Drug treatment

Retina. 2018 Jul 13. [Epub ahead of print]

Aflibercept for persistent diabetic macular edema: Forty-Eight-Week Outcomes.

Bahrami B, Hong T, Schlub TE, Chang AA.

Purpose: To evaluate functional and anatomical outcomes after a switch from intravitreal bevacizumab to aflibercept in patients with persistent diabetic macular edema.

Methods: Prospective, single-arm, open-label clinical trial of patients with persistent diabetic macular edema, despite previous treatment with bevacizumab. Five loading doses of intravitreal aflibercept were administered every 4 weeks with subsequent injections administered every 8 weeks. Patients were reviewed every 4 weeks, and best-corrected visual acuity and central macular thickness were recorded. Primary outcome measures included change in central macular thickness and best-corrected visual acuity at week 48 compared with baseline. Paired t-tests were used to assess change between baseline and follow-up visits.

Results: At baseline, 43 eyes from 43 patients were recruited with a median (interquartile range) of 12 (7-24) previous intravitreal anti-vascular endothelial growth factor injections over a period of 18 (8-34) months. Mean ± SD central macular thickness reduced by 59 ± 114 μm (P = 0.002), and best-corrected visual acuity improved by 3.9 ± 7.0 letters (P = 0.001) after 48 weeks in the 41 patients who completed the trial. Best-corrected visual acuity improvements were more marked in patients who gained ≥5 letters after the first injection (8.9 ± 5.7 vs. 1.8 ± 6.5 letter gain at 48 weeks, P = 0.002), a difference which remained significant after regression analysis with baseline best-corrected visual acuity. Vision gains and central macular thickness reduction were similar in 9 fellow eyes eligible for inclusion being concurrently treated for diabetic macular edema with bevacizumab.

Conclusion: Intravitreal aflibercept was effective in improving anatomical and visual outcomes among patients with an incomplete response to intravitreal bevacizumab with 48 weeks of follow-up. Patients with a good early response subsequent to switching had a better improvement in vision at 48 weeks.

PMID: 30015767 DOI: 10.1097/IAE.0000000000002253
Other treatment and diagnosis


Multimodal imaging of nonneovascular age-related macular degeneration.

Garrity ST, Sarraf D, Freund KB, Sadda SR.

Abstract: Nonneovascular (dry) AMD is a retinal disease with potential for significant central visual impairment. The hallmarks of this disease are macular drusen, RPE alterations, and geographic atrophy (GA). Classification schemes for nonneovascular AMD have evolved over the years as major advances in retinal imaging have enabled a greater understanding of disease pathophysiology. The original classifications of nonneovascular AMD were based on color fundus photography (CFP), while more modern schemes rely on a multimodal imaging approach. Effective diagnosis and management of nonneovascular AMD requires a thorough understanding of its multimodal imaging features as detailed in this review. Future imaging modalities and imaging biomarkers that may aid in diagnosis and management are also discussed.

PMID: 30025107 DOI: 10.1167/iovs.18-24158


Fluorescein leakage and optical coherence tomography features of choroidal neovascularization secondary to pathologic myopia.

Battaglia Parodi M, Iacono P, Romano F, Bandello F.

Purpose: We compare the fluorescein angiography (FA) patterns with morphologic alterations detectable on spectral-domain OCT (SD-OCT) in myopic choroidal neovascularization (mCNV) and evaluate whether they influence the effects of intravitreal ranibizumab (IVRI) in an as-needed (PRN) regimen.

Methods: The 49 patients enrolled in this prospective case series underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA), FA, and SD-OCT assessment. The main outcome measure was correlation between FA patterns and SD-OCT features. Secondary outcomes were changes in BCVA and central macular thickness (CMT), and characterization of subretinal hyperreflective exudation (SHE).

Results: Three main patterns were identified on the FA: no (5%), minimal (35%), and profuse (59%) leakage CNV. Comparison between minimal versus profuse leakage CNV subtypes revealed no difference regarding baseline and final BCVA, CNV area, choroidal thickness, final CMT, and proportion of intraretinal cysts, subretinal fluid, and external limiting membrane (ELM) interruption; however, the minimal leakage CNV subgroup revealed a lower percentage of SHE (P = 0.0039), required fewer IVRI (P = 0.003), and showed a baseline smaller CMT (P = 0.004). Patients presenting with SHE showed a similar baseline BCVA to those without exudation, but displayed greater final BCVA improvement. CMT was greater at the baseline and the reduction also was more marked. CNV area achieved a significant reduction only in eyes with SHE. ELM interruption was present in all cases compared to 86.3% of eyes without SHE. Lastly, the eyes with SHE required more injections (P = 0.04).

Conclusions: Different patterns of mCNV may be identified in FA and they correlate with specific SD-OCT alterations. Moreover, the type of FA leakage may assist in identifying more active mCNV.

PMID: 30025121 DOI: 10.1167/iovs.17-23640
Patterns of fundus autofluorescence lifetimes in eyes of individuals with nonexudative age-related macular degeneration.

Sauer L, Gensure RH, Andersen KM, Kreilkamp L, Hageman GS, Hammer M, Bernstein PS.

Purpose: To investigate fundus autofluorescence (FAF) lifetimes in patients with nonexudative AMD.

Methods: A total of 150 eyes of 110 patients (mean age: 73.2 ± 10.7 years) with nonexudative AMD, as well as a healthy group of 57 eyes in 38 subjects (mean age: 66.5 ± 8.7 years), were included. Investigations were conducted at the University Eye Clinic in Jena, Germany, as well as the Moran Eye Center in Salt Lake City, Utah, USA, using the Heidelberg Engineering Spectralis-based fluorescence lifetime imaging ophthalmoscope (FLIO). A 30° retinal field centered at the fovea was investigated. FAF decays were detected in short (498-560 nm) and long (560-720 nm, LSC) spectral channels. The mean fluorescence lifetimes ($\tau_m$) were calculated. Optical coherence tomography scans and fundus photographs were also recorded.

Results: In patients with nonexudative AMD, FLIO shows a ring-shaped pattern of prolonged $\tau_m$ in the LSC. This pattern occurs in all patients with AMD (including very early stages) and in one-third of the healthy controls. FAF lifetimes were longer with more advanced stages. The presence of drusen is associated with prolonged $\tau_m$ when compared with the healthy fundus, but drusen identification is difficult with FLIO only.

Conclusions: FLIO detects a clear pattern of changes within the fundus, which appears to be AMD-associated. These changes are already visible in early AMD stages and not masked by the presence of other coexisting retinal diseases. These findings may be useful for the early diagnosis of AMD and to distinguish AMD from other retinal diseases.

PMID: 30025104 PMCID: PMC6009207 DOI: 10.1167/iovs.17-23764

Hyperreflective foci number correlates with choroidal neovascularization activity in angioid streaks.

Parodi MB, Arrigo A, Romano F, Aragona E, Marchese A, Cicinelli MV, Mercuri S, Bandello F.

Purpose: To assess the changes in hyperreflective foci (HF) by means of spectral-domain optical coherence tomography (SD-OCT) in patients undergoing anti-VEGF treatment for subfoveal choroidal neovascularization (CNV) secondary to angioid streaks (AS).

Methods: Fifteen eyes with diagnosis of AS-related CNV (8 males) and 15 control eyes with uncomplicated AS were consecutively recruited. Patients and controls underwent complete ophthalmologic examination and SD-OCT. Patients were subjected to a pro re nata treatment regimen, including monthly examinations and intravitreal aflibercept injection in case of fluid detection on SD-OCT. HF were measured on horizontal scans of the six-line radial SD-OCT, in the fovea and parafovea and the subdivided as retinal or choroidal. Specifically, HF were analyzed at the following time points: baseline, dry on SD-OCT, 1 month before its reactivation, and the time of CNV reactivation.

Results: HF numbers resulted higher in all CNV phases with respect to controls, except during inactive phase. Moreover, foveal and parafoveal HF were found significantly increased in active, prereactive, and reactive phases when compared with inactive phase ($P < 0.05$). A similar trend was detected for choroidal HF. Interestingly, a subanalysis revealed that only foveal choroidal HF are significantly higher in a prereactive phase if compared with an inactive phase ($P = 0.03$). Our correlational analysis unveiled negative associations between intraretinal HF numbers and logMAR best-corrected visual acuity.

Conclusions: Our findings suggest that HF represent useful markers to monitor CNV activity. Choroidal HF appear already increased in the fovea 1 month before CNV reactivation. Validation of our results might lead
to earlier anti-VEGF reinjection and possibly better visual outcomes.

PMID: 30025095 DOI: 10.1167/iovs.18-24291


Quantity of intraretinal hyperreflective foci in patients with intermediate age-related macular degeneration correlates with 1-year progression.

Nassisi M, Fan W, Shi Y, Lei J, Borrelli E, Ip M, Sadda SR.

Purpose: The purpose of this study was to evaluate the correlation between quantity of intraretinal hyperreflective foci (HRF) in the eye with intermediate AMD and progression to late AMD.

Methods: Volume optical coherence tomography (OCT) scans from 114 eyes of 114 patients were retrospectively reviewed. HRF were assessed both qualitatively and quantitatively. Five sequential en face slabs from midretina were thresholded to isolate the HRF. These five slabs were recombined, and HRF area was measured in the whole 6 × 6-mm image (HRFTOT) and within the central 3-mm (HRF3mm) and 5-mm (HRF5mm) regions. These measurements were correlated with the development of late AMD (defined as choroidal neovascularization [CNV] and/or complete RPE and photoreceptor atrophy [cRORA]) after 1 year of follow-up.

Results: HRF area in all three regions showed significant correlations with progression to late AMD: R = 0.610 for HRF3mm, R = 0.622 for HRF5mm, and R = 0.614 for HRFTOT (all P < 0.001). Correlations remained significant with progression to cRORA alone, though not for progression to CNV alone. While qualitative assessment of HRF (i.e., presence of HRF: yes or no) also showed a significant correlation with progression to late AMD (R = 0.454, P < 0.001) and atrophy alone (R = 0.445, P < 0.001), they were weaker than by HRF quantification.

Conclusions: The area of HRF from en face OCT in eyes with intermediate AMD correlates with the 1-year risk of progression to late AMD, and in particular with the development of atrophy.

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Retina. 2018 Jul 16. [Epub ahead of print]

Typical polypoidal choroidal vasculopathy and polypoidal choroidal neovascularization.


Purpose: To compare typical polypoidal choroidal vasculopathy (T-PCV) and polypoidal choroidal neovascularization (P-CNV), which can be defined as two subtypes of PCV, and to elucidate the significance of the classification.

Methods: Seventy-seven patients diagnosed with PCV and followed up for more than 12 months were reviewed. The PCV cases were divided into a T-PCV group (n = 36) and a P-CNV group (n = 41) according to the presence of features of pachychoroid or age-related macular degeneration. Angiographic and tomographic characteristics and changes in vision during the follow-up period were compared between the two groups.

Results: Logarithm of the minimum angle of resolution visual acuity of T-PCV and P-CNV was 0.27 ± 0.31 and 0.62 ± 0.47 at baseline (P < 0.001) and 0.28 ± 0.41 and 0.54 ± 0.52 at the final visit (P = 0.006), respectively. A marginally higher rate of complete response to anti-vascular endothelial growth factor treatment was noted in the T-PCV group (47.2%) compared with the P-CNV group (26.8%) (P = 0.05). At the final visit, subfoveal fibrosis was noted in 11.1% of the T-PCV group and 39.0% of the P-CNV group (P = 0.009).
Conclusion: The two subtypes of PCV, P-CNV and T-PCV, behave differently in terms of angiographic and tomographic manifestations and visual outcomes. Classifying PCVs would be helpful not only for pathogenic implications, but also for prognostic significance.

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Retina. 2018 Jul 13. [Epub ahead of print]

Sensitivity of 840-nm spectral domain optical coherence tomography angiography in detecting type 1 neovascularization according to the height of the associated pigment epithelial detachment.

Mrejen S, Giocanti-Auregan A, Tabary S, Cohen SY.

Purpose: To evaluate the ability of optical coherence tomography angiography (OCTA) to detect abnormal vascular blood flow in Type 1 neovascularization (NV) with or without significant pigment epithelial detachment (PED).

Methods: Consecutive age-related macular degeneration patients with either treatment-naive or anti-vascular endothelial growth factor-treated Type 1 NV were divided into 2 groups based on the PED height on structural OCT: greater than 250 μm (Group 1) versus less than 250 μm (Group 2). Two independent senior retina specialists analyzed the OCTA images (Zeiss Angioplex OCT, Carl Zeiss AG, Jena, Germany) using the automatic slabs alone (first reader) versus automatic and manual segmentation slabs (second reader).

Results: In Group 1, 15 men and 42 women, aged from 51 years to 97 years (mean: 87.5), were included. Optical coherence tomography angiography was able to show an abnormal blood flow suggestive of Type 1 NV in 23 (40.3%) of 57 eyes for the first reader and in 32 (56.1%) of 57 eyes for the second reader. In Group 2, 7 men and 30 women, aged from 60 years to 96 years (mean: 80.2), were included. The first and second readers were able to observe an image suggestive of Type 1 NV in 33/37 (89.2%) and 37/37 (100%) of eyes, respectively.

Conclusion: The ability of OCTA to detect an abnormal blood flow in Type 1 NV was found to highly depend on the height of the associated PED and the use of manual segmentation slabs. Our results suggest that automatic slabs of OCTA should be interpreted with caution for the diagnosis of vascularized PED. The diagnosis of Type 1 NV using OCTA requires the use of manual segmentation and a multimodal imaging approach, especially when the height of the associated PED is >250 μm.

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Adaptive optics ophthalmoscopy: application to age-related macular degeneration and vascular diseases.


Abstract: Adaptive optics (AO)-enhanced en face retinal imaging, termed here AO ophthalmoscopy (AOO) has reached a level of robustness which fuels its increasing use in research and clinical centers. Here we will review the contribution of clinical AOO to the understanding and monitoring of 1) age-related macular degeneration and 2) vascular diseases. The main contributions of AOO to the phenotyping of AMD are a better identification of drusen, a better delineation of the limits of atrophy, and the identification of novel features such as punctate hyperreflectivity and mobile melanin-containing clumps. Characterization of progression of atrophy is facilitated by time-lapse imaging. In vessels, AOO enables the observation and measurement of parietal structures and the observation of microscopic pathological features such as small hemorrhages and inflammatory cell accumulations.
Pathogenesis


Brain-derived neurotrophic factor in patients with age-related macular degeneration and its correlation with retinal layer thicknesses.

Inanc Tekin M, Sekeroglu MA, Demirtas C, Tekin K, Doguizi S, Bayraktar S, Yilmazbas P.

Purpose: To determine brain-derived neurotrophic factor (BDNF) levels in serum and aqueous humor (AH) and to assess the relationship between BDNF levels and retinal layer thicknesses in age-related macular degeneration (AMD).

Methods: A total of 48 AMD patients (AMD group) that was composed of twenty-three nonexudative and 25 exudative patients and 26 control subjects (control group) were included in the study. Serum and AH BDNF levels were assessed by ELISA method. Retinal layer thicknesses were calculated by segmentation analysis of optical coherence tomography.

Results: The mean BDNF levels in AH were found to be significantly lower in both the nonexudative and exudative AMD groups than in the control group (P = 0.003 and P < 0.001, respectively). Optical coherence tomography segmentation analysis revealed that the total average retina pigment epithelium thickness was statistically significantly thinner in the nonexudative AMD group compared with the exudative AMD and control groups (P = 0.001 and P = 0.040, respectively). The total average outer nuclear layer (ONL) thicknesses of nonexudative and exudative AMD cases were reduced compared to control group; however, the decrement was statistically significant only in the nonexudative AMD group (P = 0.009). In the correlation analysis of BDNF levels with retinal layer thicknesses, statistically significant correlations exist between BDNF levels of AH with ONL thicknesses in cases of AMD and with retina pigment epithelium thicknesses in the nonexudative AMD group.

Conclusions: BDNF concentrations in AH decreased in the AMD group and this decrease correlates with outer retinal layer thicknesses. Low BDNF levels detected in the AMD group may be insufficient to protect the photoreceptors, resulting in thinning of ONL.

PMID: 30025135 DOI: 10.1167/iovs.18-24030


A perspective of AMD through the eyes of immunology.

Copland DA, Theodoropoulou S, Liu J, Dick AD.

Abstract: Despite strong genetic associations, compelling human histological data and numerous hypotheses generated with supportive animal data, the mechanisms of inflammation or inflammatory control of cell health during progression of age-related macular degeneration arguably remain elusive. This perspective delivers a view that maintaining tissue health requires active immune cellular and tissue pathways, but when responses are perturbed or exaggerated, chronic inflammation is destructive. There are potential pathways and processes to enable understanding and determine how potential causative factors including altered cellular metabolism, senescence, oxidative stress disrupt tissue homeostasis are engaged. Establishing differences in the immune phenotype between normal aging and AMD, and how the inter-relatedness of these triggers contribute to pathobiology is integral for future therapeutic success.

PMID: 30025105 DOI: 10.1167/iovs.18-23893

Retinal basal laminar deposits in complement fH/fP mouse model of dense deposit disease.

Song D, Mohammed I, Bhuyan R, Miwa T, Williams AL, Gullipalli D, Sato S, Song Y, Dunaief JL, Song WC.

Purpose: Dense deposit disease (DDD) is caused by dysregulation of the alternative pathway of the complement cascade and characterized by electron-dense deposits in the kidney glomerular basement membrane (GBM) and drusen in Bruch's membrane (BrM). Complement factor H (fH) and factor properdin (fP) regulate complement activation; fH inhibits alternative pathway (AP) activation, whereas fP promotes it. We report pathologic changes in eyes of an fH and fP double-mutant mouse, which we previously showed have dense deposits in the GBM and early mortality from nephropathy.

Methods: fHm/m, fP-/-, and fHm/m/fP-/- mice were generated on a C57BL/6-129J background. Fundus imaging at 8 weeks of age was followed by analysis via light and electron microscopy. Retinal function was assessed by electroretinography (ERG). Complement levels and localization were tested by immunohistochemistry and ELISA. Retinas of fHm/m/fP-/- mice treated with intraperitoneal injections of an anti-C5 antibody were compared to those of age- and genotype-matched mice injected with an isotype control antibody.

Results: fHm/m/fP-/- mice suffered early-onset retinal hypopigmented spots detected using in vivo retinal photography, and histologic examination showed basal laminar deposits (BLamD), degeneration of the photoreceptors, and RPE vacuolization. ERG showed diminished retinal function. The anti-C5 antibody was retina-protective.

Conclusions: This unique mouse represents a new model of complement-mediated rapid-onset DDD, and could be useful in exploring the pathologic changes associated with BLamD in age-related macular degeneration.

PMID: 30025090 PMCID: PMC6040236 DOI: 10.1167/iovs.18-24133


Irreversible photoreceptors and RPE cells damage by intravenous sodium iodate in mice is related to macrophage accumulation.

Moriguchi M, Nakamura S, Inoue Y, Nishinaka A, Nakamura M, Shimazawa M, Hara H.

Purpose: To determine the mechanism causing degeneration of the retinal pigment epithelium (RPE) and photoreceptors in mice after an intravenous injection of sodium iodate (NaIO3).

Methods: The time-dependent changes in NaIO3-induced retinal degeneration were determined by analyzing the retinal morphology by optical coherence tomographic (OCT) images, histological sections of the retina, physiology of the retina by electroretinography (ERG), and retinal blood flow by laser speckle flowgraphy. In addition, the expression of the genes associated with age-related macular degeneration in humans was assessed in the NaIO3-treated mice by RT-PCR. We also investigated whether macrophages were involved in the NaIO3-induced retinal degeneration.

Results: The intravenous injection of 20 mg/kg NaIO3 altered the morphology of the RPE cells and the ERGs transiently. With 40 mg/kg of NaIO3, the degeneration of the RPE cells was still present at 28 days. Aggregated melanin granules were surrounded by zonula occludens protein 1 (ZO-1)-positive cells. In addition, 40 mg/kg of NaIO3 led to a reduction in the amplitudes of the a- and b-waves of the dark-adapted ERGs. Histological studies showed that macrophages had infiltrated the retina and were present around the
altered RPE cells. Depletion of the macrophages by a prior injection of clodronate liposomes prevented the damage of the outer retina after the NaI03 injection but not the RPE.

Conclusions: The NaI03-induced retinal damage was reversible at low concentrations but permanent at high concentrations of NaI03. The accumulation of macrophages around the RPE cells caused the photoreceptor cell death.

PMID: 30025075 DOI: 10.1167/iovs.17-23532


Protective effect of a locked retinal chromophore analogue against light-induced retinal degeneration.

Gao S, Parmar T, Palczewska G, Dong Z, Golczak M, Palczewski K, Jastrzebska B.

Abstract: Continuous regeneration of the 11-cis-retinal visual chromophore from all-trans-retinal is critical for vision. Insufficiency of 11-cis-retinal arising from the dysfunction of key proteins involved in its regeneration can impair retinal health, ultimately leading to loss of human sight. Delayed recovery of visual sensitivity and night blindness caused by inadequate regeneration of the visual pigment rhodopsin, are typical early signs of this condition. Excessive concentrations of unliganded, constitutively active opsin and increased levels of all-trans-retinal, and its byproducts in photoreceptors also accelerate retinal degeneration following light exposure. Exogenous 9-cis-retinal iso-chromophore can reduce the toxicity of ligand-free opsin but fails to prevent the buildup of retinoid photoproducts when their clearance is defective in human retinopathies such as Stargardt disease or age-related macular degeneration. Here we evaluated the effect of a locked chromophore analogue, 11-cis-6-membered ring-retinal against bright light-induced retinal degeneration in Abca4-/-Rdh8-/- mice. Using in vivo imaging techniques, optical coherence tomography, scanning laser ophthalmoscopy, and two-photon microscopy, along with in vitro histological analysis of retinal morphology, we found that treatment with 11-cis-6-membered ring-retinal prior to light stimulation prevented rod and cone photoreceptor degradation and preserved functional acuity in these mice. Moreover, additive accumulation of 11-cis-6-membered ring-retinal measured in the eyes of these mice by quantitative liquid chromatography-mass spectrometry indicated stable binding of this retinoid to opsin. Together, these results suggest that eliminating excess of unliganded opsin can prevent light-induced retinal degeneration in Abca4-/-Rdh8-/- mice.

PMID: 30018116 DOI: 10.1124/mol.118.112581

Eye (Lond). 2018 Jul 16. [Epub ahead of print]

Evaluation of serum and ocular levels of membrane attack complex and C-reactive protein in CFH-genotyped human donors.


Background: There is a considerable body of evidence demonstrating a link between the membrane attack complex (MAC) and age-related macular degeneration (AMD), and between C-reactive protein (CRP) and AMD. Both the MAC and the monomeric form of CRP (mCRP) accumulate within the choriocapillaris in AMD. However, the precise contribution of these species to AMD pathophysiology has not been fully elucidated.

Methods: We sought to directly assess CRP and MAC levels between human serum and ocular tissues from the same CFH Y402H genotyped donors using ELISA of serum and RPE/choroid proteins.

Results: The Y402H polymorphism was associated with significantly increased MAC in RPE/choroid samples, but not in the serum, in a previously unstudied cohort. While MAC levels in the choroid were
independent of circulating levels, choroidal CRP was correlated to serum levels.

**Conclusion:** These data provide further evidence for local activation of complement within the choriocapillaris in AMD.

PMID: 30013157 DOI: 10.1038/s41433-018-0170-8

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**Epidemiology**


Age-related macular degeneration and progression of coronary artery calcium: The Multi-Ethnic Study of Atherosclerosis.


**Background:** Age-related macular degeneration (AMD) shares many similarities with cardiovascular disease (CVD) pathophysiology. We sought to determine the relationship of AMD to the progression of coronary artery calcium (CAC) using data from the Multi-Ethnic Study of Atherosclerosis (MESA).

**Methods:** Our cohort consisted of 5803 adults aged 45 to 84 years free of known cardiovascular disease (CVD). Retinal photographs were taken during visit 2 (Aug 2002-Jan 2004). CAC was measured with computed tomography at visit 1 (July 2000-Aug 2002) and visit 5 (April 2010-Dec 2011) and changes between visits were determined.

**Results:** Participants were categorized as with (n = 244) and without AMD (n = 5559) at visit 2. At visit 5, 92 participants with and 2684 without AMD had CAC scores. Among those with detectable CAC at baseline (>0 at visit 1), CAC progression was greater in persons with compared to those without AMD after multivariable adjustment (530 ± 537 vs. 339 ± 426 Agatston units, P<0.01).

**Conclusions:** The presence of AMD in a diverse population without known clinical CVD independently predicted higher 10-year CAC progression in participants with baseline CAC >0. The retinal exam might be a useful tool for pre-clinical assessment and prevention of CVD events.

PMID: 30020999 DOI: 10.1371/journal.pone.0201000

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**Genetics and gene therapy**


Evaluation of serum SLCO1B1 levels and genetic variants of SLCO1B1 rs4149056 and rs2306283 in patients with early and exudative age-related macular degeneration.

Liutkevičiūne R, Vilkėvičiute A, Slavinskaitė A, Petrauskaitė A, Tatarunas V, Kriauciuniene L.

**Purpose:** To determine SLCO1B1 rs4149056 and rs2306283 gene polymorphisms and SLCO1B1 serum levels in patients with early and exudative age-related macular degeneration.

**Materials and Methods:** The study enrolled 206 patients with exudative AMD, 253 patients with early AMD and 301 control subjects. DNA was extracted from peripheral venous blood leukocytes using commercial kits. Genotyping of SLCO1B1 rs4149056 and rs2306283 was carried out using a real-time polymerase chain reaction (RT-PCR) method. Serum SLCO1B1 levels were measured using SLCO1B1 ELISA kit.

**Results:** We found statistically significant differences in genotype (T/T, T/C and C/C) distribution of SLCO1B1 rs4149056 variant between the patients with exudative AMD and control group (52.4%, 47.6%...
and 0% vs. 64.8%, 31.6% and 13.7%, respectively, p < 0.001). Univariate binary logistic regression analysis showed that age was a risk factor for exudative AMD development. Also, T/C variant was associated with 1.9-fold increased Odds ratio of exudative AMD development under a codominant model (OR = 1.863; 95% CI: 1.290, 2.689; p < 0.001). The results remained of the same statistical significance after multivariate analysis. On the other hand, C allele was associated with 1.6-fold increased Odds ratio of exudative AMD development (OR = 1.563; 95% CI: 1.035; 2.359; p = 0.034) only after adjustment for age. No significant associations were found in analysis of genotypes and alleles at rs2306283. Serum SLCO1B1 concentration was significantly higher in early AMD patients than in healthy controls (median, IQR: 2.92 ng/ml, 5.01 ng/ml versus 1.26 ng/ml, 2.63 ng/ml, respectively, p = 0.025), as well as in exudative AMD patients than in controls (median, IQR: 2.72 ng/ml, 5.71 ng/ml versus 1.26 ng/ml, 2.63 ng/ml, respectively, p = 0.002). Furthermore, subjects with rs4149056 T/C genotype had higher SLCO1B1 serum levels than those with T/T genotype (median, IQR: 3.73 ng/ml, 3.14 ng/ml versus 1.23 ng/ml, 1.47 ng/ml, respectively, p = 0.037).

**Conclusion:** Our study determined that SLCO1B1 (c.521 T > C) rs4149056 T/C genotype and C allele may be associated with exudative age-related macular degeneration, as well as with elevated serum SLCO1B1 levels. Also, higher serum SLCO1B1 levels were found to be associated with early and exudative age-related macular degeneration.

PMID: 30010042 DOI: 10.1016/j.gene.2018.07.031

**HLA. 2018 Jul 16. [Epub ahead of print]**

**Extended HLA-G haplotypes in patients with age-related macular degeneration.**


**Abstract:** The study aims to determine if genetic polymorphisms in the human leukocyte antigen (HLA)-G gene are associated with age-related macular degeneration (AMD). HLA-G is important for immunological tolerance, and it is also known to have angiogenic effects. Polymorphisms in the 5'-upstream regulatory region (URR) and 3'-untranslated region (UTR) of HLA-G have been associated with a number of diseases, especially with respect to a 14 bp insertion/deletion (ins/del) polymorphism in the 3'UTR. Full gene sequencing was performed on a cohort of 146 AMD patients and 63 healthy controls aged 60 years or older and HLA-G haplotypes were determined. Analyses were performed on a publicly available gene expression dataset from the NCBI GEO database (accession number GSE29801) from which expression data for HLA-G, -C and -A were extracted. Analysis of the GEO dataset showed that both HLA-G and -C was expressed in the back of the eye and that expression was upregulated in the macular area of AMD. No differences were observed between patients and controls when analysing the distribution of haplotypes in the HLA-G promoter, coding region, 3'UTR or the 14 bp ins/del polymorphism of the 3'UTR. The increased expression of HLA-G in the macula of AMD patients indicates a role of HLA-G in the microenvironment as part of the AMD pathogenesis. This is supported by the expression of HLA-C, which has previously been shown to play a role in AMD. The HLA-G haplotype distribution did not display any differences between AMD patients and controls. This article is protected by copyright. All rights reserved.

PMID: 30009537 DOI: 10.1111/tan.13340

**Invest Ophthalmol Vis Sci. 2018 Jul 2;59(8):3608-3618.**

**Ascorbate suppresses VEGF expression in retinal pigment epithelial cells.**


**Purpose:** To investigate the impact of ascorbate, via DNA hydroxymethylation, on VEGF expression in retinal pigment epithelial (RPE) cells.
Methods: Dot-blot and hydroxymethylated DNA immunoprecipitation sequencing were applied to evaluate the impact of ascorbate on DNA hydroxymethylation in ARPE-19 cells. RNA sequencing (RNA-seq) was carried out to analyze the transcriptome. Quantitative RT-PCR and ELISA were conducted to examine the transcription and secretion of VEGF from cultured cells. Primary human fetal RPE cells and RPE-J cells were used to verify the effect of ascorbate on VEGF expression. ELISA was used to measure VEGF in the vitreous humor of Gulo-/- mice, which, like humans, cannot synthesize ascorbate de novo.

Results: Treatment with ascorbate (50 μM) promoted 5-hydroxymethylcytosine (5hmC) generation and changed the genome-wide profiles of 5hmC in ARPE-19 cells. Ascorbate also caused a dramatic shift in the transcriptome-3186 differential transcripts, of which 69.3% are correlated with altered 5hmC in promoters or gene bodies. One of the most downregulated genes was VEGFA, which encodes the VEGF protein. The suppression of VEGF by ascorbate is independent of hypoxia-inducible factor 1-alpha (HIF-1α) but correlates with increased 5hmC in the gene body. The decreased transcription and secretion of VEGF by ascorbate were verified in primary human fetal RPE cells. Furthermore, adding ascorbate in the diet for Gulo-/- mice resulted in decreased levels of VEGF in the RPE/choroid and vitreous humor.

Conclusions: Ascorbate inhibits VEGF expression in RPE cells likely via DNA hydroxymethylation. Thus, ascorbate could be implicated in the prevention or treatment of diseases such as age-related macular degeneration (AMD).

PMID: 30025088 PMCID: PMC6049987 DOI: 10.1167/iovs.18-24101

Stem cells


Stem cell treatment for age-related macular degeneration: the challenges.

Singh MS, MacLaren RE.

https://iovs.arvojournals.org/article.aspx?articleid=2687962

PMID: 30025109 DOI: 10.1167/iovs.18-24426

Diet, lifestyle and low vision


Profile of the Australian College of Optometry low vision clinic.

Chong MF, Cho HH, Jackson AJ, Bentley SA.

Background: The number of Australians living with vision impairment or blindness is expected to increase substantially due to the ageing population and prevalence of age-related eye disease. In response, the Australian College of Optometry (ACO) commenced a low vision clinic in 2013. The ACO is a not-for-profit organisation providing eye-care services to more than 60,000 Victorians per year experiencing economic or social disadvantage. Consultation fees are bulk-billed to the Australian national health care scheme - Medicare - while spectacles and visual aids are subsidised through the state government-funded Victorian Eyecare Service. The aim of this study was to determine the profile and prescribing patterns of the new optometry-led low vision clinic, and report the findings of a short-term loan magnifier pilot study.

Methods: A retrospective audit of 270 patient records was conducted. Additionally, a short-term loan magnifier program was pilot tested to ascertain the demand for, and benefits of, such a program among this cohort.
Results: The median age was 77 years (interquartile range 64 to 85 years), with 52 per cent being female. The main cause of vision impairment was age-related macular degeneration (40 per cent). At least one-third primarily spoke a language other than English. The majority (75 per cent) were referred by the optometrist to the onsite consultant occupational therapist for immediate assistance with activities of daily living and onward referral for additional comprehensive services, as required. Of the 49 participants who completed the loan magnifier study, only nine exchanged the magnifier/s initially prescribed.

Conclusions: The ACO has established a low vision service within a large optometry clinic for people experiencing social and economic disadvantage. Where a program of subsidised low-cost magnifiers is available, there is little benefit to short-term loans of magnifiers. Providing basic affordable low vision aids and rehabilitation within a large primary care optometry setting can facilitate acceptability and uptake of low vision services that increase quality of life.

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Case Reports


Atypical healing in a case with retinal pigment epithelium apertures.

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Purpose: To analyze the multimodal imaging features in a case showing resolution of retinal pigment epithelium (RPE) apertures in association with an avascular pigment epithelium detachment secondary to nonneovascular age-related macular degeneration.

Methods: Report of a case diagnosed with aperture of the RPE with multimodal imaging long-term follow-up. Color fundus photography, fundus autofluorescence, eye-tracked spectral domain optical coherence tomography (OCT), and OCT angiography findings are discussed.

Results: A 71-year-old man diagnosed with nonneovascular age-related macular degeneration presented with three different areas of RPE aperture in his right eye. At baseline, best-corrected visual acuity was 20/100 in his right eye. Dilated fundus examination showed three round areas of RPE atrophy, and fundus autofluorescence demonstrated marked hypoautofluorescence in the corresponding areas. The OCT scans showed discontinuities of the RPE band with no evidence of RPE tear. The OCT angiography showed no evidence of abnormal blood flow within the sub-RPE space. Over time, fundus autofluorescence and eye-tracked spectral domain OCT scans demonstrated spontaneous resolution of two of the RPE defects and reduction of the size of the third one, with complete flattening of the pigment epithelium detachment.

Conclusion: Distinction between RPE tears and apertures is important due to their different etiopathogenic mechanism and prognosis. To the best of our knowledge, this is the first report of a case of complete closure of an RPE aperture. The mechanism of the observed RPE closure remains unknown, and further studies are warranted to better understand the mechanisms of RPE restoration and remodeling.

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Vitreous opacities after intravitreal triamcinolone injection- a case report.

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Background: We report occurrence of peculiar tiny white thread like vitreous opacities after intravitreal triamcinolone injection. These persisted without any change for over a year. We ascribe them to
aggregation of triamcinolone crystals due to the purification methods.

Case Presentation: Seven patients (8 eyes) with macular edema developed tiny whitish thread like opacities in the vitreous 2-3 months after undergoing an intravitreal injection of triamcinolone acetonide preparation containing benzyl alcohol as preservative. These opacities persisted unchanged for more than a year. The follow up ranged from 91 to 425 days. Vitreous tap was done in one patient which was negative for infection. All patients initially showed improvement but needed re-treatment for recurrence. One patient developed steroid induced rise in intraocular pressure. Microscopic examination of the drug revealed large string like aggregates of triamcinolone crystals.

Conclusions: We hypothesize the possibility of aggregation of triamcinolone crystals into string like structures probably due to the purification methods used during manufacture which led to these thread like opacities in the vitreous.

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Pars plana vitrectomy and re-directing a dexamethasone implant into vitreous cavity following misdirected entry into the crystalline lens.

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Abstract: A known diabetic patient presented with diabetic macular edema (DME) and nonproliferative diabetic retinopathy in both eyes with a vision of 6/18, N12 in the right eye and 4/60, N36 in the left eye (LE). The patient had undergone injection of dexamethasone implant in the LE which got misdirected into the crystalline lens. The patient was taken up for phacoemulsification with intraocular lens implantation along with vitrectomy and posterior vitreous detachment induction, and redirection of the dexamethasone implant into the vitreous cavity. The DME resolved over the next 3 months.

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