Drug treatment


Long-term outcome of treat and extend intravitreal ziv-aflibercept therapy.

Mansour AM, Charbaji A, Farah ME, Mansour HA, Chhablani J.

Aim: To assess the 30-month outcome of treat and extend (TAE) intravitreal ziv-aflibercept therapy in eyes with macular diseases.

Methods: In this prospective study, consecutive subjects received intravitreal 0.05 mL ziv-aflibercept (1.25 mg) injections for various macular diseases. Outcome measures were best-corrected visual acuity (BCVA) (logarithm of the minimum angle of resolution) and central macular thickness (CMT) on spectral domain optical coherence tomography. Paired comparison was done using Wilcoxon signed-rank test calculator.

Results: Fifty-three eyes of 48 subjects (33 naïve eyes) received intravitreal ziv-aflibercept and were followed between 12 and 30 months following TAE included neovascular age-related macular degeneration (nAMD) (35 eyes) and diabetic macular oedema (DMO) (18 eyes). In eyes with nAMD, CMT decreased by 107.8 μm at the 30-month follow-up (p=0.012) with BCVA gain of 0.52 (p=0.001). In eyes with DMO, CMT decreased by 224.3 μm at the 30-month follow-up (p=0.027) with BCVA gain of 0.46 (p=0.042). Combining all disease categories, the mean number of injections was 9.2 at month 12, 2.5 between 12 and 18 months, 1.6 between 18 and 24 months and 1.0 between 24 and 30 months.

Conclusion: Using TAE regimen, intravitreal ziv-aflibercept appeared efficacious at managing retinal disease through month 30 using the TAE regimen.

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Effects of bevacizumab, ranibizumab, and aflibercept on phagocytic properties in human RPE cybrids with AMD versus normal mitochondria.

Vo TA, Abedi S, Schneider K, Chwa M, Kenney MC.

Purpose: A critical biological function of retina pigment epithelium (RPE) cells is phagocytosis of photoreceptor outer segment (POS) disc membranes. Mitochondrial damage and dysfunction are
associated with RPE cells of age-related macular degeneration (AMD) retinas. In this study, we use a transmitochondrial cybrid model to compare the phagocytic properties of RPE cells that contain AMD mitochondria versus age-matched normal mitochondria and their response to treatment with anti-vascular endothelial growth factor (VEGF) drugs: bevacizumab, ranibizumab, and aflibercept.

**Methods:** Cybrids, which are cell lines with identical nuclei but mitochondria (mt) from different subjects, are created by fusing mtDNA depleted ARPE-19 cells with platelets from AMD or age-matched normal patients. AMD (n = 5) and normal (n = 5) cybrids were treated with 1 μm fluorescent latex beads (1.52 × 10^7 beads/mL) and either 2.09 μM of bevacizumab, 2.59 μM of ranibizumab, or 5.16 μM of aflibercept. These doses of anti-VEGF drugs are equivalent to intravitreal injections given to AMD patients with choroidal neovascularization. Flow cytometry was performed using the ImageStreamX Mark II to assess phagocytic bead-uptake. The average fold values for bead-uptake and SEM were calculated using GraphPad Prism software.

**Results:** Normal cybrids showed decreased bead-uptake with a fold value of 0.65 ± 0.10 (p = 0.0098) after treatment with bevacizumab, 0.80 ± 0.034 (p = 0.0003) with ranibizumab, and 0.81 ± 0.053 (p = 0.0065) with aflibercept compared to the untreated normal cybrids (baseline fold of 1). The bevacizumab-treated, ranibizumab-treated, and aflibercept-treated AMD cybrids had decreased bead-uptake with a fold value of 0.71 ± 0.061 (p = 0.0014), 0.70 ± 0.10 (p = 0.019), and 0.74 ± 0.12 (p = 0.067), respectively, compared to the untreated AMD cybrids (baseline fold of 1).

**Conclusions:** Our initial findings showed that when treated with bevacizumab and ranibizumab, both AMD cybrids and age-matched normal cybrids had a significant decrease in bead-uptake. A similar decrease in bead-uptake was found in normal cybrids treated with aflibercept and while the AMD values trended lower, they were not significant. This data suggests that anti-VEGF drugs can cause loss of phagocytic function.

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**Klin Monbl Augenheilkd. 2018 Aug 2. [Epub ahead of print]**

**Changes in retinal vascular caliber after intravitreal aflibercept treatment for diabetic macular oedema.**

[Article in German]


**Purpose:** Diabetic retinopathy is characterised by impaired retinal vascular autoregulation with signs of early retinal hyperperfusion and subsequent capillary drop out and peripheral ischemia. Initial retinal vascular dilation indicates disease progression and subsequent constriction signals a proliferative state. In this pilot study, we examined the effect of intravitreal aflibercept on retinal vessel diameter in patients with diabetic macular oedema.

**Methods:** Twelve eyes of nine treatment-naive patients with diabetic macular oedema were examined during the first three months of treatment with aflibercept. The calibers of retinal arteries and veins and the central retinal arterial and vein equivalent were registered over the course of treatment. The evolution of the diabetic macular oedema was also registered and correlated to the retinal vascular caliber.

**Results:** During treatment, there was a significant reduction in the diameter of retinal arteries as well as in the central retinal arterial equivalent. The calibers of the retinal veins were also reduced, but not significantly. Macular oedema was significantly reduced, which however did not correlate with the vascular caliber changes.

**Conclusions:** This pilot study demonstrates for the first time a possible significant reduction in retinal arterial caliber under aflibercept treatment for diabetic macular oedema. Further studies are needed to verify whether this response to intravitreal anti-VEGF treatment also signifies an improvement in retinal vascular homeostasis.
Comparative efficacy of bevacizumab, ranibizumab, and aflibercept for treatment of macular edema secondary to retinal vein occlusion: a systematic review and network meta-analysis.

Sangroongruangsri S, Ratanapakorn T, Wu O, Anothaisintawee T, Chaikledkaew U.

Abstract: Anti-vascular endothelial growth factor (VEGF) therapy has become the most commonly used treatment for macular edema secondary to retinal vein occlusion (RVO). Although its superior efficacy as compared to other interventions has been proven, there is a lack of evidence for relative efficacy among anti-VEGF drugs. Areas covered: This work systematically reviewed and compared the efficacy of intravitreal bevacizumab, ranibizumab, and aflibercept for treating macular edema due to RVO. PubMed, EMBASE, and the Cochrane Library were searched from their inception until October 2017. Eleven randomized controlled trials (18 articles; 1,830 adult patients) were identified. The proportion of patients who gained at least 15 letters in best-corrected visual acuity (BCVA), mean change from baseline in BCVA, and mean change from baseline in central macular thickness (CMT) were reported and these efficacy outcomes at six months were analyzed in network meta-analysis. Expert commentary: Apparently, bevacizumab, ranibizumab, and aflibercept were significantly superior to sham injection in terms of BCVA improvement and CMT reduction and had good safety profiles. However, there were no statistically significant differences in any outcomes among anti-VEGF drugs. In selecting an anti-VEGF drug for individual patients, other factors including affordability, drug availability, and patient characteristics should be considered.

Real-world safety of intravitreal bevacizumab and ranibizumab treatments for retinal diseases in thailand: a prospective observational study.


Background: There is very limited evidence examining serious systemic adverse events (SSAEs) and post-injection endophthalmitis of intravitreal bevacizumab (IVB) and intravitreal ranibizumab (IVR) treatments in Thailand and low- and middle-income countries. Moreover, findings from the existing trials might have limited generalizability to certain populations and rare SSAEs.

Objectives: This prospective observational study aimed to assess and compare the safety profiles of IVB and IVR in patients with retinal diseases in Thailand.

Methods: Between 2013 and 2015, 6354 patients eligible for IVB or IVR were recruited from eight hospitals. Main outcomes measures were prevalence and risk of SSAEs, mortality, and endophthalmitis during the 6-month follow-up period.

Results: In the IVB and IVR groups, 94 and 6% of patients participated, respectively. The rates of outcomes in the IVB group were slightly greater than in the IVR group. All-cause mortality rates in the IVB and IVR groups were 1.10 and 0.53%, respectively. Prevalence rates of endophthalmitis and non-fatal strokes in the IVB group were 0.04% of 16,421 injections and 0.27% of 5975 patients, respectively, whereas none of these events were identified in the IVR group. There were no differences between the two groups in the risks of mortality, arteriothrombotic events (ATE), and non-fatal heart failure (HF). Adjustment for potential confounding factors and selection bias using multivariable models for time-to-event outcomes and propensity scores did not alter the results.
Conclusions: The rates of SAEs in both groups were low. The IVB and IVR treatments were not associated with significant risks of mortality, ATE, and non-fatal HF.

Trial Registration: Thai Clinical Trial Registry identifier TCTR20141002001.

PMID: 30069864 DOI: 10.1007/s40261-018-0678-5

**Other treatment and diagnosis**


Swept-source optical coherence tomography angiography features of subretinal fibrosis in neovascular age-related macular degeneration.


**Importance:** The study highlights the role of Optical Coherence Angiography in the management of patients with neovascular age-related macular degeneration who have developed subretinal fibrosis.

**Background:** Development of subretinal fibrosis in the context of neovascular age-related macular degeneration is known to adversely affect visual function. The aim of this study is to assess structure and flow features obtained through swept-source optical coherence tomography angiography in patients with subretinal fibrosis and associate these with visual acuity.

**Design:** Institutional retrospective cohort study

**PARTICIPANTS:** 39 eyes of 39 patients with neovascular age-related macular degeneration with subretinal fibrosis imaged with optical coherence tomography angiography were included in this study

**METHODS:** Patients underwent Swept-Source Optical Coherence Tomography Angiography. Thickness of subretinal hyper-reflective material and presence and configuration of a choroidal neovascular membrane were recorded in each case.

**Main Outcome Measures:** A univariate multiple regression was performed seeking associations between visual acuity and structural and flow optical coherence tomography angiography features.

**Results:** Average visual acuity on the date of optical coherence tomography angiography was 53 ± 22 ETDRS letters. Average thickness of center-involving subretinal hyper-reflective material was 157 ± 73 microns. A choroidal neovascular membrane was detectable in 26 cases and not detectable in 13. Visual acuity was independently influenced by thickness of subretinal hyper-reflective material (p=0.034) and presence of a detectable choroidal neovascular membrane (p=0.02) on optical coherence tomography angiography.

**Conclusions and Relevance:** Poorer visual acuity in patients with neovascular age-related macular degeneration and subretinal fibrosis is associated with presence of a detectable neovascular membrane on optical coherence tomography angiography. The role of optical coherence tomography angiography to guide nuanced management decisions in this patient population may be significant.

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**OCT angiography and evaluation of the choroid and choroidal vascular disorders.**

Borrelli E, Sarraf D, Freund KB, Sadda SR.

**Abstract:** The recent introduction of optical coherence tomography angiography (OCTA) has remarkably expanded our knowledge of the choroid through in vivo investigation of the anatomical and pathological features of this important vascular layer. New insights elucidating the morphological features of the choroid,
in both physiological and pathological conditions, indicate that this vascular structure plays a crucial role in many chorioretinal disorders. In this article, a review of the salient histological and anatomical features of the choroid, essential for the proper interpretation of in vivo imaging, is followed by a discussion of the fundamental principles of OCTA and the application of this advanced imaging modality to study and understand the choroid. The current limitations of OCTA and potential advancements that may improve the widespread adoption of this tool are also discussed. A detailed review of the OCTA features of the choroid in the healthy eye is followed by relevant findings in major chorioretinal diseases, including age-related macular degeneration, central serous chorioretinopathy, uveitis, and inherited retinal disorders.

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Choroidal structural changes correlate with neovascular activity in neovascular age related macular degeneration.


Purpose: To correlate changes in choroidal thickness and vascularity index with disease activity in patients with neovascular age-related macular degeneration (nAMD).

Methods: Eyes diagnosed with AMD that had two sequential visits within 12 months and that had no choroidal neovascularization (CNV) or had inactive CNV at the first visit were included. Those that had active CNV at follow-up were enrolled as cases. Eyes that did not developed a CNV or that were still inactive at the second visit were enrolled as controls. Disease activity was based on optical coherence tomography (OCT) and fluorescein angiography findings. Subfoveal choroidal thickness (SCT), mean choroidal thickness (MCT), and choroidal vascularity index (CVI) were assessed on enhanced depth imaging OCT and compared between the baseline and follow-up visit. Subgroup analysis accounting for lesion type and previous treatment, if any, were performed.

Results: Sixty-five eyes from 60 patients (35 females) and 50 age- and sex-matched controls were included. At the active visit, cases had an increase from 164 ± 67 μm to 175 ± 70 μm in mean ± SD SCT and from 144 ± 45 μm to 152 ± 45 μm in MCT (both P < 0.0001). The mean CVI also increased at from 54.5% ± 3.3% to 55.4% ± 3.8% (P = 0.04). Controls did not show significant changes in choroidal measurements between the two visits. Mean SCT, MCT, and CVI values were similar for previously treated and treatment-naive eyes.

Conclusions: Choroidal thickness and CVI significantly increased with active disease in nAMD eyes. Changes in choroidal thickness may predict CNV development or recurrence before they are otherwise evident clinically.

PMID: 30073357 DOI: 10.1167/iovs.18-23960

Pathogenesis


Dynamic interplay of innate and adaptive immunity during sterile retinal inflammation: insights from the transcriptome.


Abstract: The pathogenesis of many retinal degenerations, such as age-related macular degeneration (AMD), is punctuated by an ill-defined network of sterile inflammatory responses. The delineation of innate
and adaptive immune milieu among the broad leukocyte infiltrate, and the gene networks, which construct these responses, are poorly described in the eye. Using photo-oxidative damage in a rodent model of subretinal inflammation, we employed a novel RNA-sequencing framework to map the global gene network signature of retinal leukocytes. This revealed a previously uncharted interplay of adaptive immunity during subretinal inflammation, including prolonged enrichment of myeloid and lymphocyte migration, antigen presentation, and the alternative arm of the complement cascade involving Factor B. We demonstrate Factor B-deficient mice are protected against macrophage infiltration and subretinal inflammation. Suppressing the drivers of retinal leukocyte proliferation, or their capacity to elicit complement responses, may help preserve retinal structure and function during sterile inflammation in diseases such as AMD.

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Evaluation of serum sphingolipids and the influence of genetic risk factors in age-related macular degeneration.


Abstract: Sphingolipids are bioactive molecules associated with oxidative stress, inflammation, and neurodegenerative diseases, but poorly studied in the context of age-related macular degeneration (AMD), a prevalent sight-threatening disease of the ageing retina. Here, we found higher serum levels of hexosylceramide (HexCer) d18:1/16:0 in patients with choroidal neovascularization (CNV) and geographic atrophy (GA), two manifestations of late stage AMD, and higher ceramide (Cer) d18:1/16:0 levels in GA patients. A sensitivity analysis of genetic variants known to be associated with late stage AMD showed that rs1061170 (p.Y402H) in the complement factor H (CFH) gene influences the association of Cer d18:1/16:0 with GA. To understand the possible influence of this genetic variant on ceramide levels, we established a cell-based assay to test the modulation of genes in the ceramide metabolism by factor H-like protein 1 (FHL-1), an alternative splicing variant of CFH that also harbors the 402 residue. We first showed that malondialdehyde-acetaldehyde adducts, an oxidation product commonly found in AMD retinas, induces an increase in ceramide levels in WERI-Rb1 cells in accordance with an increased expression of ceramide synthesis genes. Then, we observed that cells exposed to the non-risk FHL-1: Y402, but not the risk associated variant FHL-1:H402 or full-length CFH, downregulated ceramide synthase 2 and ceramide glucosyltransferase gene expression. Together, our findings show that serum ceramide and hexosylceramide species are altered in AMD patients and that ceramide levels may be influenced by AMD associated risk variants.

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Comparison of subfoveal choroidal structures in typical neovascular age-related macular degeneration and polyposidal choroidal vasculopathy.


Purpose: To evaluate and compare the intrachoroidal structures of eyes with typical neovascular age-related macular degeneration (AMD) with those of eyes with polyposidal choroidal vasculopathy (PCV).

Study Design: Retrospective and comparative case series.

Methods: Eighty-four treatment-naïve eyes of 84 patients (22 women and 62 men) with typical neovascular AMD or PCV located in the subfoveal region were studied. Cross-sectional images of the retina and choroid were obtained by swept-source optical coherence tomography (SS-OCT). The horizontal SS-OCT images
were analyzed by a manual delineation technique and by a binarization method.

Results: Thirty-nine eyes with typical neovascular AMD and 45 eyes with PCV were studied. Although the subfoveal choroidal thickness (SCT) did not differ significantly between the 2 subtypes (255.1 ± 86.7 µm in typical neovascular AMD and 289.2 ± 116.5 µm in PCV, P = 0.29), the ratio of the large choroidal vessel layer (LCVL) thickness to the SCT was significantly larger in the eyes with PCV than in the eyes with typical neovascular AMD (0.863 ± 0.084 vs 0.803 ± 0.125, P = 0.023). The binarization method did not find significant differences in the choroidal structure between the 2 subtypes. Multivariate logistic regression analyses found the ratio of the LCVL thickness to the SCT to be the only significantly different factor between typical neovascular AMD and PCV (P = 0.035).

Conclusion: The intrachoroidal structures of typical neovascular AMD and PCV eyes differ significantly. In eyes with PCV, there seemed to be a greater dilation of the large choroidal vessels.

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Retinal thickness changes throughout the natural history of drusen in age-related macular Degeneration.

Nivison-Smith L, Wang H, Assaad N, Kalloniatis M.

Significance: Drusen are associated with retinal thinning in age-related macular degeneration (AMD). These changes, however, have mostly been examined at single time points, ignoring the evolution of drusen from emergence to regression. Understanding the full breadth of retinal changes associated with drusen will improve understanding of disease pathogenesis.

Purpose: The purpose of this study was to assess how the natural history of drusen affects retinal thickness, focusing on the photoreceptor and retinal pigment epithelium (RPE) layers.

Methods: Spectral domain optical coherence tomography of subjects with intermediate AMD (n = 50) who attended the Centre for Eye Health, Sydney, Australia, for two separate visits (476 ± 16 days between visits) was extracted. Scans were automatically segmented with manufacturer software then assessed for drusen that had emerged, grown, or regressed between visits. For each identified lesion, the thickness of each retinal layer at the drusen peak and at adjacent drusen-free areas (150 µm nasal and temporal to the druse) was compared between visits.

Results: Before drusen emergence, the RPE was significantly thicker at the drusen site (14.2 ± 2.6%) compared with neighboring drusen-free areas. There was a 71% sensitivity of RPE thickening predicting drusen emergence. Once drusen emerged, significant thinning of all outer retinal layers was observed, consistent with previous studies. Drusen growth was significantly correlated with thinning of the outer retina (r = -0.38, P < .001). Drusen regression resulted in outer retinal layers returning to thicknesses not significantly different from baseline.

Conclusions: The natural history of drusen is associated with RPE thickening before drusen emergence, thinning of the outer nuclear layer as well as photoreceptor and RPE layers proportional to drusen growth, and return to baseline thickness after drusen regression. These findings have useful clinical applications, providing a potential marker for predicting drusen emergence for AMD prognostic and intervention studies and highlighting that areas of normal retinal thickness in AMD may be former sites of regressed drusen.

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Retinal arterial dilation is impaired in eyes with drusen and reticular pseudodrusen.

Rabiolo A, Benatti L, Tomasso L, Zucchiati I, Gelormini F, Casaluc M, Querques L, Sacconi R, Bandello F, Querques G.

Purpose: To analyze static characteristics and dynamic functionality of retinal vessels in eyes with drusen and reticular pseudodrusen (RPD) using dynamic vessel analyzer.

Methods: Patients with clinical diagnosis of isolated RPD or medium-large drusen and healthy controls were enrolled in the study between July 2016 and May 2018. Participants underwent complete ophthalmologic examination, including enhanced depth imaging structural optical coherence tomography, dynamic retinal vessel analysis, and static retinal vessel analysis.

Results: Twenty-eight eyes of 23 patients with drusen (9 men, mean age 77 ± 6 years), 22 eyes of 16 patients with RPD (7 men, mean age: 76 ± 6 years), and 22 eyes of 22 control subjects (11 men, mean age of 75 ± 6 years) were enrolled. Static retinal vessel analysis did not show any significant difference between the three groups for the central retinal artery equivalent (P = 0.11), the central retinal vein equivalent (P = 0.27), and the arteriovenous ratio (P = 0.30). Dynamic vessel analysis showed significantly reduced arterial dilation in eyes with drusen (P = 0.0001) and RPD (P = 0.015) compared with control subjects. No significant difference was seen between drusen and RPD groups (P = 0.32). Dynamic vessel analysis of retinal veins showed no differences between the three groups (P = 0.10).

Conclusion: Dynamic vessel analysis in eyes with drusen and RPD revealed an impaired retinal arterial dilation in response to flicker light stimulation, which further supports the relationship between cardiovascular risk and age-related macular degeneration.

PMID: 30074940 DOI: 10.1097/IAE.0000000000002283


Retinal vascular flow and choroidal thickness in eyes with early age-related macular degeneration with reticular pseudodrusen.

Ahn SM, Lee SY, Hwang SY, Kim SW, Oh J, Yun C.

Background: To investigate the characteristics of retinal vessels and retinal thickness in eyes with early age-related macular degeneration (AMD) with or without reticular pseudodrusen.

Methods: We retrospectively evaluated the clinical history and optical coherence tomography (OCT) and OCT angiography images of consecutive patients with early AMD. We calculated the retinal vessel densities of the superficial and deep capillary plexus with the ImageJ software (National Institutes of Health, Bethesda, MD, USA) and investigated the relationship with mean retinal thickness and subfoveal choroidal thickness.

Results: We included 135 early AMD eyes and classified 60 of them into a reticular pseudodrusen group and 75 into a non-reticular pseudodrusen group. The vascular densities of the superficial and deep capillary plexus in the reticular pseudodrusen group (32.35% ± 3.67 and 26.71% ± 2.88%) were not different from those of the non-reticular pseudodrusen group (33.18% ± 2.2% and % 27.43 ± 1.79%; P = 0.546 and P = 0.318, respectively). The retinal thickness of the reticular pseudodrusen group (287.31 μm ± 24.36 μm) did not differ from that of the non-reticular pseudodrusen group (294.27 μm ± 20.71 μm; P = 0.493), while subfoveal choroidal thickness in the reticular pseudodrusen group (158.13 μm ± 42.53 μm) was lower than that in the non-reticular pseudodrusen group (237.89 μm ± 60.94 μm; P < 0.001). Multivariate analysis revealed that lower vascular density of the superficial capillary plexus and subfoveal choroidal thickness were associated with retinal thinning in reticular pseudodrusen group (P = 0.003 and P = 0.036) and older age was associated with retinal thickness in the non-reticular pseudodrusen group (P = 0.005).
Conclusions: Retinal thinning in early AMD patients with reticular pseudodrusen was accompanied by choroidal and retinal vascular loss, which suggests a possible linkage of retinal thinning with vascular alterations.

PMID: 30055588 PMCID: PMC6064139 DOI: 10.1186/s12886-018-0866-3


Nitrite ion modifies tyrosine and lysine residues of extracellular matrix proteins.

Thao MT, Karumanchi DK, Yacout SM, Gaillard ER.

Abstract: Age-related macular degeneration (AMD) is a disease characterized by degenerative changes in the retinal pigment epithelium and Bruch's membrane. Inflammation is considered a major risk factor for the development and progression of AMD. Nitrite is a potent byproduct of inflammation and has been detected at elevated concentrations in AMD donor tissue. We hypothesize that nitrite chemically modifies the extracellular matrix (ECM) of Bruch's membrane as an initial step to degenerative changes observed in AMD. Non-enzymatically nitrated synthetic ECM peptides, fibronectin and laminin, were used as model systems for inflammation. Using LC/MS, we identified that nitration preferentially occurred on tyrosine and deamination of lysine under the studied conditions. At tyrosine residues, 3-nitrotyrosine was produced and shifted the total mass by the addition of 45 amu. Deamination of lysine occurred and resulted in the formation of either an alkene or alcohol group. The alkene group was observed with a loss of 17 amu. An addition of 1 amu was observed with alcohol formation. We hypothesize that these initial chemical modifications to the structure of ECM proteins may be the responsible for altering the structure and consequent function of Bruch's membrane.

PMID: 30055286 DOI: 10.1016/j.niox.2018.07.006

Epidemiology


The association between diabetes and age-related macular degeneration among the elderly in Taiwan.

He MS, Chang FL, Lin HZ, Wu JL, Hsieh TC, Lee YC.

Objective: To investigate the relationship between diabetes and future development of age-related macular degeneration (AMD).

Research Design and Methods: Longitudinal, retrospective cohort study data for the period between 1997 and 2012 were obtained from the Longitudinal Health Insurance Database of Taiwan. The final available 71,904 patients with diabetes and 270,213 patients without diabetes ≥50 years of age were further matched by age, sex, and Charlson comorbidity index. In the end, 54,616 study subjects in each of the diabetes and nondiabetes groups were recruited. The stratified populations of patients with diabetes with diabetic retinopathy (DR) (n = 7,119) versus those with diabetes who do not have DR (n = 7,119), and populations of patients with proliferative DR (PDR) (n = 2,134) versus those with nonproliferative DR (NPDR) (n = 2,134) were also obtained. Competing risk regression models were used to assess the adjusted hazard ratio (HR) and 99% CI. The main outcome measures were the first-ever diagnosis of AMD during the observational period.

Results: The incidences of nonexudative AMD (HR 1.23; P = 0.108) and exudative AMD (HR 1.37; P = 0.023) were not significantly associated with cohorts of persons with diabetes compared with cohorts without diabetes. The stratified analysis showed that nonexudative AMD (HR 3.89; P = 0.001) and exudative AMD (HR 3.42; P < 0.001) were significantly correlated to diabetes with DR cohorts, compared
with diabetes without DR cohorts. The incidences of nonexudative AMD (HR 0.53; P = 0.277) and exudative AMD (HR 2.27; P = 0.058) were not significantly different between PDR cohorts compared with NPDR cohorts.

Conclusions: This study provides large-scale, population-based evidence that diabetes with retinopathy is independently associated with an increased risk of subsequent AMD development.

PMID: 30061321 DOI: 10.2337/dc18-0707


Progression of geographic atrophy in age-related macular degeneration: AREDS2 report number 16.


Purpose: To analyze the prevalence, incidence, and clinical characteristics of eyes with geographic atrophy (GA) in age-related macular degeneration (AMD), including clinical and genetic factors affecting enlargement.

Design: Prospective cohort study within a controlled clinical trial.

Participants: Age-Related Eye Disease Study 2 (AREDS2) participants, aged 50-85 years.

Methods: Baseline and annual stereoscopic color fundus photographs were evaluated for GA presence and area. Analyses included GA prevalence and incidence rates, Kaplan-Meier rates, mixed-model regression, and multivariable analysis of the square root of GA, area adjusted for covariates, including clinical/imaging characteristics and genotype.

Main Outcome Measures: (1) Presence or development of GA; (2) change in the square root of GA area over time.

Results: At baseline, 517 eyes (6.2%) of 411 participants (9.8%) had pre-existing GA (without neovascular AMD), with the following characteristics: 33% central, 67% noncentral; and the following configurations: 36% small, 26% solid/unifocal, 24% multifocal, 9% horseshoe/ring, and 6% indeterminate. Of the remaining 6530 eyes at risk, 1099 eyes (17.3%) of 883 participants developed incident GA without prior neovascular disease during mean follow-up of 4.4 years. The Kaplan-Meier rate of incident GA was 19% of eyes at 5 years. In eyes with incident GA, 4-year risk of subsequent neovascular AMD was 29%. In eyes with incident noncentral GA, 4-year risk of central involvement was 57%. GA enlargement rate (following square root transformation) was similar in eyes with pre-existing GA (0.29 mm/year; 95% confidence interval 0.27-0.30) and incident GA (0.28 mm/year; 0.27-0.30). In the combined group, GA enlargement was significantly faster with noncentrality, multifocality, intermediate baseline size, and bilateral GA (P < 0.0001 for interaction in each case) but not with AREDS2 treatment assignment (P = 0.33) or smoking status (P = 0.05). Enlargement was significantly faster with ARMS2 risk (P < 0.0001), C3 non-risk (P = 0.0002), and APOE non-risk (P = 0.001) genotypes.

Conclusions: Analyses of AREDS2 data on natural history of GA provide representative data on GA evolution and enlargement. GA enlargement, which was influenced by lesion features, was relentless, resulting in rapid central vision loss. The genetic variants associated with faster enlargement were partially distinct from those associated with risk of incident GA. These findings are relevant to further investigations of GA pathogenesis and clinical trial planning.

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Genetics and gene therapy

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Genome-wide association study suggests four variants influencing outcomes with ranibizumab therapy in exudative age-related macular degeneration.


Abstract: To identify factors associated with ranibizumab responses in patients with exudative age-related macular degeneration (AMD), we performed a genome-wide association study (GWAS) and a replication study using a total of 919 exudative AMD patients treated with intravitreal ranibizumab in a Japanese population. In the combined analysis of GWAS and the replication study, no loci reached genome-wide significant level; however, we found four variants showed suggestive level of associations with visual loss at month three (rs17822656, rs76150532, rs17296444, and rs75165563: \(P_{\text{combined}} < 1.0 \times 10^{-5}\)). Of the candidate genes within these loci, three were relevant to VEGF-related pathway (KCNMA1, SOCS2, and OTX2). The proportions of patients who worsened visual acuity were 13.7%, 38.8%, 58.0%, and 80.0% in patients with 0, 1, 2, and 3 or more identified risk variants, respectively. Changes in visual acuity decreased linearly as the number of risk variants increased (\(P = 1.67 \times 10^{-12}\)). The area under the curve using age, baseline visual acuity, and history of previous treatment was 0.607, and improved significantly to 0.713 in combination with identified variants (\(P < 0.0001\)). Although further study is needed to confirm their associations, our results offer candidate variants influencing response to ranibizumab therapy.

PMID: 30054556 DOI: 10.1038/s10038-018-0493-0

Stem cells


Wound healing of human embryonic stem cell-derived retinal pigment epithelial cells is affected by maturation stage.


Background: Wound healing of retinal pigment epithelium (RPE) is a complex process that may take place in common age-related macular degeneration eye disease. The purpose of this study was to evaluate whether wounding and wound healing has an effect on Ca2+ dynamics in human embryonic stem cell (hESC)-RPEs cultured different periods of time.

Methods: The 9-day-cultured or 28-day-cultured hESC-RPEs from two different cell lines were wounded and the dynamics of spontaneous and mechanically induced intracellular Ca2+ activity was measured with live-cell Ca2+ imaging either immediately or 7 days after wounding. The healing time and speed were analyzed with time-lapse bright field microscopy. The Ca2+ activity and healing speed were analysed with image analysis. In addition the extracellular matrix deposition was assessed with confocal microscopy.

Results: The Ca2+ dynamics in hESC-RPE monolayers differed depending on the culture time: 9-day-cultured cells had higher number of cells with spontaneous Ca2+ activity close to freshly wounded edge compared to control areas, whereas in 28-day-cultured cells there was no difference in wounded and control areas. The 28-day-cultured, wounded and 7-day-healed hESC-RPEs produced wide-spreading intercellular Ca2+ waves upon mechanical stimulation, while in controls propagation was restricted. Most importantly, both wave spreading and spontaneous Ca2+ activity of cells within the healed area, as well as the cell morphology of 28-day-cultured, wounded and thereafter 7-day-healed areas resembled the 9-day-cultured hESC-RPEs.

Conclusions: This acquired knowledge about Ca2+ dynamics of wounded hESC-RPE monolayers is
important for understanding the dynamics of RPE wound healing, and could offer a reliable functionality test for RPE cells. The data presented in here suggests that assessment of Ca2+ dynamics analysed with image analysis could be used as a reliable non-invasive functionality test for RPE cells.

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Case Reports


Intraocular Jarisch-Herxheimer reaction in Lemierre Syndrome.

Ramtohul P, Boulicot-Seguin C, Marc C.

Purpose: To report an intraocular Jarisch-Herxheimer reaction induced by Lemierre syndrome antibiotic.

Methods: Case report.

Results: A 43-year-old-man presented with an acute onset of bilateral blurred vision few days after intravenous antibiotic administration for Lemierre syndrome. Best-corrected visual acuity was 20/32 in both eyes. Examination revealed bilateral cystoid macular edema and peripheral retinal vasculitis, persisting despite Lemierre syndrome recovery with antibiotics. Intravitreal injection of ranibizumab 0.5 mg (0.05 mL) was performed in both eyes. After 1 month, cystoid macular edema and retinal vasculitis were totally resolved, and best-corrected visual acuity increased to 20/20 in both eyes. The paradoxical worsening of the patient's best-corrected visual acuity after initiating antibiotherapy evokes a Jarisch-Herxheimer reaction. The result of this single intravitreal injection of ranibizumab was sustained; best-corrected visual acuity remained unchanged (20/20 in both eyes), and no recurrence of cystoid macular edema or retinal vasculitis was found after 4-year follow-up.

Conclusion: To the best of our knowledge, this is the first reported case of an isolated intraocular Jarisch-Herxheimer reaction induced by Lemierre syndrome antibiotherapy and successfully treated with a single intravitreal injection of ranibizumab.

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Stellate nonhereditary idiopathic foveomacular retinoschisis in a patient with macular telangiectasia type 2.

Falb T, Malle EM, Haas A, Weger M, Wedrich A.

Purpose: To present a case of unilateral stellate nonhereditary idiopathic foveomacular retinoschisis in a patient with macular telangiectasia (MacTel) Type 2.


Results: A 61-year-old female white patient was referred to our clinic with metamorphopsia and reduction of visual acuity over a period of 2 months on her right eye. Ocular findings in her right eye included reduced best-corrected visual acuity of 20/63 Snellen, foveomacular retinoschisis with extension to the lower middle periphery, central elevation of the neurosensory retina, and macular telangiectasia (MacTel) Type 2. Other causes of foveomacular retinoschisis, such as glaucoma, myopic degeneration, optic or scleral pit, X-linked juvenile retinoschisis, degenerative retinoschisis, and vitreomacular traction, were ruled out. The patient had no history of niacin or taxane medication, which may cause rather similar appearing cases of cystoid
macular edema without leakage in fluorescein angiography. Because of the unilateral presentation, uneventful medical history, female sex, and the absence of known hereditary diseases or retinal pathologies in the patient's family history, hereditary predisposition appears to be highly unlikely.

**Conclusion:** To our knowledge, this is the first reported case of stellate nonhereditary idiopathic foveomacular retinoschisis in combination with MacTel Type 2. Whether or not MacTel Type 2 plays a role in the development of stellate nonhereditary idiopathic foveomacular retinoschisis or has an impact on its clinical course requires further investigation. Furthermore, we suggest a significant involvement of Henle fiber layer in the process of intraretinal expansion in optical coherence tomography, in accordance with the most recent published nomenclature.

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**Response to intravitreal aflibercept in a patient with peripheral exudative hemorrhagic chorioretinopathy.**

Sax J, Karpa M, Reddie I.

**Purpose:** To draw attention to a novel treatment agent for vision loss associated with peripheral exudative hemorrhagic chorioretinopathy.

**Methods:** The case of an 83-year-old man suffering with loss of left visual acuity vision in the context of vitreous hemorrhage secondary to peripheral exudative hemorrhagic chorioretinopathy is described.

**Results:** Resolution of vitreous hemorrhage and subretinal hemorrhage was demonstrated after treatment with aflibercept.

**Conclusion:** Peripheral exudative hemorrhagic chorioretinopathy is discussed in terms of its presentation, pathophysiology, and existing treatment methodologies.

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