**Drug treatment**


**Effect of glycosylated hemoglobin on response to ranibizumab therapy in diabetic macular edema: real-world outcomes in 312 patients.**


**Objective:** To investigate the effect of serum glycosylated hemoglobin (HbA1c) on the outcomes of ranibizumab therapy for diabetic macular edema (DME).

**Design:** Retrospective cohort study.

**Participants:** Patients receiving ranibizumab injections for centre-involving DME in a National Health Service setting.

**Methods:** The Moorfields OpenEyes database was used to study eyes with DME treated with ranibizumab from October 2013 to November 2015 at the Moorfields City Road, Ealing, Northwick Park, and St George’s Hospital sites. Only eyes receiving a minimum of 3 injections and completing 12 months of follow-up were included. If both eyes received treatment, the first eye treated was analyzed. When both eyes received initial treatment simultaneously, random number tables were used to select the eye for analysis. HbA1c was tested at the initiation of ranibizumab treatment. Multivariate regression analysis was used to identify relationships between HbA1c and the outcome measures.

**Outcomes:** The primary outcome was change in visual acuity (VA) Early Treatment of Diabetic Retinopathy study (ETDRS) letters. The secondary outcomes were change in central subfield thickness (CSFT) and macular volume (MV), as well as number of injections in year 1.

**Results:** Three hundred and twelve eyes of 312 patients were included in the analysis. HbA1c was not related to change in VA (p = 0.577), change in CSFT (p = 0.099), change in MV (p = 0.082), or number of injections in year 1 (p = 0.859).

**Conclusions:** HbA1c is not related to functional or anatomical outcomes at 1 year in DME treated with ranibizumab.

PMID: 30119798 DOI: 10.1016/j.jcjo.2017.10.008


Abstract: We conducted intravitreal aflibercept injections (IVAs) for 37 Japanese patients (28 males, 9 females, mean age 73.4 years) with polypoidal choroidal vasculopathy (PCV), with a treat-and-extend regimen (TER). We evaluated the impact of polyp regression after a loading dose (2-mg IVA 1×/month for 3 months) on the patients’ 2-year treatment outcomes. Thirty-seven eyes were treated with IVA by a TER for 2 years. We divided the patients into 2 groups based on their polyp status after the loading dose: polyp regression (PR+) (n=19) and no polyp regression (PR-) (n=18). We compared the groups' best-corrected visual acuity (BCVA), central retinal thickness (CRT), recurrence rate, total number of injections, and final treatment interval. Both the BCVA and CRT were significantly improved by the treatment in both groups, with no between-group difference in the amount of change (p=0.769). In the polyp regression (+) group, recurrence was significantly less common (p=0.03), the mean total number of injections was significantly lower (p=0.013), and the mean treatment interval was significantly longer (0.042). Regarding the 2-year outcomes for PCV, the eyes with post-loading-dose polyp regression demonstrated less frequent recurrence and required fewer numbers of injections compared to the eyes without polyp regression.

PMID: 30140086 DOI: 10.18926/AMO/56175


3-year-data of combined navigated laser photocoagulation (Navilas) and intravitreal ranibizumab compared to ranibizumab monotherapy in DME patients.


Purpose: The prospective, comparative evaluation of combined navigated laser photocoagulation and intravitreal ranibizumab in the treatment of diabetic macular edema has shown advantage of a combination therapy compared to ranibizumab monotherapy at year 1 with significantly reduced injections. The purpose of this retrospective study was to determine the long-term visual gains and need of injections in a 3 year-follow-up period.

Methods: Retrospective analysis of patients of the original study in the long-term follow-up from month 12 to 36. BCVA measurements following the original 1 year study were taken using logMAR charts. Injections were provided with standard of care using PRN, based on change in BCVA and CRT using SD-OCT scans. Main outcome measures were change in BCVA and mean number of injections from 12 to 36 months.

Results: BCVA was stable in both groups from 12 through 36 months, showing a change of 0.16 ± 0.1 log MAR. Following the initial reduction in required injections at month 12, combination therapy patients continued to require 1.3 times fewer injections over the next 24 months (2.91 ± 2.3 vs 3.85±3.7 injections for monotherapy).

Conclusions: Combination of navigated laser and ranibizumab achieved BCVA gains equivalent to anti-VEGF monotherapy. These results could be maintained through month 36. Required injections were 2.0 injections lower in year 1 and further 1.3 times fewer in year 2 and 3 in the combination group compared to monotherapy. Adding navigated laser photocoagulation to intravitreal anti-VEGF therapy may still represent a superior therapeutic approach to DME patients.

PMID: 30138384 DOI: 10.1371/journal.pone.0202483
Other treatment and diagnosis


Choroidal flow signal in late-onset stargardt disease and age-related macular degeneration: an OCT-angiography study.

Müller PL, Pfau M, Möller PT, Nadal J et al.

Purpose: To investigate the choroidal blood flow in areas within and adjacent to retinal pigment epithelium (RPE) atrophy secondary to late-onset Stargardt disease (STGD1) and age-related macular degeneration (AMD).

Methods: A total of 43 eyes (23 STGD1 and 20 AMD) of patients with RPE atrophy and 25 eyes of healthy controls without ocular pathology underwent multimodal imaging including optical coherence tomography angiography (OCT-A; PLEX Elite 9000 Swept-Source OCT). Using an exploratory approach, choriocapillaris and deeper choroid OCT-A slabs were evaluated in order to detect differences between STGD1 and AMD. The magnitude of absence-of-flow signal (AFS) was investigated in terms of area-fraction and size-frequency distribution.

Results: Qualitative and quantitative analysis of areas of RPE atrophy revealed more pronounced rarefaction of the choriocapillaris flow signal in STGD1 as compared to AMD (AFS area fraction: 33.15% ± 6.86% vs. 31.68% ± 8.39%; P = 0.517), while outside RPE atrophy rarefaction was less pronounced in STGD1 (AFS area fraction: 17.41% ± 5.67% vs. 21.59% ± 6.90%; P < 0.001), to the level of nonsignificance compared to controls (13.27% ± 2.99%, P = 0.368). Given this discrepancy, the ratio of the AFS area fraction within/outside of RPE atrophy could be used to differentiate between STGD1 and AMD with 65.0% sensitivity and 92.3% specificity.

Conclusions: Using OCT-A, comparison of choroidal flow signal within and outside the area of RPE atrophy revealed distinct differences between STGD1 and AMD, potentially implicating a differential role of the choroid in the pathogenesis of RPE atrophy in these two diseases.

PMID: 30140905 DOI: 10.1167/iovs.18-23819


Choriocapillaris impairment around the atrophic lesions in patients with geographic atrophy: a swept-source optical coherence tomography angiography study.

Nassisi M, Shi Y, Fan W, Borrelli E, Uji A, Ip MS, Sadda SR.

Aims: To evaluate the choriocapillaris (CC) flow alterations around geographic atrophy (GA) in eyes with dry age-related macular degeneration.

Methods: Using a swept-source optical coherence tomography angiography (SS-OCTA) device, two volume 6×6 mm scans were acquired in patients with GA presenting between June and December 2017 at the Doheny-UCLA Eye Centers. The area of GA was delineated on the en face structural OCT fundus images. For each eye, the en face OCTA slabs at the level of the CC from the two acquisitions were averaged and compensated for signal loss using the corresponding structural en face images. The resulting images were binarised and analysed for the percentage of flow voids in the para-atrophy zone (a 500 µm wide ring around the immediate edge of the atrophy) and in the peri-atrophy zone (a 500 µm wide ring around the para-atrophy zone edge), the latter considered as a reference in the comparative analysis.

Results: Thirty eyes of 20 patients were enrolled. The percentage of flow voids in the para-atrophy zone was 27.23%±6.29% and was significantly higher than in the surrounding peri-atrophy zone (23.4%±6.01%; p<0.001). There was no significant correlation between the flow void percentage in these regions and age, visual acuity, extent of the atrophic area or central choroidal thickness.
Conclusions: A significant impairment of the CC flow is present in the zone immediately surrounding the GA lesions strengthening the hypothesis that CC alterations may be relevant to the progression of GA.

PMID: 30131381 DOI: 10.1136/bjophthalmol-2018-312643


Stargardt macular dystrophy and evolving therapies.
Hussain RM, Ciulla TA, Berrocal AM, Gregori NZ, Flynn HW, Lam BL.

Abstract: Stargardt macular dystrophy (STGD1) is a hereditary retinal degeneration that lacks effective treatment options. Gene therapy, stem cell therapy, and pharmacotherapy with visual cycle modulators (VCMs) and complement inhibitors are discussed as potential treatments. Areas Covered: Investigational therapies for STGD1 aim to reduce toxic bisretinoids and lipofuscin in the retina and retinal pigment epithelium (RPE). These agents include C20-D3-vitamin A (ALK-001), isotretinoin, VM200, emixustat, and A1120. Avacincaptad pegol is a C5 complement inhibitor that may reduce inflammation-related RPE damage. Animal models of STGD1 show promising data for these treatments, though proof of efficacy in humans is lacking. Fenretinide and emixustat are VCMs for dry AMD and STGD1 that failed to halt geographic atrophy progression or improve vision in trials for AMD. A1120 prevents retinol transport into RPE and may spare side effects typically seen with VCMs (nyctalopia and chromatopsia). Stem cell transplantation suggests potential biologic plausibility in a phase I/II trial. Gene therapy aims to augment the mutated ABCA4 gene, though results of a phase I/II trial are pending. Expert Opinion: Stem cell transplantation, ABCA4 gene therapy, and VCMs offer biologically plausible treatment mechanisms for treatment of STGD1. Further trials are warranted to assess efficacy and safety in humans.

PMID: 30129371 DOI: 10.1080/14712598.2018.1513486


Baseline morphological characteristics as predictors of final visual acuity in patients with branch retinal vein occlusions: MARVEL report no. 3.

Purpose: To determine the predictive values of baseline optical coherence tomography (OCT) abnormalities on 12-month visual acuity changes in eyes with macular edema (ME) caused by branch retinal vein occlusions (BRVO).

Methods: We performed a post hoc analysis of data from 75 participants in the 12-month MARVEL trial. OCT abnormalities at baseline, including ganglion cell layer cystoid spaces (GCL), intraretinal hyper-reflective dots, and central subfield thickness (CST), were correlated with improvements in visual acuity and the number of anti-vascular endothelial growth factor injections required using a multivariate regression model.

Results: Eyes with baseline CST > 500 μm had greater visual gains compared to those with CST <500 μm (+21.09 vs +16.08 letters, P = 0.04). Eyes with hyper-reflective dots (+13.97 vs +19.93 letters, P = 0.02), and GCL cysts (+9.8 vs +18.9, P = 0.003) had inferior gains in visual acuity. Neurosensory macular detachments at the baseline did not affect gains in visual acuity. Ninety percent of the gain in visual acuity was recorded after two injections and was maintained until month 12.

Conclusion: Baseline OCT of <500 μm, hyper-reflective dots, and GCL cystoid spaces are associated with poorer gains in visual acuity. Most of the visual gain occurs after two injections.

PMID: 30127143 DOI: 10.4103/ijo.IJO_342_18

The retinal function imager and clinical applications.
Su D, Garg S.

**Background:** The Retinal Function Imager (RFI) provides in vivo and noninvasive imaging of both the retinal structure and function.

**Review:** The RFI can create capillary perfusion maps, measure blood flow velocity, and determine metabolic function including blood oximetry. It can aid clinical diagnosis as well as assess treatment response in several retinal vascular diseases including diabetic retinopathy. Blood flow velocity abnormalities have also been implicated in disease such as age-related macular degeneration and require further investigation. Compared with optical coherence tomography angiography, the RFI produces capillary maps of comparable image quality and wider field of view but it is unable to provide depth-resolved information and has longer image acquisition time. Currently, functional imaging using blood oximetry has limited applications and additional research is required.

**Conclusion:** The RFI offers noninvasive, high-resolution imaging of retinal microvasculature by creating capillary perfusion maps. In addition, it is capable of measuring retinal blood velocity directly and performs functional imaging with retinal blood oximetry. Its clinical applications are broad and additional research with functional imaging may potentially lead to diagnosis of diseases and their progression before anatomic abnormalities become evident, but longer image acquisition times may limit its clinical adoption.

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Surgical management of submacular hemorrhage: experience at an academic Canadian centre.

**Objective:** To report the anatomical and visual outcomes of patients with thick submacular hemorrhage (SMH) treated with pars plana vitrectomy (PPV), subretinal tissue plasminogen activator (t-PA), and pneumatic displacement.

**Design:** Single-centre, retrospective case series.

**Participants:** A total of 99 eyes of 99 consecutive patients with thick SMH secondary to any underlying etiology treated with PPV with subretinal t-PA and pneumatic displacement by 6 vitreoretinal surgeons at St. Michael's Hospital, Toronto, between July 2004 and August 2016.

**Methods:** All medical records and colour fundus photographs were reviewed for data collection. Blood displacement was evaluated at follow-up visits and classified as complete, partial, or none. Main outcome measures included blood displacement at final follow-up, postoperative Snellen best-corrected visual acuities (BCVA), and complication and recurrence rates.

**Results:** Patients had a mean age of 77.7 ± 12.3 years and were followed up for an average of 18.4 ± 22.3 months. Wet age-related macular degeneration was the most common etiology associated with thick SMH (80.8%). Complete blood displacement was observed by final follow-up in 85.9% of the cases, partial displacement in 12.1%, and none in 2.0%. Mean logMAR BCVA improved from 2.03 ± 0.81 (Snellen 20/2143) at baseline to 1.80 ± 1.00 (Snellen 20/1262; p = 0.009) at final follow-up, and baseline BCVA was a significant predictor of final BCVA (p < 0.001). Early postoperative complications included vitreous hemorrhage in 13 eyes and rhegmatogenous retinal detachment in 8. Recurrent SMH was observed in 12 cases.

**Conclusions:** Vitrectomy with subretinal t-PA and pneumatic displacement seems to be an effective
Pathogenes


Role of retinal pigment epithelium-derived exosomes and autophagy in new blood vessel formation.

Abstract: Autophagy and exosome secretion play important roles in a variety of physiological and disease states, including the development of age-related macular degeneration. Previous studies have demonstrated that these cellular mechanisms share common pathways of activation. Low oxidative damage in ARPE-19 cells, alters both autophagy and exosome biogenesis. Moreover, oxidative stress modifies the protein and genetic cargo of exosomes, possibly affecting the fate of surrounding cells. In order to understand the connection between these two mechanisms and their impact on angiogenesis, stressed ARPE-19 cells were treated with a siRNA-targeting Atg7, a key protein for the formation of autophagosomes. Subsequently, we observed the formation of multivesicular bodies and the release of exosomes. Released exosomes contained VEGFR2 as part of their cargo. This receptor for VEGF—which is critical for the development of new blood vessels—was higher in exosome populations released from stressed ARPE-19. While stressed exosomes enhanced tube formation, exosomes became ineffective after silencing VEGFR2 in ARPE-19 cells and were, consequently, unable to influence angiogenesis. Moreover, vessel sprouting in the presence of stressed exosomes seems to follow a VEGF-independent pathway. We propose that abnormal vessel growth correlates with VEGFR2-expressing exosomes release from stressed ARPE-19 cells, and is directly linked to autophagy.

PMID: 30133118 DOI: 10.1111/jcmm.13730


Aberrant early endosome biogenesis mediates complement activation in the retinal pigment epithelium in models of macular degeneration.

Abstract: Abnormally enlarged early endosomes (EEs) are pathological features of neurodegenerative diseases, yet insight into the mechanisms and consequences of EE expansion remains elusive. Here, we report swollen apical EEs in the retinal pigment epithelium (RPE) of aged human donors and in the pigmented Abca4-/- mouse model of Stargardt early-onset macular degeneration. Using high-resolution live-cell imaging, we show that age-related and pathological accumulation of lipofuscin bisretinoids increases ceramide at the apical surface of the RPE, which promotes inward budding and homotypic fusion of EEs. These enlarged endosomes internalize the complement protein C3 into the RPE, resulting in the intracellular generation of C3a fragments. Increased C3a in turn activates the mechanistic target of rapamycin (mTOR), a regulator of critical metabolic processes such as autophagy. The antidepressant desipramine, which decreases ceramide levels by inhibiting acid sphingomyelinase, corrects EE defects in the RPE of Abca4-/- mice. This prevents C3 internalization and limits the formation of C3a fragments within the RPE. Although uncontrolled complement activation is associated with macular degenerations, how complement contributes to pathology in a progressive disease is not well understood. Our studies link expansion of the EE compartment with intracellular complement generation and aberrant mTOR activation, which could set the stage for chronic metabolic reprogramming in the RPE as a prelude to disease. The pivotal role of ceramide in driving EE biogenesis and fusion in the Abca4-/- mice RPE suggests that therapeutic targeting of ceramide could be effective in Stargardt disease and other macular degenerations.
Subretinal macrophages produce classical complement activator C1q leading to the progression of focal retinal degeneration.


Background: The role of the alternative complement pathway and its mediation by retinal microglia and macrophages, is well-established in the pathogenesis of Age-Related Macular Degeneration (AMD). However, the contribution of the classical complement pathway towards the progression of retinal degenerations is not fully understood, including the role of complement component 1q (C1q) as a critical activator molecule of the classical pathway. Here, we investigated the contribution of C1q to progressive photoreceptor loss and neuroinflammation in retinal degenerations.

Methods: Wild-type (WT), C1qa knockout (C1qa-/-) and mice treated with a C1q inhibitor (ANX-M1; Annexon Biosciences), were exposed to photo-oxidative damage (PD) and were observed for progressive lesion development. Retinal function was assessed by electroretinography, followed by histological analyses to assess photoreceptor degeneration. Retinal inflammation was investigated through complement activation, macrophage recruitment and inflammasome expression using western blotting, qPCR and immunofluorescence. C1q was localised in human AMD donor retinas using immunohistochemistry.

Results: PD mice had increased levels of C1qa which correlated with increasing photoreceptor cell death and macrophage recruitment. C1qa-/- mice did not show any differences in photoreceptor cell death or inflammation at 7 days compared to WT, however at 14 days after the onset of damage, C1qa-/- retinas displayed less photoreceptor cell death, reduced microglia/macrophage recruitment to the photoreceptor lesion, and higher visual function. C1qa-/- mice displayed reduced inflammasome and IL-1β expression in microglia and macrophages in the degenerating retina. Retinal neutralisation of C1q, using an intravitreally-delivered anti-C1q antibody, reduced the progression of retinal degeneration following PD, while systemic delivery had no effect. Finally, retinal C1q was found to be expressed by subretinal microglia/macrophages located in the outer retina of early AMD donor eyes, and in mouse PD retinas.

Conclusions: Our data implicate subretinal macrophages, C1q and the classical pathway in progressive retinal degeneration. We demonstrate a role of local C1q produced by microglia/macrophages as an instigator of inflammasome activation and inflammation. Crucially, we have shown that retinal C1q neutralisation during disease progression may slow retinal atrophy, providing a novel strategy for the treatment of complement-mediated retinal degenerations including AMD.

PMID: 30126455 DOI: 10.1186/s13024-018-0278-0


Relationship between vascular endothelial growth factor and macular edema in retinal vein branch obstruction.


Purpose: Vascular endothelial growth factor (VEGF) plays an important role in branch retinal vein occlusion (BRVO) with cystoid macular edema (CME). Monitoring changes in VEGF is crucial for evaluating treatment but requires vitreous or aqueous humor sampling, which hampers its clinical application. We investigated the correlation between VEGF and protein concentration in the aqueous humor (flare) and whether this could be used to monitor treatment-related VEGF changes.
Design: This retrospective observational study involved 19 previously untreated patients with BRVO. Aqueous humor was obtained, and intravitreal ranibizumab (IVR) injection was administered to these patients. The correlation between VEGF and flare, central retinal thickness (CRT), and best-corrected visual acuity (BCVA) was investigated. Differences in these values were considered between pre-IVR and 1 week and 1-3 months post-IVR. Moreover, in patients with recurrence who received additional IVR, further changes in VEGF were examined.

Main outcome measures: The end point of this study was BCVA, flare, and CRT at the fovea.

Results: Significant improvement was seen in BCVA and CRT at all time points and in Flare at 1 vs 3 months post-IVR; nevertheless, additional IVR was necessary in 94% of cases. In a patient with recurrence, CRT did not improve, even though VEGF decreased.

Conclusion: Flare may be effective for estimating VEGF levels in aqueous humor pre-IVR. Inflammation-related molecules other than VEGF may be related to recurrence.

PMID: 30122890 PMCID: PMC6086099 DOI: 10.2147/OPTH.S159109

Epidemiology


Natural history of drusenoid pigment epithelial detachment associated with age-related macular degeneration: age-related eye disease study 2 Report No. 17.

Yu JJ, Agrón E, Clemons TE, Domalpally A, van Asten F, Keenan TD, Cukras C, Chew EY; Age-Related Eye Disease Study 2 (AREDS2) Research Group.

Purpose: To investigate the natural history and genetic associations of drusenoid pigment epithelial detachment (DPED) associated with age-related macular degeneration (AMD).

Design: Retrospective analysis of a prospective cohort study.

Participants: Of the 4203 Age-Related Eye Disease Study 2 (AREDS2) participants, 391 eyes (325 participants) were identified as having DPED without late AMD at the time of DPED detection. Genetic analyses included 120 white AREDS2 participants and 145 AREDS participants with DPED.

Methods: Baseline and annual stereoscopic fundus photographs were graded according to a standardized protocol to detect DPED, a well-defined yellow elevated mound of confluent drusen, measuring ≥ 433 μm in diameter, and to evaluate progression rates to late AMD: geographic atrophy (GA) and neovascular (NV) AMD. Five single nucleotide polymorphisms (CFH [rs10611670], C3 [rs2230199], CFI [rs10033900], C2/CFB [rs114254831], ARMS2 [rs10490924]) and genetic risk score (GRS) group were investigated for association with DPED development. Kaplan-Meier analyses and multivariable proportional hazard regressions were performed.

Main Outcome Measures: Progression rates to late AMD and decrease of ≥ three lines in visual acuity (VA) from time of DPED detection; association of rate of DPED development with genotype.

Results: Mean (SD) follow-up time from DPED detection was 4.7 (0.9) years. Presence of DPED was associated with increased risk of progression to late AMD (hazard ratio [HR]=2.36, 95% confidence interval [CI]=1.98-2.82, p<0.001); 67% of eyes progressed to late AMD five years after DPED detection. DPED was associated with increased risk of ≥ three lines of VA loss (HR=3.08, CI=2.41-3.93, p<0.001) with 46% of eyes experiencing vision loss at five years (with or without progression to late AMD). ARMS2 risk alleles (1 vs. 0: HR=2.72, CI=1.58-4.70, p<0.001; 2 vs. 0: HR=3.16, CI=1.60-6.21, p<0.001) and increasing GRS group (4 vs. 1) (HR=12.17, CI=3.66-40.45, p<0.001) were significantly associated with DPED development in AREDS. There were no significant genetic results in the AREDS2 analyses.
Conclusions: This study replicates the results of previous natural history studies of eyes with DPED including the high rates of progression to late AMD and vision loss (regardless of progression to late AMD). The genetic associations are consistent with genes associated with AMD progression.

PMID: 30142373 DOI: 10.1016/j.ophtha.2018.08.017


Low incidence of choroidal neovascularization following subthreshold diode micropulse laser (SDM) in high-risk AMD.
Luttrull JK, Sinclair SH, Elmann S, Glaser BM.

Purpose: To determine the incidence of new choroidal neovascularization (CNV) in eyes with dry age-related macular degeneration (AMD) following subthreshold diode micropulse laser (SDM).

Method: In an observational retrospective cohort study, the records of all patients active in the electronic medical records database were reviewed to identify eyes with dry AMD treated with SDM. Identified eyes were classified by simplified AREDS categories, and analyzed for the primary endpoint of new CNV after treatment.

Results: The EMR revealed SDM was offered to 373/392 (95%) patients with dry AMD and elected by 363/373 (97%) between 2008-2017. Follow up was available for 354/363 patients (547 eyes, 98%) (range 6-108 mos., avg. 22). CNV risk factors included age (median 84 years, 67% > 80); reticular pseudodrusen (214 eyes, 39%); AREDS category (78% category 3 and 4); and fellow eye CNV (128 eyes, 23%). New CNV developed in 9/547 eyes (1.6%, annualized rate 0.87%). Visual acuity was unchanged. There were no adverse treatment effects.

Summary: In a review of a large group of eyes with exceptionally high-risk AMD, SDM was followed by a very low incidence of new CNV. If confirmed by further study, SDM would offer a new and highly effective treatment to reduce the risk of vision loss from AMD.

PMID: 30138455 DOI: 10.1371/journal.pone.0202097


Early recurrent hemorrhage in submacular hemorrhage secondary to type 3 neovascularization or retinal angiomatous proliferation: incidence and influence on visual prognosis.
Kim JH, Chang YS, Kim JW, Kim CG, Lee DW.

Purpose: To evaluate the incidence of early recurrent hemorrhage in submacular hemorrhage secondary to type 3 neovascularization or retinal angiomatous proliferation (RAP) and its influence on visual prognosis.

Methods: This retrospective study included 32 eyes with submacular hemorrhage secondary to type 3 neovascularization or RAP that underwent anti-vascular endothelial growth factor (VEGF) therapy. The eyes exhibiting an increase in the extent of hemorrhage within 6 months after hemorrhage development were included in the early recurrent hemorrhage group, and the remaining eyes were included in the non-early recurrent hemorrhage group. The best-corrected visual acuities (BCVAs) measured at the time of hemorrhage development and at 12 months were compared between the two groups.

Results: During the follow-up period, 8 eyes underwent vitrectomy to clear vitreous hemorrhage, and the remaining 24 eyes underwent anti-VEGF monotherapy. In the early recurrent hemorrhage group (n = 12), the mean logarithm of the minimal angle of resolution BCVA at the time of hemorrhage development and after 12 months was 1.17 ± 0.40 (Snellen equivalents: 20/295) and 2.35 ± 0.59 (20/4477), respectively. In the non-early recurrent hemorrhage group (n = 20), the corresponding values were 1.07 ± 0.43 (20/234).
and $1.44 \pm 0.71$ (20/550), respectively. The BCVA at 12 months was significantly worse in the early recurrent hemorrhage group ($P = 0.003$) despite comparable BCVA at diagnosis between the two groups ($P = 1.000$).

**Conclusions:** Early recurrent hemorrhage was noted in 37.5% of eyes with submacular hemorrhage secondary to type 3 neovascularization or RAP and was closely associated with a poor prognosis.

PMID: 30136868 DOI: 10.1080/08820538.2018.1511814


Evaluation of clinical questions and patient-important outcomes associated with the treatment of age-related macular degeneration.

Lindsley KB, Hutfless S, Hawkins BS, Blim JF, et al.

**Importance:** Identifying and prioritizing unanswered clinical questions may help to best allocate limited resources for research associated with the treatment of age-related macular degeneration (AMD).

**Objective:** To identify and prioritize clinical questions and outcomes for research associated with the treatment of AMD through engagement with professional and patient stakeholders.

**Design, Setting, and Participants:** Multiple cross-sectional survey questions were used in a modified Delphi process for panel members of US and international organizations, the American Academy of Ophthalmology (AAO) Retina/Vitreous Panel ($n=7$), health care professionals from the American Society of Retinal Specialists (ASRS) ($n=90$), Atlantic Coast Retina Conference (ACRC) and Macula 2017 meeting ($n=34$); and patients from MD (Macular Degeneration) Support ($n=46$). Data were collected from January 20, 2015, to January 9, 2017.

**Main Outcomes and Measures:** The prioritizing of clinical questions and patient-important outcomes for AMD.

**Results:** Seventy clinical questions were derived from the AAO Preferred Practice Patterns for AMD and suggestions by the AAO Retina/Vitreous Panel. The AAO Retina/Vitreous Panel assessed all 70 clinical questions and rated 17 of 70 questions (24%) as highly important. Health care professionals assessed the 17 highly important clinical questions and rated 12 of 17 questions (71%) as high priority for research to answer; 9 of 12 high-priority clinical questions were associated with aspects of anti-vascular endothelial growth factor agents. Patients assessed the 17 highly important clinical questions and rated all as high priority. Additionally, patients identified 6 of 33 outcomes (18%) as most important to them (choroidal neovascularization, development of advanced AMD, retinal hemorrhage, gain of vision, slowing vision loss, and serious ocular events).

**Conclusions and Relevance:** Input from 4 stakeholder groups suggests good agreement on which 12 priority clinical questions can be used to underpin research related to the treatment of AMD. The 6 most important outcomes identified by patients were balanced between intended effects of AMD treatment (eg, slowing vision loss) and adverse events. Consideration of these patient-important outcomes may help to guide clinical care and future areas of research.

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**Stem cells**

**Stem Cell Reports. 2018 Aug 4. pii: S2213-6711(18)30314-X. [Epub ahead of print]**

Immunological properties of human embryonic stem cell-derived retinal pigment epithelial cells.

Abstract: Age-related macular degeneration is caused by dysfunction and loss of retinal pigment epithelium (RPE) cells, and their transplantation may rescue visual functions and delay disease progression. Human embryonic stem cells (hESCs) may be an unlimited source of RPE cells for allotransplantation. We analyzed the immunomodulatory properties of hESC-derived RPE (hESC-RPE) cells, and showed that they inhibited T cell responses. Co-culture experiments showed that RPE cells inhibited interferon-γ secretion and proliferation of activated T cells. Furthermore, hESC-RPE cells enhanced T cell apoptosis and secretion of the anti-inflammatory cytokine interleukin-10 (IL-10). In addition, RPE cells altered the expression of T cell activation markers, CD69 and CD25. RPE cells transplanted into RCS rats without immunosuppression survived, provided retinal rescue, and enhanced IL-10 blood levels. Our data suggest that hESC-RPE cells have immunosuppressive properties. Further studies will determine if these properties are sufficient to alleviate the need for immunosuppression therapy after their clinical allotransplantation.

PMID: 30122442 DOI: 10.1016/j.stemcr.2018.07.009

Genetics and gene therapy


Sorsby fundus dystrophy: Insights from the past and looking to the future.

Anand-Apte B, Chao JR, Singh R, Stöhrl H.

Abstract: Sorsby fundus dystrophy (SFD), an autosomal dominant, fully penetrant, degenerative disease of the macula, is manifested by symptoms of night blindness or sudden loss of visual acuity, usually in the third to fourth decades of life due to choroidal neovascularization (CNV). SFD is caused by specific mutations in the Tissue Inhibitor of Metalloproteinase-3, (TIMP3) gene. The predominant histo-pathological feature in the eyes of patients with SFD are confluent 20-30 μm thick, amorphous deposits found between the basement membrane of the retinal pigment epithelium (RPE) and the inner collagenous layer of Bruch's membrane. SFD is a rare disease but it has generated significant interest because it closely resembles the exudative or "wet" form of the more common age-related macular degeneration (AMD). In addition, in both SFD and AMD donor eyes, sub-retinal deposits have been shown to accumulate TIMP3 protein. Understanding the molecular functions of wild-type and mutant TIMP3 will provide significant insights into the patho-physiology of SFD and perhaps AMD. This review summarizes the current knowledge on TIMP3 and how mutations in TIMP3 cause SFD to provide insights into how we can study this disease going forward. Findings from these studies could have potential therapeutic implications for both SFD and AMD.

PMID: 30129971 DOI: 10.1002/jnr.24317

Diet, lifestyle and low vision


Fonts designed for macular degeneration: impact on reading.

Xiong YZ, Lorsung EA, Mansfield JS, Bigelow C, Legge GE.

Purpose: People with macular degeneration (MD) experience difficulties in reading due to central-field loss. Two new fonts, Eido and Maxular Rx, have been designed specifically for individuals with MD. We have compared reading performance of these new fonts with three mainstream fonts (Times-Roman, Courier, and Helvetica).
Methods: Subjects with MD (n = 19) and normally sighted subjects (n = 40) were tested with digital versions of the MNREAD test using the five fonts. Maximum reading speed (MRS), critical print size (CPS), and reading acuity (RA) were estimated to characterize reading performance. Physical properties of the fonts were quantified by interletter spacing and perimetric complexity.

Results: Reading with MD showed font differences in MRS, CPS, and RA. Compared with Helvetica and Times, Maxular Rx permitted both smaller CPS and RA, and Eido permitted smaller RA. However, the two new fonts presented no advantage over Courier. Spacing, but not Complexity, was a significant predictor of reading performance for subjects with MD.

Conclusions: The two fonts, designed specifically for MD, permit smaller print to be read, but provide no advantage over Courier.

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Case Report


Pathologic study of early manifestations of polypoidal choroidal vasculopathy and pathogenesis of choroidal neo-vascularization.

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Purpose: To describe the histopathologic features of an early case of presumably bilateral polypoidal choroidal vasculopathy (PCV) in two eyes obtained at autopsy from a patient with no prior ocular therapy.

Observations: The choroid of both eyes at the macular and peripapillary regions was greatly thickened with dilated, thin walled choroidal venules intertwining with arteriosclerotic arterioles in the Sattler’s layer of the choroidal vasculature. At the temporal and nasal equatorial regions of both eyes many of these congested venular channels abruptly disappeared and were replaced by loose connective tissue with loss of the normal choroidal stromal tissue and uveal melanocytes. A few remaining venules showed intraluminal sloughing of endothelial cells and deposition of fibrinous material networks suggesting occlusion of these choroidal venules. At this equatorial location, serous detachment of retinal pigment epithelium (RPE) appeared and a thin neovascular membrane with cords of endothelial cell invaded into the sub-RPE space. Anteriorly, the neovascular membrane expanded and bulged into the sub-retinal space with dilated neovascular capillaries in a "grape like" or polypoidal configuration.

Conclusion and importance: Polypoidal Choroidal Vasculopathy is a disease of the dilated and multi-layered choroidal venules. Occlusion of these choroidal vascular channels might give rise to choroidal stasis and ischemia leading to serous RPE detachment and a sub-RPE neovascular membrane. Gross dilatation of the choroidal venules and capillaries in the sub-RPE neovascular membrane leads to the characteristic "grape like" structures, a unique clinical feature in this disease entity. These pathologic features of PCV are different from the pathologic changes of neovascular age-related macular degeneration (nAMD). Consequently, PCV and nAMD are two distinct diseases. However, in the late stage of both entities, choroidal ischemia in both diseases, lead to sub-RPE neovascularization and subsequent sub-RPE and/or sub-retinal hemorrhage. These results in both entities showed comparable clinical and pathologic features that are frequently mistaken PCV as a sub-type of Neovascular AMD.

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