Drug treatment

Ophthalmology. 2017 Sep 8. [Epub ahead of print]

Treat-and-Extend versus Monthly Regimen in Neovascular Age-Related Macular Degeneration: Results with Ranibizumab from the TREND Study.


PURPOSE: To evaluate the efficacy and safety of ranibizumab 0.5 mg treat-and-extend (T&E) versus monthly regimens in patients with neovascular age-related macular degeneration (nAMD) from the TReat and extEND (TREND) study.

DESIGN: A 12-month phase 3b visual acuity (VA) assessor-masked, multicenter, randomized, interventional study.

PARTICIPANTS: Six hundred fifty patients.

METHODS: Treatment-naïve nAMD patients (age, ≥50 years) were randomized 1:1 to receive either a ranibizumab 0.5 mg T&E (n = 323) or monthly (n = 327) regimen.

MAIN OUTCOMES MEASURES: The primary objective was to show noninferiority of ranibizumab 0.5 mg T&E versus monthly regimen, as assessed by the change in best-corrected VA (BCVA) from baseline to the end of the study. Secondary objectives included change in retinal central subfield thickness (CSFT) from baseline to the end of study, treatment exposure, and safety.

RESULTS: Overall, 89.8% (T&E) and 90.2% (monthly) of patients completed the study. Patient demographic and baseline characteristics were well balanced between the 2 treatment groups. The T&E regimen was noninferior (P < 0.001) to the monthly regimen, with a least squares mean BCVA change from baseline of 6.2 versus 8.1 letters to the end of study, respectively. In both treatment groups, most BCVA improvements occurred during the first 6 months and were maintained until the end of the study. The mean change in CSFT from baseline to the end of study was -169.2 μm and -173.3 μm in the T&E and monthly groups, respectively. Fewer injections were required in patients receiving the T&E (8.7) versus monthly (11.1) regimen, with mean number of postbaseline visits of 8.9 and 11.2, respectively. Types and rates of adverse events were comparable between the treatment groups.

CONCLUSIONS: Ranibizumab 0.5 mg administered according to a T&E regimen was statistically noninferior and clinically comparable with a monthly regimen in improving VA from baseline to the end of study. No new safety signals for ranibizumab were identified.

PMID: 28893454
New Treatment Modalities for Geographic Atrophy.

Kandasamy R, Wickremasinghe S, Guymer R.

Abstract: Age-related macular degeneration (AMD) is a significant cause of global visual morbidity and is projected to affect 288 million people by the year 2040. The advent of treatment with anti–vascular endothelial growth factor (anti-VEGF) drugs has revolutionized the treatment of neovascular AMD (nAMD) but there have been no similar breakthroughs for the treatment of geographic atrophy (GA) to retard its progression. The advancements in imaging and new understanding of disease mechanisms, based on molecular and genetic models, have paved the way for the development of novel experimental treatment options for GA that aim to cater to a thus far largely unmet need. This review paper focuses on the recent clinical trials of new treatment options for slowing GA progression rates with emphasis on the agents that are currently undergoing, or have already undergone, significant clinical trial testing. Several new groups of drugs, including those targeting the complement cascade and agents considered as neuroprotective, have shown some promising results and could potentially pave the way forward in the treatment of this devastating disease.

PMID: 28905539

Two-Year Outcomes of a Treat-and-Extend Regimen Using Intravitreal Aflibercept Injections for Typical Age-Related Macular Degeneration.

Ito A, Matsumoto H, Morimoto M, Mimura K, Akiyama H.

PURPOSE: The aim of this study was to evaluate the efficacy of a treat-and-extend (TAE) regimen using intravitreal injection of aflibercept (IVA) for typical age-related macular degeneration (tAMD).

METHODS: We retrospectively studied 61 treatment-naïve eyes with tAMD. Best-corrected visual acuity (BCVA), central macular thickness (CMT), central choroidal thickness (CCT), number of injections, and complications during 2 years were evaluated.

RESULTS: BCVA significantly improved by on average 0.13 logMAR units, and CMT and CCT significantly decreased after 2 years. The number of injections was on average 13.6. In the second year, eyes with classic choroidal neovascularization (CNV) needed significantly fewer treatments than eyes with occult CNV. Fourteen eyes, which developed subfoveal fibrosis, showed significantly poorer BCVA after 2 years. Subfoveal fibrosis was significantly common in classic CNV.

CONCLUSION: A TAE regimen using IVA for tAMD might be effective for improving BCVA and exudative changes. The exudation may be suppressed with fewer treatments in classic CNV compared to occult CNV.

PMID: 28898873

A Retrospective Analysis of the Real-Life Utilization of Ranibizumab in Patients with Wet Age-Related Macular Degeneration from Portugal.


INTRODUCTION: Anti-vascular endothelial growth factor therapy has revolutionized the treatment of wet age-related macular degeneration; however, it is important to monitor actual use of ranibizumab and related
treatment outcomes in routine practice.

MATERIAL AND METHODS: This was a retrospective, observational study to monitor the 2-year outcomes following ranibizumab treatment for wet age-related macular degeneration in Portugal. Patients treated between January 2009 and December 2009 were retrospectively evaluated. All decisions were made by the treating physician in accordance with their usual routine clinical practice. The primary assessment was mean change in visual acuity score using Early Treatment Diabetic Retinopathy Study or Snellen equivalent.

RESULTS: A total of 128 patients with wet age-related macular degeneration were analyzed (mean age 79.4 years; mean visual acuity score 54.2 letters). Mean change in visual acuity score from baseline was -1.6 letters (n = 82) at year one and -5.1 letters (n = 72) at year two. The mean number of ranibizumab injections was 3.8 (year one) and 1.6 (year two). On average, patients attended 8.6 and 5.0 visits and optical coherence tomography was used in 75.0% of patients in year one and in 56.3% of patients in year two, respectively.

DISCUSSION: Despite a relatively high number of visits, including monitoring visits and use of optical coherence tomography-guided therapy, few injections were administered and visual acuity was not improved.

CONCLUSION: These findings indicate that as-needed treatment resulted in under-dosing in a real-life setting in Portugal. Such limitations may also be related to increasing numbers of patients, resulting in clinic saturation.

PMID: 28898611


Five-year Outcomes of Ranibizumab in Neovascular Age-related Macular Degeneration: Real Life Clinical Experience.

Ozkaya A, Alkin Z, Togac M, Ahmet S, Perente I, Taskapili M.

PURPOSE: To evaluate the outcomes of 5-year ranibizumab treatment in neovascular age-related macular degeneration (nAMD) in a single center and real life clinical setting.

METHODS: The records of nAMD patients who were treated with ranibizumab between January 2010 and June 2011 were retrospectively reviewed. Patients who completed 5 years of follow-up were included. Main outcome measures were change in best-corrected visual acuity, central retinal thickness, and visit and injection numbers.

RESULTS: Forty-four eyes of 37 patients were included. Mean best-corrected visual acuity decreased from 0.82 ± 0.69 to 1.11 ± 0.65 logarithm of minimal angle of resolution after 5 years. Twenty-four eyes (54.5%) had visual acuity loss ≥3 lines, and 20 eyes (45.5%) had stable or improved vision (loss <3 lines, remained stable, or gained ≥1 line) at month 60. The mean total number of visits was 25.3 ± 5.8 (range, 14 to 42), and the mean total number of injections was 12.6 ± 6.4 (range, 3 to 26) at month 60.

CONCLUSIONS: Half of the ranibizumab-treated nAMD patients maintained their vision during the 5 years of follow-up. Visit and injection numbers were found to be lower than in prospective studies, reflecting a real world clinical practice.

PMID: 28913999
Intravitreal injection of ziv-aflibercept in the treatment of choroidal and retinal vascular diseases.

Jodjat Jalali K, Mehravaran S, Faghihi H, Hashemi H, Kazemi P, Rastad H.

PURPOSE: To investigate the short-term outcomes after intravitreal injection of ziv-aflibercept in the treatment of choroidal and retinal vascular diseases.

METHODS: Thirty-four eyes of 29 patients with age-related macular degeneration (AMD), diabetic retinopathy, and retinal vein occlusion (RVO) received a single dose intravitreal injection of 0.05 ml ziv-aflibercept (1.25 mg). Visual acuity, spectral domain optical coherence tomography (SD-OCT) activity, and possible side effects were assessed before and at 1 week and 1 month after the intervention.

RESULTS: At 1 month after treatment, mean central macular thickness (CMT) significantly decreased from 531.09 μm to 339.5 μm (P < 0.001), and no signs of side effects were observed in any subject. All patients responded to treatment in terms of reduction in CMT. The improvement in visual acuity was statistically non-significant.

CONCLUSION: Our findings suggest that a single dose intravitreal injection of ziv-aflibercept may have acceptable relative safety and efficacy in the treatment of patients with intraocular vascular disease.

PMID: 28913517 PMCID: PMC5587245

Eur J Pharm Sci. 2017 Sep 12. [Epub ahead of print]

Recombinant humanized anti-vascular endothelial growth factor monoclonal antibody efficiently suppresses laser-induced choroidal neovascularization in rhesus monkeys.

Ji WW, Yu DA, Yang P, Fang P, Cao YX, Li H, Xie N, Yan SS.

Abstract: Neovascular age-related macular degeneration, characterized by abnormal choroidal neovascularization (CNV), is a major cause of blindness worldwide. Anti-vascular endothelial growth factor (VEGF) antibodies have demonstrated significant efficacy in improving visual acuity. TMAB001 is a new recombinant humanized rabbit anti-VEGF monoclonal antibody. It presents high activities in vitro studies. In the binding affinity assay, TMAB001 exhibited a high binding capability to VEGF with an affinity constant of 10^{11} M. In the receptor antagonist activity assay, IC50 of TMAB001 was 0.15 μg/ml. In a cell-based assay, TMAB001 inhibited VEGF165-induced HUVEC cells proliferation in a dose-dependent manner. Furthermore, in the rhesus monkey model of laser-induced CNV, results showed the growth and leakage of experimental CNV were significantly decreased with a single bilateral intravitreal injection of TMAB001, and the grade 4 lesions were complete absence in TMAB001 groups. The efficacy of TMAB001 was maintained for at least 28 days. In a mice model of oxygen-induced retinopathy, the retina fluorescence leakage was reduced and the vascular morphology in retina was normalized by TMAB001 intraperitoneal administration. In conclusion, those results indicate that TMAB001 might be a potential drug candidate for wet AMD.

PMID: 28916483

Retina. 2017 Sep 7. [Epub ahead of print]

RETINAL MICROVASCULATURE AND VISUAL ACUITY AFTER INTRAVITREAL AFLIBERCEPT IN EYES WITH CENTRAL RETINAL VEIN OCCLUSION: An Optical Coherence Tomography Angiography Study.

PURPOSE: To investigate vascular perfusion and foveal avascular zone area in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) after intravitreal aflibercept therapy in central retinal vein occlusion eyes and their association with best-corrected visual acuity.

METHODS: Thirty-five subjects with central retinal vein occlusion and macular edema were evaluated. After macular edema resolution following intravitreal aflibercept, subjects underwent optical coherence tomography angiography to measure SCP and DCP perfusion and the foveal avascular zone within a 3 × 3-mm area. Correlations between best-corrected visual acuity and optical coherence tomography angiography measurements were examined.

RESULTS: After intravitreal aflibercept therapy, mean retinal vascular area was 3.41 ± 0.74 mm in the SCP and 3.25 ± 0.91 mm in the DCP. Foveal avascular zone area was 1.03 ± 1.04 mm in the SCP and 1.78 ± 1.73 mm in the DCP. Improved best-corrected visual acuity was significantly associated with better SCP and DCP perfusion (both P < 0.001) and with smaller SCP and DCP foveal avascular zone areas (both P < 0.001). Additionally, SCP and DCP perfusion were negatively correlated with macular edema before treatment (P < 0.05) and ischemia (determined via pretreatment fluorescein angiography, P < 0.05), and positively correlated with photoreceptor integrity (P < 0.001).

CONCLUSION: Patients with better retinal perfusion and less retinal ischemia are associated with better visual outcomes after aflibercept in eyes with central retinal vein occlusion.

PMID: 28902097


Switching to Aflibercept in Diabetic Macular Edema Not Responding to Ranibizumab and/or Intravitreal Dexamethasone Implant.

Herbaut A, Fajnkuchen F, Qu-Knafo L, Nghiem-Buffet S, Bodaghi B, Giocanti-Auregan A.

PURPOSE: To assess short-term functional and anatomical outcomes of refractory diabetic macular edema (DME) following a switch from ranibizumab or dexamethasone to aflibercept.

METHODS: We included retrospectively eyes with persistent DME after at least 3 ranibizumab and/or one dexamethasone implant intravitreal injections (IVI). The primary endpoint was the mean change in visual acuity (VA) at month 6 (M6) after switching.

RESULTS: Twenty-five eyes were included. Before switching to aflibercept, 23 eyes received a median of 9.5 ranibizumab, and among them, 6 eyes received one dexamethasone implant after ranibizumab and 2 eyes received only one dexamethasone implant. Baseline VA, before any IVI, was 52.9 ± 16.5 letters, and preswitch VA was 57.1 ± 19.6 letters. The mean VA gain was +8 letters (p = 0.01) between preswitch and M6. The mean central retinal thickness was 470.8 ± 129.9 μm before the switch and 303.3 ± 59.1 μm at M6 (p = 0.001).

CONCLUSION: Switching to aflibercept in refractory DME results in significant functional and anatomical improvement.

PMID: 28900543 PMCID: PMC5576400

Other treatment & diagnosis


Microperimetry - A New Tool for Assessing Retinal Sensitivity in Macular Diseases.
Laishram M, Srikanth K, Rajalakshmi AR, Nagarajan S, Ezhumalai G.

INTRODUCTION: Macular disease is the leading cause of low vision in the Western world. Drusen and pigmentary irregularities are common among the rural Northern Indian population. The disease process leads to loss of central vision, metamorphopsia, macropsia or micropsia and colour vision defect.

AIM: To study the retinal sensitivity changes in macular diseases using microperimetry.

MATERIALS AND METHODS: It was an observational study, conducted in the Department of Ophthalmology at a rural tertiary care hospital. This study was started from December 2014 until June 2016, in all patients with macular disease above the age of 20 years attending the outpatient department. Microperimetry was done for 84 eyes of 52 patients with macular disease. Mean retinal Sensitivity (MS) and fixation stability was evaluated. The statistical analysis of mean retinal sensitivity, central 2° and 4° fixation was done by calculating the mean and standard deviation using 95% confidence interval.

RESULTS: The range of age was between 20-81 years. Majority were 32 males (62%) and 20 females (38%). Out of the 84 eyes studied, majority of the macular disease were Age-Related Macular Degeneration (AMD) (50%). Rest 50% were other macular diseases. The mean retinal sensitivity (dB) shown by microperimetry was 10.83 in AMD, 9.12 in Cystoid Macular Oedema (CME), 10.34 in Epiretinal Membrane (ERM), 10.74 in Pigment Epithelial Detachment (PED), 8.96 in Central Serous Chorioretinopathy (CSCR), 6.43 in macular dystrophy, 7.15 in Lamellar Hole (LMH), 9.8 in Pseudomacular Hole (PMH), 3 in geographic atrophy, 5.6 in Berlin oedema, 12.3 in macular scar and 15.2 in haemorrhage in macula. The study showed 64% of the eyes had stable 2° central fixation, 35% had relatively unstable fixation and 1% had unstable fixation. No significant correlation between retinal sensitivity and retinal thickness in AMD was found.

CONCLUSION: This study shows that microperimetry can be a useful tool for objective evaluation of macular function and progression of the disease.

PMID: 28892948 PMCID: PMC5583893


Repeatability and Reproducibility of Superficial Macular Retinal Vessel Density Measurements Using Optical Coherence Tomography Angiography En Face Images.

Lei J, Durbin MK, Shi Y, Uji A, Balasubramanian S, Baghdasaryan E, Al-Sheikh M, Sadda SR.

IMPORTANCE: The repeatability and reproducibility of quantitative metrics from optical coherence tomographic angiography (OCTA) must be assessed before these data can be confidently interpreted in clinical research and practice.

OBJECTIVE: To evaluate the repeatability and reproducibility of OCTA-derived retinal vascular quantitative metrics.

DESIGN, SETTING AND PARTICIPANTS: In this cross-sectional study, 21 healthy volunteers (42 eyes) and 22 patients with retinal disease (22 eyes), including 14 with age-related macular degeneration, 3 with epiretinal membrane, 2 with diabetic retinopathy, 2 with myopic macular degeneration, and 1 with retinal vein occlusion, were enrolled. Participants were recruited from September 1 through November 31, 2016. Each eye underwent 3 repeated scans with 3 instruments for a total of 9 acquisitions. Eyes were randomly assigned to scanning with a 3 × 3-mm or 6 × 6-mm pattern. Eyes were excluded from subsequent analysis if any acquisition had a signal strength of less than 7. Repeatability (defined as the agreement in measurements within a device) and reproducibility (defined as the agreement between devices of the same type) were assessed by intraclass correlation coefficient (ICC) and coefficient of variation.

EXPOSURES: All eyes underwent scanning using 3 separate devices.

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MAIN OUTCOMES AND MEASURES: Vessel length density (VLD) and perfusion density (PD) of the superficial retinal vasculature.

RESULTS: A total of 21 healthy volunteers (8 men and 13 women; mean [SD] age, 36 [6] years) and 22 patients with retinal disease (15 men and 7 women; mean [SD] age, 79 [9] years) underwent evaluation. Of these, 40 of 42 normal eyes and 15 of 22 eyes with retinal disease met signal strength criteria and were included in this analysis. The ICC among the 3 consecutive scans ranged from 0.82 to 0.98 for VLD and from 0.83 to 0.95 for PD. The coefficient of variation (CV) ranged from 2.2% to 5.9% for VLD and from 2.4% to 5.9% for PD. For reproducibility, the ICC ranged from 0.62 to 0.95 and the CV was less than 6% in all groups. The agreement was highest for the 3 × 3-mm pattern in the inner ring (ICC range, 0.92 [95% CI, 0.85-0.96] to 0.96 [95% CI, 0.93-0.98]) and 6 × 6-mm pattern in the outer ring (ICC range, 0.93 [95% CI, 0.86-0.97] to 0.96 [95% CI, 0.92-0.98]).

CONCLUSIONS AND RELEVANCE: Vessel length density and PD of the superficial retinal vasculature can be obtained from OCTA images with high levels of repeatability and reproducibility but can vary with scan pattern and location.

PMID: 28910435


[OCT Angiography of RPE Tears in Exudative AMD: Morphological Analysis of the Choriocapillaris and the RPE].[Article in German]


Abstract: Background Retinal pigment epithelium (RPE) tears are a typical complication of vascular pigment epithelium detachment in age-related macular degeneration (AMD). During proactive intense anti-VEGF therapy, stabilisation or improvement of function may occur. With the new method of OCT angiography (OCT-A), retinal vessels and flow density can be quantified. This pilot study investigates changes in the choriocapillars (CC) in areas with increasing FAF in OCT following an RPE-tear. Methods In six eyes with an RPE-tear, prospectively initially and every three months thereafter, multimodal imaging was performed, including fundus autofluorescence (FAF) (HRA2, Heidelberg Engineering, Heidelberg, Deutschland) and OCT-A (RTVue XR Avanti, SSDA-Modus, Angiovue, Optovue, Freemont, CA, USA). With interactive MATLAB-software (MATLAB, MathWorks, Natick, MA, USA), FAF and OCT were geometrically superimposed. With the help of the Fiji software (National Institutes of Health, Bethesda, MD, USA), areas with increasing FAF flow intensity in OCT-A with CC-segmentation were measured during an average follow-up period of 12 months. Results We measured a reduction in the RPE-free area - due to an increase in autofluorescence tissue - of an average of 2.94 mm² (SD 2.1 mm²; 42.1% of initial RPE-free area) in the boundary area of RPE-tears. At the end of the different follow-ups, some patients exhibited lower flow density in areas of regenerated autofluorescence than the initial findings. On the other hand, in some follow-ups, the same or increased flow density was seen. Conclusion In this pilot study, OCT-A was tested to analyse the structure of CC in areas of regenerated FAF after RPE-tears. Using external image editing software, FAF and OCT-A were compared during the follow-up. Thus apparent initial regression of the CC in the area mentioned above could be observed. During the follow-up and development of autofluorescent SHT, CC also regenerates up to the level of the initial findings of CC.

PMID: 28895631


The Role of New Imaging Methods in Managing Age-Related Macular Degeneration.
Talks SJ, Aftab AM, Ashfaq I, Soomro T.

Abstract: The use of imaging for age-related macular degeneration (AMD) depends on how it benefits clinical management and on reimbursement. The latter should relate to the former. This review assesses how different forms of AMD can be imaged and what information this provides. For nonneovascular AMD, high-resolution optical coherence tomography (OCT), autofluorescence, and near infrared imaging can identify the type of drusen, such as reticular pseudodrusen, which influences prognosis, and the amount of atrophy, for which phase 3 trials are underway. Clarifying the correct diagnosis for late-onset Stargardt and macular telangiectasia, if treatment becomes available, will be especially important. Choroidal thickness can be measured and changes with anti-vascular endothelial growth factor treatment, but how this influences management is less clear. The finding of a thick choroid may alter the diagnosis to pachychoroid neovasculopathy, which may have a different treatment response. Peripheral retinal changes are commonly found on ultrawide-field imaging but their importance is not yet determined. The mainstay of imaging is OCT, which can detect neovascular AMD by detecting thickening and be used for follow-up, as the presence or absence of thickening is the main determinant of treatment. Higher resolution systems and now OCT angiography are able to distinguish neovascular type, especially type 2 choroidal neovascularization but also polypoidal choroidal vasculopathy and retinal angiomatus proliferation. Fundus fluorescein and indocyanine green angiographies still have a role, although that partly depends on whether photodynamic therapy is being considered. Automated image analysis and machine learning will be increasingly important in supporting clinician decisions.

PMID: 28905541


Correlation of Macular Focal Electroretinogram with Ellipsoid Zone Extension in Stargardt Disease.


Abstract: Stargardt disease (STGD1) is the most common cause of inherited juvenile macular degeneration. This disease is characterized by a progressive accumulation of lipofuscin in the outer retina and subsequent loss of photoreceptors and retinal pigment epithelium. The aim of this study was to evaluate the relationship between cone photoreceptor function and structure in STGD1. Macular function was assessed by visual acuity measurement and focal electroretinogram (FERG) recording while spectral domain optical coherence tomography (SD-OCT) imaging was performed to evaluate the integrity of photoreceptors. FERG amplitude was significantly reduced in patients with Stargardt disease (p < 0.0001). The amplitude of FERG showed a negative relationship with interruption of ellipsoid zone (EZ) (R2 = 0.54, p < 0.0001) and a positive correlation with average macular thickness (AMT). Conversely, visual acuity was only weakly correlated with central macular thickness (CMT) (R2 = 0.12, p = 0.04). In conclusion, this study demonstrates that FERG amplitude is a reliable indicator of macular cone function while visual acuity reflects the activity of the foveal region. A precise assessment of macular cone function by FERG recording may be useful to monitor the progression of STGD1 and to select the optimal candidates to include in future clinical trials to treat this disease.

PMID: 28912967 PMCID: PMC5585538


Human Plasma Metabolomics Study across All Stages of Age-Related Macular Degeneration Identifies Potential Lipid Biomarkers.

PURPOSE: To characterize the plasma metabolomic profile of patients with age-related macular degeneration (AMD) using mass spectrometry (MS).

DESIGN: Cross-sectional observational study.

PARTICIPANTS: We prospectively recruited participants with a diagnosis of AMD and a control group (>50 years of age) without any vitreoretinal disease.

METHODS: All participants underwent color fundus photography, used for AMD diagnosis and staging, according to the Age-Related Eye Disease Study classification scheme. Fasting blood samples were collected and plasma was analyzed by Metabolon, Inc. (Durham, NC), using ultrahigh-performance liquid chromatography (UPLC) and high-resolution MS. Metabolon's hardware and software were used to identify peaks and control quality. Principal component analysis and multivariate regression were performed to assess differences in the metabolomic profiles of AMD patients versus controls, while controlling for potential confounders. For biological interpretation, pathway enrichment analysis of significant metabolites was performed using MetaboAnalyst.

MAIN OUTCOME MEASURES: The primary outcome measures were levels of plasma metabolites in participants with AMD compared with controls and among different AMD severity stages.

RESULTS: We included 90 participants with AMD (30 with early AMD, 30 with intermediate AMD, and 30 with late AMD) and 30 controls. Using UPLC and MS, 878 biochemicals were identified. Multivariate logistic regression identified 87 metabolites with levels that differed significantly between AMD patients and controls. Most of these metabolites (82.8%; n = 72), including the most significant metabolites, belonged to the lipid pathways. Analysis of variance revealed that of the 87 metabolites, 48 (55.2%) also were significantly different across the different stages of AMD. A significant enrichment of the glycerophospholipids pathway was identified (P = 4.7 \times 10^{-9}) among these metabolites.

CONCLUSIONS: Participants with AMD have altered plasma metabolomic profiles compared with controls. Our data suggest that the most significant metabolites map to the glycerophospholipid pathway. These findings have the potential to improve our understanding of AMD pathogenesis, to support the development of plasma-based metabolomics biomarkers of AMD, and to identify novel targets for treatment of this blinding disease.

PMID: 28916333


The use of optical coherence tomography angiography in pachychoroid spectrum diseases: a concurrent comparison with dye angiography.

Demirel S, Yanik Ö, Nalcı H, Batıoğlu F, Özmert E.

PURPOSE: The study objective was to compare dye angiography and optical coherence tomography angiography (OCTA) in detecting choroidal neovascularization (CNV) in patients presenting with pachychoroid features and flat irregular pigment epithelial detachment (PED).

METHODS: Nineteen eyes of 17 patients, presenting with flat PED and pachychoroid features, and without age-related macular degeneration or any other degenerative change, were analyzed. Fluorescein angiography (FA)/Indocyanine green angiography (ICGA) and OCTA were performed during the same visit. Subfoveal choroidal thickness was measured by enhanced depth imaging using spectral domain optical coherence tomography.

RESULTS: The mean age of the patients was 59.1 years. Mean subfoveal choroidal thickness was 388 μm. FA revealed non-patognomonic features including RPE alterations, window defects, leaking points and leakage from an undetermined source. ICGA revealed choroidal vascular plaque in eight eyes (42%) and
suspicious plaque in five eyes (26%). Nonneovascular features, such as hyperpermeability or dilated choroidal vessels, were observed in six eyes (32%). OCTA showed choroidal neovascularization in 14 (74%). For all of the eyes, which ICGA was positive for presence of CNV, OCTA also showed CNV, and in one case it also revealed polypoidal characteristics of the neovascular network. OCTA was also able to detect CNV in all of the eyes with suspicious plaque, and in one eye without CNV appearance using ICGA.

CONCLUSIONS: OCTA demonstrated greater sensitivity in detecting type 1 CNV than conventional dye angiography in cases with pachychoroid spectrum disease.

PMID: 28891028

Retina. 2017 Sep 4. [Epub ahead of print]

DETECTION OF TREATMENT-NAIVE CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION BY SWEPT SOURCE OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY.


PURPOSE: To compare the detection rate of choroidal neovascularization (CNV) in treatment-naive neovascular age-related macular degeneration by swept source optical coherence tomography angiography (SS-OCTA, Topcon's DRI Triton) working at 1,050 nm wavelength versus fluorescence angiography.

METHODS: Cross-sectional analysis of 156 eyes (107 neovascular age-related macular degeneration and 49 dry AMD) in 98 patients, previously diagnosed by multimodal imaging using fluorescein (FA) and indocyanine green angiography (Heidelberg's Spectralis) in a tertiary retina center, evaluated by SS-OCTA 4.5 mm × 4.5 mm and 6 mm × 6 mm macular cubes. Main outcome measures were sensitivity and specificity of SS-OCTA in AMD. Potential factors influencing CNV detection rate were analyzed.

RESULTS: Swept source optical coherence tomography angiography detected CNV in 81 of 107 eyes, resulting in a sensitivity of 75.7%. In 49 eyes with dry AMD, no CNV could be identified (specificity 100%). A statistical significance was calculated for nondetection of treatment-naive CNV by SS-OCTA in pigment epithelial detachment over 400 μm (P = 0.0238).

CONCLUSION: Topcon's SS-OCTA was not able to detect all CNV lesions. Large pigment epithelial detachments were associated with signal loss. Fluorescence angiography still remains the gold standard, but the tested SS-OCTA device can be considered as a feasible additional diagnostic tool in AMD.

PMID: 28902095


Periostin in vitreoretinal diseases.

Yoshida S, Nakama T, Ishikawa K, Nakao S, Sonoda KH, Ishibashi T.

Abstract: Proliferative vitreoretinal diseases such as diabetic retinopathy, proliferative vitreoretinopathy (PVR), and age-related macular degeneration are a leading cause of decreased vision and blindness in developed countries. In these diseases, retinal fibro(vascular) membrane (FVM) formation above and beneath the retina plays an important role. Gene expression profiling of human FVMs revealed significant upregulation of periostin. Subsequent analyses demonstrated increased periostin expression in the vitreous of patients with both proliferative diabetic retinopathy and PVR. Immunohistochemical analysis showed co-
localization of periostin with α-SMA and M2 macrophage markers in FVMs. In vitro, periostin blockade inhibited migration and adhesion induced by PVR vitreous and transforming growth factor-β2 (TGF-β2). In vivo, a novel single-stranded RNAi agent targeting periostin showed the inhibitory effect on experimental retinal and choroidal FVM formation without affecting the viability of retinal cells. These results indicated that periostin is a pivotal molecule for FVM formation and a promising therapeutic target for these proliferative vitreoretinal diseases.

PMID: 28913545


**Biochemical Measurements of Free Opsin in Macular Degeneration Eyes: Examining the 11-CIS Retinal Deficiency Hypothesis of Delayed Dark Adaptation (An American Ophthalmological Society Thesis).**

Hanneken A, Neikirk T, Johnson J, Kono M.

PURPOSE: To test the hypothesis that delayed dark adaptation in patients with macular degeneration is due to an excess of free unliganded opsin (apo-opsin) and a deficiency of the visual chromophore, 11-cis retinal, in rod outer segments.

METHODS: A total of 50 human autopsy eyes were harvested from donors with and without macular degeneration within 2-24 hrs. postmortem. Protocols were developed which permitted dark adaptation of normal human eyes after death and enucleation. Biochemical methods of purifying rod outer segments were optimized and the concentration of rhodopsin and apo-opsin was measured with UV-visible scanning spectroscopy. The presence of apo-opsin was calculated by measuring the difference in the rhodopsin absorption spectra before and after the addition of 11-cis retinal.

RESULTS: A total of 20 normal eyes and 16 eyes from donors with early, intermediate and advanced stages of macular degeneration were included in the final analysis. Dark adaptation was achieved by harvesting whole globes in low light, transferring into dark (light-proof) canisters and dissecting the globes using infrared light and image converters for visualization. Apo-opsin was readily detected in positive controls after the addition of 11-cis retinal. Normal autopsy eyes showed no evidence of apo-opsin. Eyes with macular degeneration also showed no evidence of apo-opsin, regardless of the severity of disease.

CONCLUSIONS: Methods have been developed to study dark adaptation in human autopsy eyes. Eyes with age-related macular degeneration do not show a deficiency of 11-cis retinal or an excess of apo-opsin within rod outer segments.

PMID: 28900371 PMCID: PMC5572981

**Ophthalmic Surg Lasers Imaging Retina. 2017 Sep 1;48(9):700-704.**

**Cataract Surgery in Patients With Wet Macular Degeneration.**

Ober MD, Fine HF, Saraf SS.

PMID: 28902329

**Pathogenesis**

**J Biol Chem. 2017 Sep 14. [Epub ahead of print]**
Cavin-2 regulates the activity and stability of endothelial nitric oxide synthase (eNOS) in angiogenesis.

Boopathy GTK, Kulkarni M, Ho SY, Boey A, Chua EWM, Barathi VA, Carney TJ, Wang X, Hong W.

Abstract: Angiogenesis is a highly regulated process for formation of new blood vessels from pre-existing ones. Angiogenesis is dysregulated in various pathologies, including age-related macular degeneration, arthritis, and cancer. Inhibiting pathological angiogenesis therefore represents a promising therapeutic strategy for treating these disorders, highlighting the need to study angiogenesis in more detail. To this end, identifying the genes essential for blood vessel formation and elucidating their function are crucial for a complete understanding of angiogenesis. Here, focusing on potential candidate genes for angiogenesis, we performed a morpholino-based genetic screen in zebrafish and identified Cavin-2, a membrane-bound phosphatidylinerine-binding protein and critical organizer of caveolae (small microdomains in the plasma membrane), as a regulator of angiogenesis. Using endothelial cells, we show that Cavin-2 is required for in vitro angiogenesis and also for endothelial cell proliferation, migration, and invasion. We noted a high level of Cavin-2 expression in the neovascular tufts in the mouse model of oxygen-induced retinopathy, suggesting a role for Cavin-2 in pathogenic angiogenesis. Interestingly, we also found that Cavin-2 regulates the production of nitric oxide (NO) in endothelial cells by controlling the stability and activity of the endothelial nitric oxide synthase (eNOS) and that Cavin-2 knockdown cells produce much less NO than WT cells. Also, mass spectrometry, flow cytometry, and electron microscopy analyses indicated that Cavin-2 is secreted in endothelial microparticles (EMPs) and is required for EMP biogenesis. Taken together, our results indicate that in addition to its function in caveolae biogenesis, Cavin-2 plays a critical role in endothelial cell maintenance and function by regulating eNOS activity.

PMID: 28912276

J Neurochem. 2017 Sep 11. [Epub ahead of print]

Serine racemase deficiency attenuates choroidal neovascularization and reduces nitric oxide and VEGF levels by retinal pigment epithelial cells.


Abstract: Choroidal neovascularization (CNV) is a leading cause of blindness in age-related macular degeneration. Production of VEGF and macrophage recruitment by retinal pigment epithelial cells (RPE) significantly contributes to the process of CNV in an experimental CNV model. Serine racemase (SR) is expressed in retinal neurons and glial cells, and its product, D-serine, is an endogenous co-agonist of N-methyl-D-aspartate receptor (NMDAR). Activation of the receptor results in production of nitric oxide (NO), a molecule that promotes retinal and choroidal neovascularization. These observations suggest possible roles of SR in CNV. With laser-injured CNV mice, we found that inactivation of SR-coding gene (Srrnull) significantly reduced CNV volume, neovascular density, and invading macrophages. We exploited the underlying mechanism in vivo and ex vivo. RPE from wild-type (WT) mice expressed SR. To explore the possible downstream target of SR inactivation, we showed that choroid/RPE homogenates extracted from laser-injured Srrnull mice contained less inducible nitric oxide synthase (iNOS) and decreased phospho-VEGFR2 compared to amounts in WT mice. In vitro, inflammation-primed WT RPEs expressed more iNOS, produced more NO and VEGF than did inflammation-primed Srrnull RPEs. When co-cultured with inflammation-primed Srrnull RPE, significantly fewer RF/6A-a cell line of choroidal endothelial cell (CEC), migrated to the opposite side of the insert membrane than did cells co-cultured with pre-treated WT RPE. Altogether, SR deficiency reduces RPE response to laser-induced inflammatory stimuli, resulting in decreased production of a cascade of pro-angiogenic cytokines, including NO and VEGF, and reduced macrophage recruitment, which contribute synergistically to attenuated angiogenesis.

PMID: 28892569
Epidemiology

Curr Eye Res. 2017 Sep 14:1-10. [Epub ahead of print]

Gender Differences in the Relationship between Sex Hormone Deficiency and Soft Drusen.
Kwon HJ, Lee SM, Pak KY, Park SW, Lee JE, Byon IS.

PURPOSE: To investigate the association between sex hormone deficiency and soft drusen in women and men.

MATERIALS AND METHODS: We retrospectively reviewed the medical records and fundus photographs of subjects who underwent a health screening for additional examination of climacterium and age-related changes including sex hormone status. In women, sex hormone deficiency was defined as cessation of menstruation that had lasted for at least 12 months and follicular stimulating hormone (FSH) levels ≥ 25 mIU/mL; in men, it was defined as testosterone levels ≤ 3.5 ng/mL. The subjects were divided into two groups-the soft drusen and control groups-based on the presence of soft drusen in the fundus photographs. The total drusen area was measured using ImageJ™ software.

RESULTS: Of total 2036 subjects, 638 (271 women; 367 men) were included. Two hundred thirteen subjects (33.4%) had soft drusen (97/271 women, 116/367 men). In women, sex hormone deficiency was more common in the soft drusen group than in the control group (P < 0.001); this was not the case in men. Multivariate logistic regression analysis revealed that sex hormone deficiency was an independent risk factor for soft drusen in women (P < 0.001; odds ratio [OR] = 3.494), as was age (P < 0.001; OR = 1.092). A long post-menopausal period was a risk factor for large soft drusen (≥ 125 μm). (P < 0.001; OR = 1.220). Age was significantly associated with total drusen area in both women (P = 0.022; β = 0.406) and men (P = 0.015; β = 0.246).

CONCLUSIONS: Sex hormone deficiency and its duration were significantly associated with the development and progression of soft drusen in women but not in men. It may be necessary to assess and manage the sex hormone deficiency in women with age-related macular degeneration.

PMID: 28910205


Updates on the Epidemiology of Age-Related Macular Degeneration.
Jonas JB, Cheung CMG, Panda-Jonas S.

Abstract: This meta-analysis reports on current estimates of the prevalence of age-related macular degeneration (AMD) based on a review of recent meta-analyses and literature research. Within an age of 45-85 years, global prevalences of any AMD, early AMD, and late AMD were 8.7% [95% credible interval (CrI), 4.3–17.4], 8.0% (95% CrI, 4.0–15.5), and 0.4% (95% CrI, 0.2–0.8). Early AMD was more common in individuals of European ancestry (11.2%) than in Asians (6.8%), whereas prevalence of late AMD did not differ significantly. AMD of any type was less common in individuals of African ancestry. The number of individuals with AMD was estimated to be 196 million (95% CrI, 140–261) in 2020 and 288 million (95% CrI, 205–399) in 2040. The worldwide number of persons blind (presenting visual acuity < 3/60) or with moderate to severe vision impairment (MSVI; presenting visual acuity < 6/18 to 3/60 inclusive) due to macular disease in 2010 was 2.1 million [95% uncertainty interval (UI), 1.9–2.7] individuals out of 32.4 million individuals blind and 6.0 million (95% UI, 5.2–8.1) persons out of 191 million people with MSVI. Age-standardized prevalence of macular diseases as cause of blindness in adults aged 50+ years worldwide decreased from 0.2% (95% UI, 0.2–0.2) in 1990 to 0.1% (95% UI, 0.1–0.2) in 2010; as cause for MSVI, it remained mostly unchanged (1990: 0.4%; 95% UI, 0.3–0.5; 2010: 0.4%; 95% UI, 0.4–0.6), with no significant sex difference. In 2015, AMD was the fourth most common cause of blindness globally (in
approximately 5.8% of blind individuals) and third most common cause for MSVI (3.9%). These data show the globally increasing importance of AMD.

PMID: 28906084

Ophthalmic Surg Lasers Imaging Retina. 2017 Sep 1;48(9):705-710.

Centrifugal Extension of Retinal Atrophy in Retinal Pigment Epithelium Tears Secondary to Age-Related Macular Degeneration.

Capuano V, Farcì R, Miere A, Amoroso F, Bandello F, Souied EH, Querques G.

BACKGROUND AND OBJECTIVE: To investigate the progression of retinal atrophy in patients with retinal pigment epithelium (RPE) tears secondary to neovascular age-related macular degeneration.

PATIENTS AND METHODS: In this retrospective case series, patients were analyzed at two high-volume referral centers. The extension of the areas without RPE was analyzed yearly from baseline to last examination through fundus autofluorescence (FAF) imaging using Region Finder (Heidelberg Engineering, Heidelberg, Germany).

RESULTS: Sixteen eyes of 14 patients were included in the study. Mean follow-up was 70.11 months ± 15.5 months. The average area of atrophy was 6.89 mm² ± 5.4 mm² at baseline and 9.21 mm² ± 7.7 mm² at the last visit (P < .0001). This accounts for a progression of 0.36 mm² ± 0.46 mm²/year. In all cases, FAF revealed centrifugal extension of retinal atrophy.

CONCLUSIONS: In this series, the area of retinal atrophy enlarged over time. Atrophy enlargement is characterized by centrifugal extension from the base of the tear.

PMID: 28902330


Early Age-related Macular Degeneration with Cardiovascular and Renal Comorbidities: An Analysis of the National Health and Nutrition Examination Survey, 2005-2008.

Cheng Q, Saaddine JB, Klein R, Rothenberg R, Chou CF, Il'yasova D.

PURPOSE: A cross sectional study was designed to examine the relationship of early age-related macular degeneration (AMD) with comorbidities of cardiovascular and renal conditions in the representative population using National Health and Nutrition Examination Survey (NHANES), 2005-2008.

METHODS: Participants (≥40 years) who underwent retinal photography were included. Early AMD was defined by the retinal digital images. The comorbidities were self-reported stroke and heart disease (HD), including angina pectoris (AP), coronary heart disease (CHD), congestive heart failure (CHF), and myocardial infarction (MI). Chronic kidney disease (CKD) was determined based on self-report, estimation of glomerular filtration rate (GFR), or the level of urine albumin.

RESULTS: The age-adjusted odds ratio (OR) and 95% CI for having early AMD for persons with the selected conditions were: 2.6 (1.9, 3.6) for any type of HD. When the conditions were considered separately, ORs (95% CIs) were: 2.0 (1.2, 3.4) for AP; 2.5 (1.6, 3.8) for CHD; 2.4 (1.6, 3.6) for MI; 2.3 (1.3, 3.9) for CHF; 3.3 (2.2, 5.0) for stroke; and 2.4 (1.8, 3.2) for CKD. Covariate-adjusted ORs (AOR) were attenuated for all examined conditions, but remained statistically significant. Having any single condition (AOR [95% CI]: 2.7 [1.5, 4.8]) was significantly associated with early AMD, as was having ≥2 conditions (AOR [95% CI]: 5.2 [3.0, 9.0]). The strongest association was between early AMD and the combination of HD and stroke (AOR [95% CI]: 6.3 [2.9, 13.8]).
CONCLUSION: Cardiovascular and renal comorbidities are associated with early AMD in a representative sample of the US general population.

PMID: 28891729


Methodology of the ZOC-BHVI High Myopia Cohort Study: The Onset and Progression of Myopic Pathologies and Associated Risk Factors in Highly Myopic Chinese.


PURPOSE: The increasing prevalence of high myopia and its associated pathologies has raised challenges to ophthalmic services. This project aims to explore the onset and progression of myopic pathologies in highly myopic eyes through a prospective research cohort established in South China.

METHODS: Patients with high myopia (sphere ≤ -6.00 D) visiting the optometric clinic of Zhongshan Ophthalmic Center (ZOC) were invited to participate in the baseline examinations and follow-up visit over a 10-year period. People having secondary myopia, history of any refractive surgery, significant ocular media opacity, or other severe health problems were excluded. The measurements included visual acuity, ocular biometry, visual function, cycloplegic refraction, fundus imaging, ocular shape by MRI, blood tests and questionnaires.

RESULTS: A total of 890 participants completed the baseline examinations, with a mean age at baseline of 22.7 ± 12.4 years. The mean spherical equivalent at baseline was 10.13 ± 3.65 D, and the mean axial length (AL) was 27.52 ± 1.63 mm. The older subjects tended to have more severe myopia and longer ALs.

CONCLUSION: The study will provide new knowledge on the relationship between high myopia and pathological changes such as myopic macular degeneration and staphyloma.

PMID: 28891727

Genetics & gene therapy

J Mol Graph Model. 2017 Sep 6;77:280-285. [Epub ahead of print]

Exploring the association of rs10490924 polymorphism with age-related macular degeneration: An in silico approach.

Jahanfar F, Hamishehkar H.

Abstract: The polymorphism rs10490924 (A69S) in the age-related maculopathy susceptibility 2 (ARMS2) gene is highly associated with age-related macular degeneration, which is the leading cause of blindness among the elderly population. The ARMS2 gene encodes a putative small (11kDa) protein, which the function and localization of the ARMS2 protein remain under debate. For a better understanding of functional impacts of the A69S mutation, we performed a detailed analysis of the ARMS2 sequence with a broad set of bioinformatics tools. In silico analysis was followed to predict the tertiary structure, putative binding site regions, and binding site residues. Also, the effects of this mutation on protein stability, aggregation propensity, and homodimerization were analyzed. Next, a molecular dynamic simulation was carried out to understand the dynamic behavior of wild-type, A69S, and phosphorylated A69S structures. The results showed alterations in the putative post-translational modification sites on the ARMS2 protein, due to the mutation. Furthermore, the stability of protein and putative homodimer conformations were affected by the mutation. Molecular dynamic simulation results revealed that the A69S mutation enhances the rigidity of the ARMS2 structure and residue serine at position 69 is buried and may not be
phosphorylated; however, phosphorylated serine enhances the flexibility of the ARMS2 structure. In conclusion, our study provides new insights into the deleterious effects of the A69S mutation on the ARMS2 structure.

PMID: 28915445


Niche harmony search algorithm for detecting complex disease associated high-order SNP combinations.


Abstract: Genome-wide association study is especially challenging in detecting high-order disease-causing models due to model diversity, possible low or even no marginal effect of the model, and extraordinary search and computations. In this paper, we propose a niche harmony search algorithm where joint entropy is utilized as a heuristic factor to guide the search for low or no marginal effect model, and two computationally lightweight scores are selected to evaluate and adapt to diverse of disease models. In order to obtain all possible suspected pathogenic models, niche technique merges with HS, which serves as a taboo region to avoid HS trapping into local search. From the resultant set of candidate SNP-combinations, we use G-test statistic for testing true positives. Experiments were performed on twenty typical simulation datasets in which 12 models are with marginal effect and eight ones are with no marginal effect. Our results indicate that the proposed algorithm has very high detection power for searching suspected disease models in the first stage and it is superior to some typical existing approaches in both detection power and CPU runtime for all these datasets. Application to age-related macular degeneration (AMD) demonstrates our method is promising in detecting high-order disease-causing models.

PMID: 28912584 PMCID: PMC5599559

Eye (Lond). 2017 Sep 15. [Epub ahead of print]

Assessing individual risk for AMD with genetic counseling, family history, and genetic testing.


Purpose: The goal was to develop a simple model for predicting the individual risk profile for age-related macular degeneration (AMD) on the basis of genetic information, disease family history, and smoking habits.

Patients and methods: The study enrolled 151 AMD patients following specific clinical and environmental inclusion criteria: age >55 years, positive family history for AMD, presence of at least one first-degree relative affected by AMD, and smoking habits. All of the samples were genotyped for rs1061170 (CFH) and rs10490924 (ARMS2) with a TaqMan assay, using a 7500 Fast Real Time PCR device. Statistical analysis was subsequently employed to calculate the real individual risk (OR) based on the genetic data (ORgn), family history (ORf), and smoking habits (ORsm).

Results and conclusion: The combination of ORgn, ORf, and ORsm allowed the calculation of the Ort that represented the realistic individual risk for developing AMD. In this report, we present a computational model for the estimation of the individual risk for AMD. Moreover, we show that the average distribution of risk alleles in the general population and the knowledge of parents’ genotype can be decisive to assess the real disease risk. In this contest, genetic counseling is crucial to provide the patients with an understanding of their individual risk and the availability for preventive actions.

PMID: 28912512
Association of Apolipoprotein E Polymorphisms with Age-related Macular Degeneration Subtypes: An Updated Systematic Review and Meta-analysis.

Xiying M, Wenbo W, Wangyi F, Qinghuai L3.

BACKGROUND AND AIMS: Age-related macular degeneration (AMD) is the worldwide leading cause of blindness among the elderly, especially in developed countries. The possible association between apolipoprotein E (ApoE) polymorphism (ε2, ε3, ε4) and AMD has been extensively investigated with conflicting results, especially when specifying different clinical phenotypes of AMD. Herein, we conducted a meta-analysis by integrating several recent large-sample studies to verify the effect of ApoE polymorphisms on AMD subtypes.

METHODS: The retrieve for targeted literature was conducted based on the PubMed, Embase, Cochrane library, and Web of Science. Summary odds ratio (OR) and its 95% confidence intervals (CIs) were used for estimation of risk. The p-value was adjusted due to the multiple comparison.

RESULTS: A total of 12 studies included in the final summary analysis, including 13842 cases and 38647 controls. ApoE ε4 carrier was inversely associated with early stage AMD (OR = 0.889, 95% CI = 0.82-0.97), geographic atrophy (OR = 0.594, 95% CI = 0.43-0.83) and neovascular AMD (OR = 0.670, 95% CI = 0.58-0.76). Stratification analysis by ethnicity revealed that the ApoE ε4 carriers was associated with neovascular AMD in both Caucasians (OR = 0.62, 95% CI = 0.47-0.83) and East Asians (OR = 0.68, 95% CI = 0.58-0.79). A significant association of ApoE ε2 carriers was only found with early AMD in Black and East Asian population, however small samples and limited studies restrict its generalization.

CONCLUSION: Our meta-analysis revealed a significantly protective role of ε4 on each subtypes of AMD, but no supportive evidence of the association of ε2 with AMD. Thus, further studies with larger samples are needed to understand the precise role of ε2 on AMD susceptibility.

PMID: 28889998

Stem cells

Stem Cells. 2017 Sep 15. [Epub ahead of print]

An iPSC Patient Specific Model of CFH (Y402H) Polymorphism Displays Characteristic Features of AMD and Indicates a Beneficial Role for UV Light Exposure.


Abstract: Age related macular degeneration (AMD) is the most common cause of blindness, accounting for 8.7% of all blindness globally. Vision loss is caused ultimately by apoptosis of the retinal pigment epithelium (RPE) and overlying photoreceptors. Treatments are evolving for the wet form of the disease, however these do not exist for the dry form. Complement factor H (CFH) polymorphism in exon 9 (Y402H) has shown a strong association with susceptibility to AMD resulting in complement activation, recruitment of phagocytes, retinal pigment epithelium (RPE) damage and visual decline. We have derived and characterised induced pluripotent stem cell (iPSCs) lines from two patients without AMD and low risk genotype and two patients with advanced AMD and high risk genotype and generated RPE cells that show local secretion of several proteins involved in the complement pathway including factor H (FH), factor I (FI) and factor H like 1 (FHL-1). The iPSC RPE cells derived from high risk patients mimic several key features of AMD including increased inflammation and cellular stress, accumulation of lipid droplets, impaired autophagy and deposition of “drüsen” like deposits. The low and high risk RPE cells respond differently to
intermittent exposure to UV light which leads to an improvement in cellular and functional phenotype only in the high risk AMD-RPE cells. Taken together our data indicate that the patient specific iPSC model provides a robust platform for understanding the role of complement activation in AMD, evaluating new therapies based on complement modulation and drug testing.

PMID: 28913923

**Ophthalmic Surg Lasers Imaging Retina. 2017 Sep 1;48(9):772-775.**

**Bilateral Retinal Detachments After Intravitreal Injection of Adipose-Derived ‘Stem Cells’ in a Patient With Exudative Macular Degeneration.**

Saraf SS, Cunningham MA, Kuriyan AE, Read SP, Rosenfeld PJ, Flynn HW Jr, Albini TA.

Abstract: A 77-year-old woman with exudative macular degeneration underwent bilateral intravitreal injections of "stem cells" at a clinic in Georgia. One month and 3 months after injection, she developed retinal detachments in the left and right eyes, respectively. Increased awareness within the medical community of such poor outcomes is critical so that clinics offering untested practices that have been shown to be potentially harmful to patients can be identified and brought under U.S. Food and Drug Administration oversight.

PMID: 28902341

**Diet, lifestyle & low vision**

**Invest Ophthalmol Vis Sci. 2017 Sep 1;58(11):4569-4578.**

**Associations Between Vitamin D Intake and Progression to Incident Advanced Age-Related Macular Degeneration.**

Merle BMJ, Silver RE, Rosner B, Seddon JM.

PURPOSE: There is growing evidence of the importance of nutrition in age-related macular degeneration (AMD), but no prospective studies have explored the impact of vitamin D. We evaluated the association between vitamin D intake and progression to advanced AMD.

METHODS: Among 2146 participants (3965 eyes), 541 (777 eyes) progressed from early or intermediate AMD to advanced disease (mean follow-up: 9.4 years) based on ocular imaging. Nutrients were log transformed and calorie adjusted. Survival analysis was used to assess associations between incident advanced disease and vitamin D intake. Neovascular disease (NV) and geographic atrophy (GA) were evaluated separately. Combined effects of dietary vitamin D and calcium were assessed based on high or low consumption of each nutrient.

RESULTS: There was a lower risk of progression to advanced AMD in the highest versus lowest quintile of dietary vitamin D intake after adjustment for demographic, behavioral, ocular, and nutritional factors (hazard ratio [HR]: 0.60; 95% confidence interval [CI]: 0.43-0.83; P trend = 0.0007). Similar results were observed for NV (HR: 0.59; 95% CI: 0.39-0.89; P trend = 0.005) but not GA (HR: 0.83; 95% CI: 0.53-1.30; P trend = 0.35). A protective effect was observed for advanced AMD among participants with high vitamin D and low calcium compared to the group with low levels for each nutrient (HR: 0.67; 95% CI: 0.50-0.88; P = 0.005). When supplement use was considered, the effect was in the protective direction but was not significant.

CONCLUSIONS: A diet rich in vitamin D may prevent or delay progression to advanced AMD, especially NV. Additional exploration is needed to elucidate the potential protective role of vitamin D and its contribution to reducing visual loss.

PMID: 28892825 PMCID: PMC5595226
Depressive Symptoms and Quality of Life in Age-related Macular Degeneration Based on Korea National Health and Nutrition Examination Survey (KNHANES).


PURPOSE: This study was conducted to investigate the depressive symptoms and quality of life (QOL) in patients with age-related macular degeneration (AMD) using data obtained from the Korea National Health and Nutritional Examination Survey V-2 (KNHANES V-2) conducted in 2011.

METHODS: This was a population-based, cross-sectional study that selected 329 participants from the fifth KNHANES (2011) who were diagnosed with AMD by an ophthalmologist based on fundus photography. The prevalence of depressive symptoms and the health-related QOL (using EuroQol indices) in this cohort were also estimated. Factors associated with depressive symptoms, including socioeconomic status, QOL indices, and associated chronic diseases, were investigated using multivariate regression models.

RESULTS: Depressive symptoms were observed more frequently in AMD patients than in non-AMD controls (p = 0.013). Among the total 329 AMD participants, 65 (19.8%) had depressive symptoms. There were 16 males (24.6%) and 49 females (75.4%). Upon multivariate analysis, significant factors found to be associated with depressive symptoms were female gender (odds ratio [OR], 2.082; 95% confidence interval [CI], 1.001 to 4.330), being in the "dependent" group for activities of daily living (OR, 4.638; 95% CI, 2.061 to 10.435), and having "some problems" in the "anxiety-depression" dimension of the EQ-5D (OR, 7.704; 95% CI, 1.890 to 31.408).

CONCLUSIONS: Female gender and being dependent on others for activities of daily living increased the association of depressive symptoms in this cohort of AMD participants. Screening for depressive symptoms in East Asian AMD patients with these characteristics should be an important component of their care.

PMID: 28913998