDNA fragmentation and higher susceptibility to amyloid-β-induced toxicity compared to NL cybrids. In AMD cybrids, HNG protected the AMD mitochondria, reduced pro-apoptosis gene and protein levels, upregulated gp130 (a component of the HN receptor complex), and increased the protection against amyloid-β-induced damage. In summary, in cybrids, damaged AMD mitochondria mediate cell death that can be reversed by HNG treatment. Our results also provide evidence of Humanin playing a pivotal role in protecting cells with AMD mitochondria. In the future, it may be possible that AMD patient's blood samples containing damaged mitochondria may be useful as biomarkers for this condition. In conclusion, HNG may be a potential therapeutic target for treatment of dry AMD, a debilitating eye disease that currently has no available treatment. Further studies are needed to establish HNG as a viable mitochondria-targeting therapy for dry AMD.

PMID: 28726777
Pathogenesis


Hyperhomocysteinemia and Age-related Macular Degeneration: Role of Inflammatory Mediators and Pyroptosis; A Proposal.

Singh M, Tyagi SC.

Abstract: Age-related macular degeneration (AMD) and pyroptosis cause irreversible vascular changes in the eyes leading to central vision loss in patients. It is the most common eye disease affecting millions of people aged 50 years or older, and is slowly becoming a major health problem worldwide. The disease mainly affects macula lutea, an oval-shaped pigmented area surrounding fovea near the center of retina, a region responsible for visual acuity. It is fairly a complex disease as genetics of patients, environmental triggers as well as risk factors such as age, family history of CVDs, diabetes, gender, obesity, race, hyperopia, iris color, smoking, diabetes, exposure to sun light and pyroptosis have all been clubbed together as probable causes of macular degeneration. Among genes that are known to play a role include variant polymorphisms in the complement cascade components such as CFH, C2, C3, and CFB as potential genetic risk factors. So far, AMD disease hypothesized theories have not resulted into the anticipated impact towards the development of effective or preventive therapies in order to help alleviate patients' suffering because, as of today, it is still unclear what actually initiates or leads to this dreaded eye condition. Based upon our extensive work on the metabolism of homocysteine (Hcy) in various disease conditions we, therefore, are proposing a novel hypothesis for AMD pathogenesis as we strongly believe that Hcy and events such as pyroptosis make a greater contribution to the overall etiology of AMD disease in a target population of susceptible hosts by inciting and accelerating the inherent inflammatory changes in the retina of these patients (Fig. 2). In this context, we further state that Hcy and pyroptosis should be considered as legitimate and valuable markers of retinal dysfunction as they not only aid and abet in the development but also in the progression of AMD in older people as discussed in this paper. This discussion should open up new avenues in tackling inflammatory and pyroptosis centered pathways that are up-regulated or solely promoted by Hcy interaction within the ocular compartment of AMD susceptible hosts.

PMID: 28735646


Mitochondrial expression and activity of P-glycoprotein under oxidative stress in outer blood-retinal barrier.

Zhang YH, Li J, Yang WZ, Xian ZH, Feng QT, Ruan XC.

AIM: To investigate the role of oxidative stress in regulating the functional expression of P-glycoprotein (P-gp) in mitochondria of D407 cells.

METHODS: D407 cells were exposed to different ranges of concentrations of H2O2. The mitochondrial location of P-gp in the cells subjected to oxidative stress was detected by confocal analysis. Expression of P-gp in isolated mitochondria was assessed by Western blot. The pump activity of P-gp was evaluated by performing the efflux study on isolated mitochondria with Rhodamine 123 (Rho-123) alone and in the presence of P-gp inhibitor (Tariquidar) using flow cytometry analysis. The cells were pretreated with 10 mmol/L N-acetylcysteine (NAC) for 30min before exposing to H2O2, and analyzed the mitochondrial extracts by Western blot and flow cytometry.

RESULTS: P-gp was co-localized in the mitochondria by confocal laser scanning microscopy, and it was also detected in the mitochondria of D407 cells using Western blot. Exposure to increasing concentrations of H2O2 led to gradually increased expression and location of P-gp in the mitochondria of cells. Rho-123 efflux assay showed higher uptake of Rho-123 on isolated mitochondria in the presence of Tariquidar both in normal and oxidative stress state. H2O2 up-regulated P-gp in D407 cells, which could be reversed by NAC treatment.
CONCLUSION: H2O2 could up-regulate the functional expression of P-gp in mitochondria of D407 cells, while antioxidants might suppress oxidative-stress-induced over-expression of functional P-gp. It is indicative that limiting the mitochondrial P-gp transport in retinal pigment epithelium cells would be to improve the effect of mitochondria-targeted antioxidant therapy in age-related macular degeneration-like retinopathy.

PMID: 28730106 PMCID: PMC5514265


AIM: To investigate the roles of PKC-α/ezrin signals in phagocytosis crisis of retinal pigment epithelium (RPE) cells in light damage model.

METHODS: Light induced mice RPE injury model was established by continuously irradiating cool white light at different exposure time (0, 4, 8h light intensity: 4.18×10-6 J/cm2). In vitro, human ARPE-19 cells treated with the doses and intensity (1.57×10-6 J/cm2) of laser irradiation. Histology analysis was evaluated by hematoxylin and eosin (HE) staining. In vivo RPE phagocytosis was quantified by measuring the accumulation of photoreceptor outer segments in the sub-retinal space. In vitro RPE phagocytosis was assessed by calculating the relative fluorescence intensity of FITC-labeled microspheres in ARPE-19 cells. To further investigate the molecular mechanism, the activation of PKC-α/ezrin signal was evaluated by Western blot in vivo and in vitro.

RESULTS: HE staining revealed that the thickness of outer nuclear layer decreased significantly after 4 and 8h light exposure. By immunostaining with rhodopsin, a significant greater accumulation of photoreceptor outer segment was noticed after light injury. In vitro, light injured RPE cells had less phagocytic activity in a dose dependent manner than that of the normal control (P<0.01). Western blot suggested the activation of PKC-α/ezrin signaling was down-regulated in a dose-dependent manner after light exposure.

CONCLUSION: Our data suggest that light induced phagocytic crisis of RPE cells may result from the down-regulation of PKC-α/ezrin signaling.

PMID: 28730104 PMCID: PMC5514263

Apatinib, an Inhibitor of Vascular Endothelial Growth Factor Receptor 2, Suppresses Pathologic Ocular Neovascularization in Mice.

Kim KL, Suh W.

PURPOSE: Vascular endothelial growth factor (VEGF) signaling via VEGF receptor 2 (VEGFR2) plays a crucial role in pathologic ocular neovascularization. In this study, we investigated the antiangiogenic effect of apatinib, a pharmacologic inhibitor of VEGFR2 tyrosine kinase, against oxygen-induced retinopathy (OIR) and laser-induced choroidal neovascularization (CNV) in mice.

METHODS: Western blotting and in vitro angiogenesis assays were performed using human retinal microvascular endothelial cells (HRMECs). OIR was induced in neonatal mice by exposure to 75% oxygen from postnatal day (P) 7 to P12 and to room air from P12 to P17. Experimental CNV was induced in mice using laser photocoagulation. Apatinib was intravitreally and orally administered to mice. Neovascularization and phosphorylation of VEGFR2 were evaluated by immunofluorescence staining. 
RESULTS: Apatinib inhibited VEGF-mediated activation of VEGFR2 signaling and substantially reduced VEGF-induced proliferation, migration, and cord formation in HRMECs. A single intravitreal injection of apatinib significantly attenuated retinal or choroidal neovascularization in mice with OIR or laser injury-induced CNV, respectively. Retinal or choroidal tissues of the eyes treated with apatinib exhibited substantially lower phosphorylation of VEGFR2 than those of controls injected with vehicle. Intravitreal injection of apatinib did not cause noticeable ocular toxicity. Moreover, oral administration of apatinib significantly reduced laser-induced CNV in mice.

CONCLUSIONS: Our study demonstrates that apatinib inhibits pathologic ocular neovascularization in mice with OIR or laser-induced CNV. Apatinib may, therefore, be a promising drug for the prevention and treatment of ischemia-induced proliferative retinopathy and neovascular age-related macular degeneration.

PMID: 28715845


Geographic atrophy phenotype identification by cluster analysis.

Monés J, Biarnés M.

BACKGROUND/AIMS: To identify ocular phenotypes in patients with geographic atrophy secondary to age-related macular degeneration (GA) using a data-driven cluster analysis.

METHODS: This was a retrospective analysis of data from a prospective, natural history study of patients with GA who were followed for ≥6 months. Cluster analysis was used to identify subgroups within the population based on the presence of several phenotypic features: soft drusen, reticular pseudodrusen (RPD), primary foveal atrophy, increased fundus autofluorescence (FAF), greyish FAF appearance and subfoveal choroidal thickness (SFCT). A comparison of features between the subgroups was conducted, and a qualitative description of the new phenotypes was proposed. The atrophy growth rate between phenotypes was then compared.

RESULTS: Data were analysed from 77 eyes of 77 patients with GA. Cluster analysis identified three groups: phenotype 1 was characterised by high soft drusen load, foveal atrophy and slow growth; phenotype 3 showed high RPD load, extrafoveal and greyish FAF appearance and thin SFCT; the characteristics of phenotype 2 were midway between phenotypes 1 and 3. Phenotypes differed in all measured features (p≤0.013), with decreases in the presence of soft drusen, foveal atrophy and SFCT seen from phenotypes 1 to 3 and corresponding increases in high RPD load, high FAF and greyish FAF appearance. Atrophy growth rate differed between phenotypes 1, 2 and 3 (0.63, 1.91 and 1.73 mm2/year, respectively, p=0.0005).

CONCLUSION: Cluster analysis identified three distinct phenotypes in GA. One of them showed a particularly slow growth pattern.

PMID: 28729371


Diagnosing Choroidal Neovascularization in Asymptomatic Individuals Using Optical Coherence Tomography Angiography.


Abstract: Optical coherence tomography angiography (OCTA) is a noninvasive, rapid imaging technique that generates angiographic images without intravenous dye injections. Cross-sectional studies have described the presence of asymptomatic choroidal neovascularization (CNV) in patients with intermediate age-related macular degeneration (AMD). This case report describes the OCT features on longitudinal
follow-up of a patient who started with unilateral asymptomatic CNV and eventually developed symptomatic exudative AMD.

PMID: 28728188

J Vis Exp. 2017 Jul 3;(125).


Agrawal R, Balne PK, Tun SBB, Sia Wey Y, Khandelwal N, Barathi VA.

Abstract: The retinal and choroidal blood flow dynamics may provide insight into the pathophysiology and sequelae of various ocular diseases, such as glaucoma, diabetic retinopathy, age-related macular degeneration (AMD) and other ocular inflammatory conditions. It may also help to monitor the therapeutic responses in the eye. The proper labeling of the blood cells, coupled with live-cell imaging of the labeled cells, allows for the investigation of the flow dynamics in the retinal and choroidal circulation. Here, we describe the standardized protocols of 1.5% indocyanine green (ICG) and 1% sodium fluorescein labeling of mice erythrocytes and leukocytes, respectively. Scanning laser ophthalmoscopy (SLO) was applied to visualize the labeled cells in the retinal circulation of C57BL/6J mice (wild type). Both methods demonstrated distinct fluorescently labeled cells in the mouse retinal circulation. These labeling methods can have wider applications in various ocular disease models.

PMID: 28715402


Role of quercetin in protecting ARPE-19 cells against H2O2-induced injury via nuclear factor erythroid 2 like 2 pathway activation and endoplasmic reticulum stress inhibition.

Weng S, Mao L, Gong Y, Sun T, Gu Q.

Abstract: Age-related macular degeneration (AMD) is a common cause of irreversible blindness in the elderly in the western world. Research has demonstrated that degenerative and progressive conditions of retinal pigmented epithelial (RPE) cells are the key pathogenic mechanisms in AMD. Previous research has indicated the anti-apoptosis, anti-oxidant, anti-inflammatory and anti-cancer properties of quercetin. Therefore, the present study aimed to investigate the protective effects of quercetin on the ARPE-19 human retinal pigment epithelial cell line. ARPE-19 cells were pretreated with various concentrations of quercetin (0-80 µM) before exposure to 300 µM H2O2. Cell viability was assessed and reactive oxygen species (ROS) were determined. The importance of the NF-E2-related factor 2 (Nrf2) signaling pathway was corroborated by western blotting and immunostaining. The protein expression levels of endoplasmic reticulum-associated stress responsive genes and apoptotic markers were assessed by western blotting. The results demonstrated that in the H2O2 group, cell viability was weakened, but preserved in quercetin group in a dose-dependent manner, particularly at 20 µM. The level of ROS decreased in the quercetin group compared with the control groups. In the quercetin group, the expression levels of Nrf2 and phase II enzymes (NQO1 and HO-1) were increased, whereas the levels of ER stress markers (binding of immunoglobulin protein, CCAAT/enhancer-binding protein homologous protein and phosphorylated eukaryotic translation initiation factor 2α) were reduced. Cell apoptosis-associated protein expression levels were altered, with the increase of B-cell lymphoma 2 and reduction of Bcl-2 X-associated protein. In conclusion, quercetin protected ARPE-19 cells from H2O2-induced cytotoxicity by activating the Nrf2 pathway, inhibiting ER stress and targeting anti-apoptotic proteins.

PMID: 28713895
**Epidemiology**

**Ophthalmology. 2017 Jul 14. [Epub ahead of print]**

**Prevalence of Age-Related Macular Degeneration in Europe: The Past and the Future.**


Collaborators (139)

**PURPOSE:** Age-related macular degeneration (AMD) is a frequent, complex disorder in elderly of European ancestry. Risk profiles and treatment options have changed considerably over the years, which may have affected disease prevalence and outcome. We determined the prevalence of early and late AMD in Europe from 1990 to 2013 using the European Eye Epidemiology (E3) consortium, and made projections for the future.

**DESIGN:** Meta-analysis of prevalence data.

**PARTICIPANTS:** A total of 42,080 individuals 40 years of age and older participating in 14 population-based cohorts from 10 countries in Europe.

**METHODS:** AMD was diagnosed based on fundus photographs using the Rotterdam Classification. Prevalence of early and late AMD was calculated using random-effects meta-analysis stratified for age, birth cohort, gender, geographic region, and time period of the study. Best-corrected visual acuity (BCVA) was compared between late AMD subtypes: geographic atrophy (GA) and choroidal neovascularization (CNV).

**MAIN OUTCOME MEASURES:** Prevalence of early and late AMD, BCVA, and number of AMD cases.

**RESULTS:** Prevalence of early AMD increased from 3.5% (95% confidence interval [CI] 2.1%-5.0%) in those aged 55-59 years to 17.6% (95% CI 13.6%-21.5%) in those aged ≥85 years; for late AMD these figures were 0.1% (95% CI 0.04%-0.3%) and 9.8% (95% CI 6.3%-13.3%), respectively. We observed a decreasing prevalence of late AMD after 2006, which became most prominent after age 70. Prevalences were similar for gender across all age groups except for late AMD in the oldest age category, and a trend was found showing a higher prevalence of CNV in Northern Europe. After 2006, fewer eyes and fewer ≥80-year-old subjects with CNV were visually impaired (P = 0.016). Projections of AMD showed an almost doubling of affected persons despite a decreasing prevalence. By 2040, the number of individuals in Europe with early AMD will range between 14.9 and 21.5 million, and for late AMD between 3.9 and 4.8 million.

**CONCLUSION:** We observed a decreasing prevalence of AMD and an improvement in visual acuity in CNV occurring over the past 2 decades in Europe. Healthier lifestyles and implementation of anti-vascular endothelial growth factor treatment are the most likely explanations. Nevertheless, the numbers of affected subjects will increase considerably in the next 2 decades. AMD continues to remain a significant public health problem among Europeans.

PMID: 28712657

**Genetics**

**Ophthalmic Genet. 2017 Jul 20:1-5. [Epub ahead of print]**

**Double hyperautofluorescent ring on fundus autofluorescence in ABCA4.**
Abalem MF, Qian CX, Branham K, Schlegel D, Fahim AT, Khan NW, Heckenlively JR, Jayasundera KT.

Abstract: We report an unusual phenotype in a child with a clinical diagnosis of recessive Stargardt disease (STGD1) and two pathogenic variants in the ABCA4 gene. Typically, the diagnosis of early-onset STGD1 is challenging because children may present with a variety of fundus changes and a variable rate of progression. At the time of his initial visit, the 6-year-old boy presented with 20/200 OD (right eye) and 20/150 OS (left eye), symmetrical mild foveal atrophy without flecks on fundus exam, and foveal hypoautofluorescence surrounded by a homogeneous hyperautofluorescent background on wide-field fundus autofluorescence. Over 4 years of follow-up, the retinal atrophy continued to progress, resulting in two well-defined and concentric hyperautofluorescent rings: one ring located at the posterior pole and the other located around the peripapillary region. Visual acuity also deteriorated to counting fingers at 4ft OD and 20/500 OS. To the best of our knowledge, this phenotype has not been previously described with the ABCA4 gene.

PMID: 28726568


Gene therapy for age-related macular degeneration.
Moore NA, Bracha P, Hussain RM, Morral N, Ciulla TA.

INTRODUCTION: In neovascular age related macular degeneration (nAMD), gene therapy to chronically express anti-vascular endothelial growth factor (VEGF) proteins could ameliorate the treatment burden of chronic intravitreal therapy and improve limited visual outcomes associated with ‘real world’ undertreatment. Areas covered: In this review, the authors assess the evolution of gene therapy for AMD. Adeno-associated virus (AAV) vectors can transduce retinal pigment epithelium; one such early application was a phase I trial of AAV2-delivered pigment epithelium derived factor gene in advanced nAMD. Subsequently, gene therapy for AMD shifted to the investigation of soluble fms-like tyrosine kinase-1 (sFLT-1), an endogenously expressed VEGF inhibitor, binding and neutralizing VEGF-A. After some disappointing results, research has centered on novel vectors, including optimized AAV2, AAV8 and lentivirus, as well as genes encoding other anti-angiogenic proteins, including ranibizumab, aflibercept, angiostatin and endostatin. Also, gene therapy targeting the complement system is being investigated for geographic atrophy due to non-neovascular AMD. Expert opinion: The success of gene therapy for AMD will depend on the selection of the most appropriate therapeutic protein and its level of chronic expression. Future investigations will center on optimizing vector, promoter and delivery methods, and evaluating the risks of the chronic expression of anti-angiogenic or anti-complement proteins.

PMID: 28726562

Stem cells


Stem Cell Derived Retinal Pigment Epithelium: The Role of Pigmentation as Maturation Marker and Gene Expression Profile Comparison with Human Endogenous Retinal Pigment Epithelium.
Bennis A, Jacobs JG, Catsburg LAE, Ten Brink JB, Koster C, Schlingemann RO, van Meurs J, Gorgels TGMF, Moerland PD, Heine VM, Bergen AA.

Abstract: In age-related macular degeneration (AMD) the retinal pigment epithelium (RPE) deteriorates, leading to photoreceptor decay and severe vision loss. New therapeutic strategies aim at RPE replacement by transplantation of pluripotent stem cell (PSC)-derived RPE. Several protocols to generate RPE have been developed where appearance of pigmentation is commonly used as indicator of RPE differentiation and maturation. It is, however, unclear how different pigmentation stages reflect developmental stages and
functionality of PSC-derived RPE cells. We generated human embryonic stem cell-derived RPE (hESC-RPE) cells and investigated their gene expression profiles at early pigmentation (EP) and late pigmentation (LP) stages. In addition, we compared the hESC-RPE samples with human endogenous RPE. We used a common reference design microarray (44 K). Our analysis showed that maturing hESC-RPE, upon acquiring pigmentation, expresses markers specific for human RPE. Interestingly, our analysis revealed that EP and LP hESC-RPE do not differ much in gene expression. Our data further showed that pigmented hESC-RPE has a significant lower expression than human endogenous RPE in the visual cycle and oxidative stress pathways. In contrast, we observed a significantly higher expression of pathways related to the process adhesion-to-polarity model that is typical of developing epithelial cells. We conclude that, in vitro, the first appearance of pigmentation hallmarks differentiated RPE. However, further increase in pigmentation does not result in much significant gene expression changes and does not add important RPE functionalities. Consequently, our results suggest that the time span for obtaining differentiated hESC-RPE cells, that are suitable for transplantation, may be greatly reduced.

PMID: 28730556


Comparative proteomic analysis of human embryonic stem cell-derived and primary human retinal pigment epithelium.


Abstract: Human embryonic stem cell-derived retinal pigment epithelial cells (hESC-RPE) provide an unlimited cell source for retinal cell replacement therapies. Clinical trials using hESC-RPE to treat diseases such as age-related macular degeneration (AMD) are currently underway. Human ESC-RPE cells have been thoroughly characterized at the gene level but their protein expression profile has not been studied at larger scale. In this study, proteomic analysis was used to compare hESC-RPE cells differentiated from two independent hESC lines, to primary human RPE (hRPE) using Isobaric tags for relative quantitation (iTRAQ). 1041 common proteins were present in both hESC-RPE cells and native hRPE with majority of the proteins similarly regulated. The hESC-RPE proteome reflected that of normal hRPE with a large number of metabolic, mitochondrial, cytoskeletal, and transport proteins expressed. No signs of increased stress, apoptosis, immune response, proliferation, or retinal degeneration related changes were noted in hESC-RPE, while important RPE specific proteins involved in key RPE functions such as visual cycle and phagocytosis, could be detected in the hESC-RPE. Overall, the results indicated that the proteome of the hESC-RPE cells closely resembled that of their native counterparts.

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Diet, lifestyle & low vision

J Nutr Health Aging. 2017;21(7):772-780.

Vitamin D Status and Prevalent Early Age-Related Macular Degeneration in African Americans and Caucasians: The Atherosclerosis Risk in Communities (ARIC) Study.

Millen AE, Nie J, Sahli MW, Mares JA, Meyers KJ, Klein BEK, LaMonte MJ, Lutsey PL, Andrews CA, Klein R.

OBJECTIVES: Vitamin D status has been hypothesized to protect against development of early age-related macular degeneration (AMD) via its anti-inflammatory properties and its possible beneficial influence on blood pressure control. We investigated the association between vitamin D status and prevalent early AMD in a community-based cohort.
DESIGN: This was a cross-sectional study.

SETTING: This was a secondary data analysis of already existing data from the Atherosclerosis Risk in Communities Study (ARIC) cohort collected from 1990 to 1995.

PARTICIPANTS: There were 9,734 (7,779 Caucasians, 1,955 African American) ARIC participants (aged 46 to 70 at visit 2 [1990-1992]) with 25(OH)D data available at visit 2, AMD assessment at visit 3 (1993-1995), and complete covariate data.

MEASUREMENTS: Vitamin D status was assessed with serum 25-hydroxyvitamin D (25(OH)D) concentrations from bloods drawn at visit 2. Prevalent, early AMD (n=511) was assessed at visit 3 (1993-95) with nonmydriatic retinal photographs of one randomly chosen eye. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for early AMD by categories of 25(OH)D in nmol/L (deficient <30, inadequate 30-<50, and two categories of adequate status: 50-<75 and ≥75). Linear trend was estimated using continuous 25(OH)D concentrations. ORs were adjusted for age, race, and smoking status. We further adjusted for hypertension status to examine if vitamin D status influenced early AMD via its effects on blood pressure. Exploratory analyses of effect modification by age, sex, race and high risk genotypes [Y402H complement factor H (CFH) rs1061170 and the A69S age-related maculopathy susceptibility 2 (ARMS2) rs10490924 polymorphisms] were conducted.

RESULTS: The prevalence of early AMD was 5%, and 5% of participants were vitamin D deficient. The adjusted OR (95% CIs) for early AMD among those with adequate (≥75 nmol/L) compared to deficient (<30 nmol/L) vitamin D status was 0.94 (0.59-1.50), p-trend=0.86. Further adjustment for hypertension status did not influence results (OR [95% CI]=0.95 [0.59-1.52], p-trend=0.84). Results did not vary significantly by age, race, sex, early AMD subtype (soft drusen or retinal pigment epithelium depigmentation), or ARMS2 genotype. Results did not vary significantly by CFH genotype in African Americans. The p for multiplicative interaction between 25(OH)D and CFH genotype was 0.06 in Caucasians, but OR [95% CIs] for AMD by vitamin D status were similar in each CFH genotype and not statistically significant.

CONCLUSIONS: Vitamin D status was not associated with early AMD in this cohort sample.

PMID: 28717807