Comparison of one and three initial monthly intravitreal ranibizumab injection in patients with macular edema secondary to branch retinal vein occlusion.


Aim: To compare three initial monthly intravitreal ranibizumab (IVR) injections followed by pro re nata (PRN) dosing with one initial monthly IVR injections followed by PRN dosing for macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

Methods: Forty-two eyes of 42 patients who had IVR injections for BRVO were retrospectively studied. Eighteen eyes received 1 initial IVR injection (1+PRN group) and 24 eyes received 3 monthly IVR injections (3+PRN). At 1, 3, 6 and 12mo; spectral-domain optical coherence tomography (SD-OCT) was performed. Central macular thickness (CMT), the integrity of the external limiting membrane (ELM), the presence of subretinal fluid, cyst size, the presence of inner segment/outer segment (IS/OS) defect were determined.

Results: At baseline the mean CMT was 521.3±153.2 µm in the 3+PRN group while it was 438.1±162.4 µm in 1+PRN group. At the final visit, mean CMT was 278.3±87.8 µm in the 3+PRN group and 285.2±74.2 µm in the 1+PRN group (P=0.079). The changes in CMT over the entire study period were also comparable in both groups (243±160 µm in the 3+PRN group, and 152.9±175.3 µm in the 1+PRN group; P=0.090). At baseline, best-corrected visual acuity (BCVA) was 0.92±0.60 logMAR of the minimal angle of resolution (logMAR) in the 3+PRN group, while it was 0.72±0.46 logMAR in the 1+PRN group. Final BCVA was 0.42±0.55 logMAR in the 3+PRN group and 0.38±0.50 logMAR in the 1+PRN group (P=0.979). Additionally, the BCVA changes from baseline to final visit were not significantly different (-0.50±0.45 logMAR in the 3+PRN group, and -0.33±0.39 logMAR in the 1+PRN group; P=0.255).

Conclusion: No significant differences in the anatomical or functional results are found between 3+PRN and 1+PRN regimens in the patients receiving ranibizumab for ME secondary to BRVO. Intact IS/OS and baseline BCVA are good predictor of the visual gain, while baseline CMT is a good predictor of the anatomical gain.

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Bressler SB, Odia I, Glassman AR, et al.

Purpose: To explore 5-year changes from baseline in diabetic retinopathy severity among eyes treated with ranibizumab for diabetic macular edema.

Methods: Diabetic retinopathy severity was assessed from study visits and annual fundus photographs among participants in Protocol I (DRCR.net). The proportion of eyes that improved at annual examinations and the cumulative probability of worsening through 5 years were estimated.

Results: Among 235 participants with nonproliferative diabetic retinopathy at baseline, there were 29%, 28%, and 32% of eyes with retinopathy improvement at 1, 3, and 5 years, respectively. Among 111 participants with proliferative diabetic retinopathy, corresponding improvement percentages were 38%, 35%, and 23%. The 5-year cumulative probability of worsening was 18% (95% CI: 14%-25%) among nonproliferative diabetic retinopathy eyes and 31% (95% CI: 23%-42%) among proliferative diabetic retinopathy eyes (P = 0.01). In Years 1, 3, and 5, the mean (SD) number of ranibizumab injections was 8.1 (2.5), 2.2 (2.6), and 1.8 (2.6) for nonproliferative diabetic retinopathy eyes, and 9.0 (2.8), 2.3 (2.9), and 1.7 (2.6) for proliferative diabetic retinopathy eyes, respectively. Proportions with improvement or rates of worsening did not change with time.

Conclusion: Individuals receiving ranibizumab therapy for diabetic macular edema may have favorable changes in DR severity throughout a 5-year period concomitant with sequential reduction in anti-vascular endothelial growth factor therapy.

PMID: 30234859 DOI: 10.1097/IAE.0000000000002302

Baseline visual acuity as a prognostic factor for visual outcomes in patients treated with aflibercept for wet age-related macular degeneration: data from the INSIGHT study using the Swedish Macula Register.

Lövestam Adrian M, Vassilev ZP, Westborg I.

Purpose: To assess mean change in visual acuity (VA) overall and stratified by baseline VA after 1 and 2 years' treatment with aflibercept in a real-life setting.

Methods: This was an observational cohort study using nationwide data from the Swedish Macula Register. Treatment-naïve patient eyes with wet age-related macular degeneration and prescribed aflibercept from January 2013 to December 2014 were followed for 1 year (2478 eyes) or 2 years (831 eyes) to assess VA. Eyes were grouped by baseline VA.

Results: Mean number of injections in patients treated according to label (72%) versus patients treated not according to label was 8.0 ± 1.5 versus 4.4 ± 0.8 (p < 0.0001) at 1 year, and 12.5 ± 3.2 versus 7.3 ± 1.9 (p < 0.0001) at 2 years. Among all eyes, mean VA increased from 61.3 ± 13.4 Early Treatment Diabetic Retinopathy Study letters at baseline to 64.5 ± 15.6 at 1 year and 65.1 ± 15.1 letters at 2 years. At 2 years, eyes with good baseline vision (≥70 letters) lost a mean of 2.4 ± 11.3 to 72.3 letters, eyes with intermediate baseline VA (36-69 letters) gained 5.7 ± 14.1 to 62.7 letters, and eyes with poor baseline VA (≤35 letters) gained 13.2 ± 18.3 to 41.0 letters. Also at 2 years, 75% of treated eyes were stable or had improved VA. Among eyes with intermediate baseline VA, near vision was significantly better among those treated according to label versus not according to label at 3 (p = 0.019), 6 (p = 0.0002) and 12 months (p ≤ 0.0001).

Conclusion: While gain in vision was especially pronounced in eyes with poor baseline VA, good baseline
VA was important for best prognosis.

PMID: 30238648 DOI: 10.1111/aos.13864

Initiation and maintenance of a Treat-and-Extend regimen for ranibizumab therapy in wet age-related macular degeneration: recommendations from the UK Retinal Outcomes Group.

Abstract: The treatment of neovascular (wet) age-related macular degeneration (AMD) with ranibizumab is now very well established in terms of efficacy and safety. Recent clinical trials and real-world studies have demonstrated the advantages of a Treat-and-Extend (T&E) regimen, and many hospital departments are now in the process of adopting this new regimen in favor of the pro re nata regimen for initiating and continuing ranibizumab therapy for patients with wet AMD. The comprehensive spectrum of issues related to implementation of the regimen is covered qualitatively in ten didactic topics provided by a group of clinicians with direct experience of this regimen in their department. The topics include definition, new and previously treated eyes, management of high-frequency injections, maximum extensions, discontinuing T&E, bilateral cases, clerical, audit, and patient counseling. This article aims to provide a useful resource for the implementation of the T&E regimen. A quantitative summary of the visual outcomes in key publications is also provided in this article. This article should be a valuable resource for staff training.

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Flare levels after intravitreal injection of ranibizumab, aflibercept, or triamcinolone acetonide for diabetic macular edema.

Purpose: To evaluate anterior flare intensity (AFI) and central retinal thickness (CRT) values after intravitreal injection of aflibercept (IVA), ranibizumab (IVR), or triamcinolone acetonide (IVTA) in patients with diabetic macular edema (DME).

Methods: This research was conducted as a prospective study for patients with DME. Patients with phakia received either IVA or IVR, whereas patients with pseudophakia received IVA, IVR, or IVTA. AFI and CRT were measured using a laser flare meter and spectral domain optical coherence tomography, respectively, at days 0, 1, 7, 30, and 90.

Results: Forty patients with phakia and 60 patients with pseudophakia were enrolled this study. In the IVTA group, AFI of pseudophakic eyes was significantly decreased at days 1 (p = 0.0487), 7 (p = 0.0201), and 30 (p = 0.0211). In the IVA group, AFI of phakic eyes was transiently increased at day 1 (p = 0.0078) and returned to baseline at day 7, whereas no significant change was observed in AFI of pseudophakic eyes. In the IVR group, there was no significant change in AFI regardless of phakic condition. All groups showed significant reduction in CRT at day 7 and later.

Conclusion: DME improved after treatment by IVTA, IVR, or IVA, whereas AFI was reduced only in eyes treated with IVTA. The temporal profiles of AFI are likely related to differences in the pharmacological properties of the drugs.

PMID: 30238189 DOI: 10.1007/s00417-018-4141-3
Visual acuity outcomes in diabetic macular edema with fluocinolone acetonide 0.2 μg/day versus ranibizumab plus deferred laser (DRCR Protocol I).


Background & Objective: Visual outcomes of the FAME study (0.2 μg/day fluocinolone acetonide [FAc]) and Protocol I (0.5 mg ranibizumab plus deferred laser) were compared using the area under the curve (AUC) analysis method.

Patients & Methods: Best-corrected visual acuity (BCVA) data collected during a period of 3 years of follow-up for patients enrolled in FAME or Protocol I were used to calculate AUC of the change in BCVA over a time curve.

Results: In the overall population, there was a greater treatment effect for ranibizumab plus deferred laser compared with FAc. However, for subgroups of pseudophakic eyes, eyes with chronic diabetic macular edema (DME), and pseudophakic eyes with chronic DME, ranibizumab plus deferred laser and FAc were not found to be significantly different. The ranibizumab group received a median of 14 injections during a 36-month period compared with a mean of 1.3 injections in the FAc group.

Conclusion: In pseudophakic and chronic DME subgroups, FAc was comparable to ranibizumab plus deferred laser with fewer injections.

PMID: 30222805 DOI: 10.3928/23258160-20180831-08

Other treatment and diagnosis


Quantitative evaluation of choroidal neovascularization under pro re nata anti-vascular endothelial growth factor therapy with OCT angiography.


Purpose: To use optical coherence tomography angiography (OCTA) derived quantitative metrics to assess the response of choroidal neovascularization to pro-re-nata (PRN) anti-endothelial growth factor (anti-VEGF) treatment in neovascular age-related macular degeneration (AMD).

Design: Prospective longitudinal cohort study.

Participants: Fourteen eyes from 14 study participants with treatment-naïve neovascular AMD were enrolled.

Methods: Subjects were evaluated monthly and treated with intravitreal anti-VEGF agents under a PRN protocol for one year. At each visit, two 3×3 mm2 OCTA scans were obtained. Custom image processing was applied to segment the outer retinal slab, suppress projection artifact, and automatically detect CNV. CNV membrane area (mm2) and CNV vessel area (mm2) was calculated.

Main Outcomes: Individual and mean CNV membrane area and CNV vessel area at each visit; within-visit repeatability determined by coefficient of variation.

Results: Eight eyes had entire CNV within 3×3 mm2 scanning area and had adequate image quality for CNV quantification. One case (case #2) was excluded from analysis due to the presence of a large subretinal hemorrhage overlying the CNV membrane. In the remaining cases, CNV vessel area was reduced by 39%, 50%, 43%, and 41% at months 1, 3, 6, and 12 respectively. CNV membrane area was reduced by 39%, 51%, 54%, and 45% at months 1, 3, 6, and 12. At month 6, mean change from baseline
was not statistically significant for CNV vessel area, while it was statistically significant for CNV membrane area. Neither metric was significantly different compared to baseline at month 12. Individual analyses revealed each CNV had a unique response under PRN treatment. Within-visit repeatability was 7.96% (coefficient of variation) for CNV vessel area and 7.37% for CNV membrane area.

**Conclusions:** In this small exploratory study of CNV response to PRN anti-VEGF treatment, both CNV vessel area and membrane area were reduced compared to baseline after three months. After one year of follow-up, these reductions were no longer statistically significant. When anti-VEGF treatment was held, increasing CNV vessel area over time often resulted in exudation, but it was not possible to exactly when exudation occurs.


**Sub-threshold Nanosecond Laser Intervention in Age-Related Macular Degeneration: The LEAD Randomized Controlled Clinical Trial.**


**Purpose:** There is an urgent need for a more effective intervention to slow or prevent progression of age-related macular degeneration (AMD) from its early stages to vision-threatening late complications. Sub-threshold nanosecond laser (SNL) treatment has been shown in preclinical studies and a pilot study in intermediate AMD (iAMD) to reverse the signs of AMD without causing damage to the overlying retina, thus demonstrating promise as a potential treatment. We aimed to evaluate the safety of SNL treatment in iAMD and its efficacy for slowing progression to late AMD.

**Design:** The Laser intervention in Early stages of Age-related macular Degeneration (LEAD) study is a 36-month, multicenter, randomized, sham-controlled trial conducted from 2012-2015.

**Participants:** 292 participants with bilateral large drusen and without optical coherence tomography signs of atrophy.

**Interventions:** Participants were randomly assigned to receive SNL or sham treatment to the study eye at six-monthly intervals.

**Main Outcomes & Measures:** The primary efficacy outcome was the time to develop late AMD defined by multimodal imaging (MMI). Safety was assessed by adverse events.

**Results:** Overall, progression to late AMD was not significantly slowed with SNL compared to sham treatment (adjusted hazard ratio [HR] 0.61, 95% CI 0.33-1.14; p=0.122). However, a post-hoc analysis showed that progression was slowed for the 222 (76.0%) participants without coexistent reticular pseudodrusen (RPD) at baseline (adjusted HR 0.23, 95% CI 0.09-0.59; p=0.002), whilst an increased progression rate (adjusted HR 2.56, 95% CI 0.80-8.18; p=0.112) was observed for the 70 (24.0%) participants with RPD with SNL treatment (adjusted interaction p=0.002). Differences between the groups in serious adverse events were not significant.

**Conclusions:** In participants with iAMD without MMI-detected signs of late AMD, no significant difference in the overall progression rate to late AMD between those receiving SNL and sham treatment were observed. However, SNL treatment may have a role in slowing progression for those without coexistent RPD and may be inappropriate in those with RPD, warranting caution when considering treatment in clinical phenotypes with RPD. Our findings provide compelling evidence for further trials of the 2RTTM laser, but they should not be extrapolated to other short pulse lasers.

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Choriocapillaris changes in dry age-related macular degeneration and geographic atrophy: a review.

Arya M, Sabrosa AS, Duker JS, Waheed NK.

Abstract: Age-related macular degeneration (AMD) is a leading cause of central vision loss worldwide. The progression of dry AMD from early to intermediate stages is primarily characterized by increasing drusen formation and adverse impact on outer retinal cells. Late stage AMD consists of either geographic atrophy (GA), the non-exudative (dry) AMD subtype, or choroidal neovascularization, the exudative (wet) AMD subtype. GA is characterized by outer retinal and choroidal atrophy, specifically the photoreceptor layer, RPE, and choriocapillaris. Much remains to be discovered regarding the pathogenesis of AMD progression and subsequent development of GA. As the functionality of all three layers is closely linked, the temporal sequence of events that end up in atrophy is important in the understanding of the pathogenic pathway of the disease. The advent of OCTA, and particularly of swept-source technology, has allowed for depth-resolved imaging of retinal vasculature and the choriocapillaris. With the use of OCTA, recent studies demonstrate that choriocapillaris flow alterations are closely associated with the development and progression of AMD. Such changes may even possibly offer predictive value in determining progression of GA. This article reviews studies demonstrating choriocapillaris changes in dry AMD and summarizes the existing literature on the potential role of the choriocapillaris as a key factor in the pathogenesis of AMD.

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Retinal pigment epithelium hyperplasia overlying pigment epithelial detachment in age-related macular degeneration can masquerade as neovascularization on optical coherence tomography angiography.


Purpose: To report the image artifacts due to retinal pigment epithelium (RPE) hyperplasia overlying retinal pigment epithelial detachment (PED) in age-related macular degeneration (AMD), which can masquerade as neovascularization on optical coherence tomography angiography (OCTA).

Methods: A hospital-based, retrospective, and cross-sectional study. Twenty-two eyes from 16 patients with non-vascularized PED related to AMD were included in this study. All patients were examined by OCTA, spectral-domain optical coherence tomography, fluorescence angiography, and indocyanine green angiography. Vascular flow signals (VFS) on both the outer retinal slab of en face OCTA and cross-sectional OCTA and their correspondence with RPE hyperplasia were evaluated.

Results: Fifteen eyes (68.2%) showed VFS on both the outer retina slab of en face OCTA and cross-sectional OCTA, all corresponding to the RPE hyperplasia overlying PED. Among them, 12 eyes with lump RPE hyperplasia outside foveal avascular zone (FAZ) all showed obvious VFS on the outer retina slab of OCTA, and 3 eyes with scattered RPE hyperplasia outside FAZ showed VFS fragments. Of note, 4 eyes had accompanied RPE hyperplasia inside FAZ, and 7 eyes without RPE hyperplasia overlying PED showed no corresponding VFS on the outer retina slab of OCTA. Additionally, a round-like dark band at the edge of PED was observed in the outer retina slab on en face OCTA in 17 eyes (77.3%).

Conclusions: RPE hyperplasia overlying PED in AMD can masquerade as neovascularization on OCTA. To avoid misdiagnosis and unnecessary treatment, this RPE hyperplasia-related image artifact should be considered when interpreting OCTA images.

PMID: 30229304 DOI: 10.1007/s00417-018-4138-y
Application of artificial intelligence in ophthalmology.

Du XL, Li WB, Hu BJ.

Abstract: Artificial intelligence is a general term that means to accomplish a task mainly by a computer, with the least human beings participation, and it is widely accepted as the invention of robots. With the development of this new technology, artificial intelligence has been one of the most influential information technology revolutions. We searched these English-language studies relative to ophthalmology published on PubMed and Springer databases. The application of artificial intelligence in ophthalmology mainly concentrates on the diseases with a high incidence, such as diabetic retinopathy, age-related macular degeneration, glaucoma, retinopathy of prematurity, age-related or congenital cataract and few with retinal vein occlusion. According to the above studies, we conclude that the sensitivity of detection and accuracy for proliferative diabetic retinopathy ranged from 75% to 91.7%, for non-proliferative diabetic retinopathy ranged from 75% to 94.7%, for age-related macular degeneration it ranged from 75% to 100%, for retinopathy of prematurity ranged over 95%, for retinal vein occlusion just one study reported ranged over 97%, for glaucoma ranged 63.7% to 93.1%, and for cataract it achieved a more than 70% similarity against clinical grading.

PMID: 30225234 PMCID: PMC6133903 DOI: 10.18240/ijo.2018.09.21

Repeatability of split-spectrum amplitude-decorrelation angiography to assess capillary perfusion density within optical coherence tomography.

Conti FF, Young JM, Silva FQ,

Background & Objective: To evaluate the repeatability of retinal thickness and vascular density measurements using split-spectrum amplitude-decorrelation angiography (SSADA) with optical coherence tomography (OCT).

Patients & Methods: Forty patients were divided into seven categories according to their diagnosis: no retinopathy (control), retinal vein occlusion, diabetes with no retinopathy, diabetes with retinopathy, non-exudative age-related macular degeneration (AMD), exudative AMD, and epiretinal membrane. Capillary density and retinal thickness measurements were taken and evaluated for reliability by determination of statistically significant differences and coefficient of variability (CoV) between measurements.

Results: No significant differences (P > .05) were found in any of the within-visit measurements. CoVs ranged from 0.26% to 52.76%, depending on the measure and the disease settings.

Conclusion: The SSADA OCT angiography analysis has a low level of variability between measurements and, thus, is a reliable tool for evaluation of retinal perfusion.

PMID: 30222814 DOI: 10.3928/23258160-20180907-02


Objective: To characterize features of extra-vascular optical coherence tomography angiography (OCTA) signals corresponding to hyperreflective intraretinal fluid across various exudative maculopathies.

Design: Multicenter, retrospective, observational study.

Participants: Eyes with various forms of exudative maculopathy including diabetic retinopathy (DR), retinal vein occlusion (RVO), and neovascular-age related macular degeneration (nvAMD).

Methods: Patients with extra-vascular OCTA signal identified on en face OCTA images were included in this study. This signal was readily distinguishable from projection artifacts. The regions with the extra-vascular motion signal on OCTA were named "Suspended Scattering Particles in Motion (SSPiM)." Depth-encoded, color, en face OCTA images (3mm × 3mm) centered on the fovea and their corresponding structural OCT scans were used to quantify features of SSPiM and its corresponding hyperreflective fluid. Longitudinal data were collected when available.

Main outcome measures: Anatomic location, the association with hyperreflective material, changes in location and appearance of SSPiM over time, and replication of SSPiM OCTA signal in an in vitro phantom.

Results: Seventy-six eyes in 62 patients with various forms of exudative maculopathy were evaluated; 60 eyes with DR, 9 eyes with RVO, and 5 eyes nvAMD, 1 eye with macroaneurysm, and 1 eye with radiation retinopathy. Intraretinal accumulations of fluid with increased OCT signal intensity corresponded to regions of SSPiM in several exudative maculopathies. An in vitro phantom model demonstrates that particulate matter in suspension can generate similar OCTA signal. SSPiM showed an anatomic preference for vascular-avascular junctions. The hyperreflective fluid corresponding to SSPiM appeared more frequently in Henle's fiber layer (HFL) than the inner nuclear layer (INL) and was highly associated with hyperreflective material (HRM) found bordering the fluid. In five of eight longitudinal cases, the resolution of SSPiM resulted in the formation of confluent HRM. Clinically, this appeared as hard exudate on funduscopic images.

Conclusions: Clinical data suggest that SSPiM is a novel imaging feature of retinal vascular diseases that was not appreciated prior to the use of OCTA. We characterized several novel features of SSPiM and demonstrated that at least in some cases it resolves with residual hard exudate.


Effect of phacoemulsification on visual acuity and macular morphology in patients with wet age-related macular degeneration.

Figurska M, Bogdan-Bandurska A, Rękas M.

Background: This article discusses the effectiveness of phacoemulsification cataract surgery with intraocular lens implantation in patients with wet age-related macular degeneration in the inactive phase of the disease.

Material & Methods: Forty-nine patients (50 eyes) aged 78.94±5.54 years, previously treated with intravitreal injections of anti-vascular endothelial growth factor agents, were qualified for a prospective, randomized 12-month study. The participants were divided into 2 groups. Group I consisted of 25 patients (25 eyes) who were subjected to phacoemulsification cataract surgery. Group II consisted of 24 patients (25 eyes) who were not subjected to phacoemulsification cataract surgery despite having a lens opacity of grade II or higher according to the Lens Opacities Classification System.

Results: After 12 months of follow-up, patients in group I gained on average 8.04 letters (p<0.001). Furthermore, 20% of the eyes had a significant improvement in best corrected visual acuity of ≥15 Early Treatment of Diabetic Retinopathy Study Chart letters. Patients in group II lost on average 1.96 letters (p>0.05). No significant differences between central retinal thickness values in either group (p>0.05) were
noted. The mean number of intravitreal injections of anti-vascular endothelial growth factor agents during the study was 2.64±1.98 in group I and 2.92±2.40 in group II (p>0.05).

Conclusions: Phacoemulsification performed in eyes with wet age-related macular degeneration during the inactive phase of the disease significantly improves visual acuity. In addition, it does not significantly influence the frequency of intravitreal injections of anti-vascular endothelial growth factor agents or disease activity.

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**Pathogenesis**


**Systemic immunosuppression and risk of age-related macular degeneration.**

Sandhu HS, Lambert J, Xu Y, Kaplan HJ.

**Abstract:** A local immune response has been implicated in the pathogenesis of age-related macular degeneration (AMD), but it is unclear if systemic immunosuppressive/immunomodulatory therapy (IMT) protects against the onset and/or progression of AMD. We performed a retrospective cohort study using a Cox proportional hazards model of two cohorts. Cohort 1 included patients with stage V chronic kidney disease (CKD) status post kidney transplantation, on at least one IMT agent, and older than 50. Cohort 2 included patients with stage IV or V CKD who had not undergone kidney transplantation, were not on IMT, and were older than 50. The main outcomes were hazard ratios of a new diagnosis of dry AMD, wet AMD, or conversion from dry to wet. There were 10,813 patients in cohort 1, and 217,081 patients in cohort 2. After controlling for sex and age, there was no significant difference in the hazard of developing a new diagnosis of dry AMD (HR = 0.95, 95% CI 0.87-1.05, p = 0.32), developing a new diagnosis of wet AMD without any prior diagnosis of dry AMD (HR = 0.85, 95% CI 0.66-1.08, p = 0.18), or converting from dry to wet AMD (HR 1.24, 95% CI 0.94-1.62, p = 0.12). For patients over 70 on mycophenolate mofetil, there was a reduced hazard of converting from dry to wet AMD (HR = 0.92, 95% CI = 0.85-0.99, p = 0.02). In contrast, everolimus had an increased hazard of dry AMD (HR = 2.14, 95% CI 1.24-3.69, p < 0.01). Most systemic IMT does not affect the risk of onset or progression of AMD in patients with CKD. However, mycophenolate mofetil may confer some degree of protection against the conversion of dry AMD to wet AMD, suggesting that modulation of the immune response may prevent progression of the disease.

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**Drug Des Devel Ther. 2018 Sep 4;12:2715-2730. eCollection 2018.**

**17β-estradiol ameliorates oxidative stress and blue light-emitting diode-induced retinal degeneration by decreasing apoptosis and enhancing autophagy.**


**Purpose:** This study aimed to assess the effects of 17β-estradiol (βE2) on blue light-emitting diode (LED)-induced retinal degeneration (RD) in rats and hydrogen peroxide (H2O2)-induced retinal pigment epithelium cell injury in humans and elucidate the protective mechanism of βE2 underlying these processes.

**Methods:** Female ovariectomized (OVX) rats were intravitreally injected with βE2 before blue LED exposure (3,000 lux, 2 hours). Retinal function and morphology were assayed via electoretinogram (ERG) and H&E, respectively. Cell viability was assayed using the Cell Counting Kit-8. Cell ROS were measured using dichlorofluorescein fluorescence. Apoptosis was evaluated by TUNEL and Annexin V/prodipidum iodide staining. Gene expression and protein expression were quantified using quantitative real-time RT-PCR, Western blotting, and immunohistochemistry. Autophagosomes were examined by electron microscopy.
Results: Female OVX rats were exposed to blue LED, inducing RD. βE2 significantly prevented the reduction in the a- and b-wave ERG amplitudes and the disruption of retinal structure, the loss of photoreceptor cells, and the decrease in the thickness of the outer nuclear layer caused by blue LED exposure. βE2 also decreased cell apoptosis in the retina in blue LED-induced RD. Additionally, βE2 reduced ROS levels and apoptosis in H2O2-treated human retinal pigment epithelial (ARPE-19) cells. Furthermore, βE2 increased the protein expression of p-Akt and Bcl-2 and decreased the protein expression of cleaved caspase-3 and Bax during blue LED-induced retinal damage and in H2O2-treated ARPE-19 cells. βE2 also increased the number of autophagosomes and upregulated the expression of LC3-II/LC3-I and Beclin 1 in these processes.

Conclusion: βE2 protects against blue LED-induced RD and H2O2-induced oxidative stress by acting as an antioxidant, and its protective mechanism might occur by reducing apoptosis and enhancing autophagy; βE2 may be a novel and effective therapy for age-related macular degeneration.

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Leukotriene B4 promotes neovascularization and macrophage recruitment in murine wet-type AMD models.


Abstract: Age-related macular degeneration (AMD), a progressive chronic disease of the central retina, is associated with aging and is a leading cause of blindness worldwide. Here, we demonstrate that leukotriene B4 (LTB4) receptor 1 (BLT1) promotes laser-induced choroidal neovascularization (CNV) in a mouse model for wet-type AMD. CNV was significantly less in BLT1-deficient (BLT1-KO) mice compared with BLT1-WT controls. Expression of several proangiogenic and profibrotic factors was lower in BLT1-KO eyes than in BLT1-WT eyes. LTB4 production in the eyes was substantially increased in the early phase after laser injury. BLT1 was highly expressed in M2 macrophages in vitro and in vivo, and ocular BLT1+ M2 macrophages were increased in the aged eyes after laser injury. Furthermore, M2 macrophages were rapidly attracted by LTB4 and subsequently produced VEGF-A through BLT1-mediated signaling. Consequently, intravitreal injection of M2 macrophages augmented CNV formation, which was attenuated by BLT1 deficiency. Thus, laser-induced injury to the retina triggered LTB4 production and attracted M2 macrophages via BLT1, leading to development of CNV. A selective BLT1 antagonist (CP105696) and 3 LTB4 inhibitors (zileuton, MK-886, and bestatin) reduced CNV in a dose-dependent manner. CP105696 also inhibited the accumulation of BLT1+ M2 macrophages in the laser-injured eyes of aged mice. Together, these results indicate that the LTB4-BLT1 axis is a potentially novel therapeutic target for CNV of wet-type AMD.

PMID: 30232269 DOI: 10.1172/jci.insight.96902


Complement system and age-related macular degeneration: implications of gene-environment interaction for preventive and personalized medicine.

Maugeri A, Barchitta M, Mazzone MG, et al.

Abstract: Age-related macular degeneration (AMD) is the most common cause of visual loss in developed countries, with a significant economic and social burden on public health. Although genome-wide and gene-candidate studies have been enabled to identify genetic variants in the complement system associated with AMD pathogenesis, the effect of gene-environment interaction is still under debate. In this review we provide an overview of the role of complement system and its genetic variants in AMD, summarizing the consequences of the interaction between genetic and environmental risk factors on AMD onset, progression, and therapeutic response. Finally, we discuss the perspectives of current evidence in the field
of genomics driven personalized medicine and public health.

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Biosci Rep. 2018 Sep 17. pii: BSR20181493. [Epub ahead of print]

A review of the multifunctionality of angiopoietin-like 4 in eye disease.

Yang X, Cheng Y, Su G.

Abstract: Angiopoietin-like protein 4 is a multifunctional cytokine regulating vascular permeability, angiogenesis, and inflammation. Dysregulations on these responses contribute to the pathogenesis of ischemic retinopathies such as diabetic retinopathy, age-related macular degeneration, retinal vein occlusion and sickle cell retinopathy. However, the role of ANGPTL4 in these diseases remains controversial. Here, we summarize the functional mechanisms of ANGPTL4 in several diseases. We highlight original studies that provide detailed data about the mechanisms of action for ANGPTL4, its applications as a diagnostic or prognostic biomarker, and its use as a potential therapeutic target. Taken together, the discussions in this review will help us gain a better understanding of the molecular mechanisms by which ANGPTL4 functions in eye disease and will provide directions for future research.

PMID: 30224378 DOI: 10.1042/BSR20181493

Epidemiology


Rim TH, Yoo TK, Kwak J, et al.

Purpose: The association between long-term cardioprotective aspirin use and neovascular age-related macular degeneration is controversial. This study was undertaken to estimate the risk of neovascular age-related macular degeneration with long-term regular use of low-dose aspirin.

Design: Retrospective population-based study, using a nationwide cohort from a variety of clinics and hospitals in South Korea.

Participants: Nonregular aspirin users and regular aspirin users under national health insurance, aged ≥45 years, who were followed from 2010 through 2015, were identified.

Methods: Incidence per 10,000 person-years for neovascular age-related macular degeneration was estimated. Long-term regular use of low-dose aspirin was defined as sustained intake of ≤100 mg aspirin with ≥1044 days-prescription between 2005 and 2009. Nonregular aspirin users included occasional users or nonusers. The analyses included a propensity score-adjusted analysis in a large, randomly selected, unmatched whole cohort (n = 482,613); propensity score-matched analysis in a matched cohort (n = 74,196); and maximally adjusted analysis in the unmatched whole cohort (n = 482,613).

Main Outcome Measures: Incidence of newly developed neovascular age-related macular degeneration using the registration code for intractable disease under national health insurance.

Results: Incidence of neovascular age-related macular degeneration was 3.5 among nonregular aspirin users and 7.2 among regular aspirin users, per 10,000 person-years in the unmatched whole cohort. However, propensity score-adjusted analyses revealed no association between aspirin use and neovascular age-related macular degeneration (adjusted hazard ratio, 0.98; 95% confidence interval, 0.73-1.30). Similarly, propensity score-matched analyses showed no association; incidences of neovascular age
-related macular degeneration were 7.5 and 7.1 among nonregular aspirin users and regular aspirin users (crude hazard ratio, 0.94; 95% confidence interval, 0.70-1.28), respectively. A maximally adjusted model, including age, sex, income, residential area, and history of 100 randomly selected types of generic drugs, showed no association (adjusted hazard ratio, 0.95; 95% confidence interval, 0.71-1.28).

Conclusions: We found no association between long-term regular use of low-dose aspirin for 5 years and future incidence of neovascular age-related macular degeneration. Thus, this large-scale study suggests that regular, long-term use of low-dose aspirin appears to be safe with respect to the new development of neovascular age-related macular degeneration.

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The economic and humanistic burden of patients in receipt of current available therapies for nAMD.

Jaffe DH, Chan W, Bezlyak V, Skelly A.

Aim: To determine the economic and humanistic burden of neovascular age-related macular degeneration (nAMD) in a cohort of patients treated with anti-VEGF in Europe and the US.

Patients & Methods: Seventy-nine respondents from the EU and 63 from the US with a self-reported diagnosis of nAMD and in current receipt of treatment, as reported in an international, general population survey, were compared with non-nAMD controls.

Results: Anti-VEGF-treated nAMD patients in the EU had a greater utilization of healthcare resources, poorer quality of life and greater overall activity impairment versus non-nAMD controls. In the US cohort, treated nAMD patients had significantly greater resource utilization for ophthalmologist visits only.

Conclusion: The burden of care associated with nAMD on EU and US healthcare systems, and on patients who are in receipt of nAMD therapy, is significant and likely to be unsustainable.

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Genetics and gene therapy

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The small GTPase Rab28 is required for phagocytosis of cone outer segments by the murine retinal pigmented epithelium.


Abstract: Rab28, a member of the RAS oncogene family is a ubiquitous, farnesylated, small GTPase of unknown function present in photoreceptors and the retinal pigmented epithelium (RPE). Nonsense mutations of the human RAB28 gene cause recessive cone-rod dystrophy 18 (CRD18), characterized by macular hyperpigmentation, progressive loss of visual acuity, RPE atrophy and severely attenuated cone and rod electroretinography (ERG) responses. In an attempt to elucidate the disease-causing mechanism, we generated Rab28-/- mice by deleting exon 3 and truncating Rab28 after exon 2. We found that Rab28-/- mice recapitulate features of the human dystrophy, i.e., they exhibited reduced cone and rod ERG responses and progressive retina degeneration. Cones of Rab28-/- mice extended their outer segments (OSs) to the RPE apical processes and formed enlarged, balloon-like distal tips before undergoing degeneration. The visual pigment content of WT and Rab28-/- cones was comparable before the onset of degeneration. Cone phagosomes were almost absent in Rab28-/- mice, whereas rod phagosomes displayed normal levels. A protein-protein interaction screen identified several Rab28-interacting proteins,
including the prenyl-binding protein phosphodiesterase 6 δ-subunit (PDE6D) and a voltage-gated potassium channel subfamily J member 13 (KCNJ13) present in the RPE apical processes. Of note, loss of PDE6D prevented delivery of Rab28 to OSs. Taken together, these findings reveal that Rab28 is required for shedding and phagocytosis of cone OS discs.

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Diet, lifestyle & low vision

Nutrients. 2018 Sep 18;10(9). pii: E1321.
The effect of lutein on eye and extra-eye health.

Abstract: Lutein is a carotenoid with reported anti-inflammatory properties. A large body of evidence shows that lutein has several beneficial effects, especially on eye health. In particular, lutein is known to improve or even prevent age-related macular disease which is the leading cause of blindness and vision impairment. Furthermore, many studies have reported that lutein may also have positive effects in different clinical conditions, thus ameliorating cognitive function, decreasing the risk of cancer, and improving measures of cardiovascular health. At present, the available data have been obtained from both observational studies investigating lutein intake with food, and a few intervention trials assessing the efficacy of lutein supplementation. In general, sustained lutein consumption, either through diet or supplementation, may contribute to reducing the burden of several chronic diseases. However, there are also conflicting data concerning lutein efficacy in inducing favorable effects on human health and there are no univocal data concerning the most appropriate dosage for daily lutein supplementation. Therefore, based on the most recent findings, this review will focus on lutein properties, dietary sources, usual intake, efficacy in human health, and toxicity.

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Adherence to a Mediterranean diet, lifestyle and age-related macular degeneration: the Coimbra Eye Study - report 3.
Raimundo M, Mira F, Cachulo MDL, et al.

Purpose: To characterize the lifestyle and nutritional risk profile associated with the Mediterranean diet in a Portuguese population with and without age-related macular degeneration (AMD).

Methods: Nested case-control study (n = 883) within the Coimbra Eye Study, including 434 subjects with AMD and 449 age- and sex-matched subjects without AMD. All enrolled subjects underwent a full risk assessment, including lifestyle-related risk factors and a thorough food frequency questionnaire. This allowed us to build an adherence score to the Mediterranean diet (mediSCORE, range 0-9) constructed from individual food intakes. Food intake was also further analysed by conversion to micronutrient consumption.

Results: Our results suggest that physical activity has a protective role in AMD [p = 0.018 after multivariate adjustment, OR: 0.69 (0.51-0.93)]. High (mediSCORE ≥6) was also found to be protective [p = 0.041, OR: 0.62 (95% CI: 0.38-0.97)]. Food group analysis unveiled a specific protective role for increased fruits consumption (p = 0.029). Finally, micronutrient analysis revealed a protective role associated with increased consumption of caffeine, fibres, beta-carotene, vitamin C and vitamin E (p < 0.05).

Conclusion: High mediSCORE appears to confer protection against the development of AMD in a
Mediterranean population. This effect is driven by increased consumption of fruits and some antioxidant micronutrients, which emerged as statistically significant protective factors. Further studies are required to establish dietary recommendations with clinical application.

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