Drug treatment

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*Intravitreal aflibercept versus intravitreal ranibizumab in patients with age-related macular degeneration: a comparative effectiveness study.*

Smit C, Wiertz-Arts K, van de Garde EM.

**Aim:** A hospital-wide, unselected switch of ranibizumab to aflibercept in treatment of age-related macular degeneration (AMD) allowed us to compare the clinical effectiveness of these agents.

**Method:** In a single-center before-after, observational study design new AMD-patients started with aflibercept treatment in 2013-2014 were compared with a control group of AMD-patients on ranibizumab before the switch.

**Results:** The mean difference in visual acuity (in logMAR units) after 1 year was comparable (+0.012 [aflibercept, n = 37] vs +0.17 [ranibizumab, n = 30], p = 0.154). However, the aflibercept-group did receive more intravitreal injections (5.8 vs 4.7 injections, p = 0.004) and were treated longer (265.7 vs 197.7 days; p = 0.011).

**Conclusion:** With no difference in clinical effectiveness, longer treatment intervals for aflibercept should be investigated.

PMID: 29855194 DOI: 10.2217/cer-2017-0099


*Comparison of ranibizumab versus dexamethasone for macular oedema following retinal vein occlusion: 1-year results of the COMRADE extension study.*


**Purpose:** The COMRADE studies are the first randomized controlled head-to-head trials comparing the efficacy and safety of intravitreal ranibizumab versus dexamethasone (DEX) in patients with macular oedema secondary to retinal vein occlusion (RVO). The COMRADE extension trial was designed to provide additional 6-month data of patients who completed the core studies.

**Methods:** In this open-label, phase IV study patients who completed the COMRADE core studies were
prospectively enrolled. Overall, 92 branch RVO (BRVO) patients (ranibizumab 52, DEX 40) and 83 central RVO (CRVO) patients (ranibizumab 61, DEX 22) were treated, and 94.6% of BRVO patients and 97.6% of CRVO patients completed the extension study. Patients were assigned to the same treatment group as in the core studies. Patients were monitored monthly and received either 0.5 mg ranibizumab or a 0.7 mg DEX implant as needed.

Results: Over the course of the extension, treatment-emergent adverse events (TEAEs) of the study eye occurred in 55.8% of BRVO patients on ranibizumab and in 62.5% of those on DEX. Among CRVO patients, 65.5% in the ranibizumab group and 59.1% in the DEX group developed TEAEs. Overall, elevated intraocular pressure (IOP) was more frequent with DEX than ranibizumab treatment. Mean average change in best-corrected visual acuity (BCVA) in BRVO patients was significantly better for ranibizumab than DEX (p = 0.0249). The CRVO results were consistent with BRVO's, although not significant (p = 0.1119).

Conclusion: When used according to the European labels, ranibizumab revealed a better ocular safety profile and produced greater average BCVA gains than DEX. By the end of the additional 6-month study period, this difference in BCVA was more pronounced in BRVO as in CRVO patients. The main limitation of the COMRADE studies was that DEX patients received only a single intravitreal treatment during the first 6 months, which is presumably not adequate. However, frequent DEX implants could lead to more steroid-related side effects, especially to an increased intraocular pressure.

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Usability of the Ranibizumab 0.5-mg Prefilled Syringe: Human Factors Studies to Evaluate Critical Task Completion by Healthcare Professionals.


Purpose: A ranibizumab prefilled syringe (PFS) has been approved by the US Food and Drug Administration. Here we evaluate the use of the ranibizumab PFS for intravitreal injection by assessing whether the PFS enables healthcare providers to successfully prepare and administer an injection without prior training.

Design: Simulated-use and actual-use human factors usability studies.

Participants: Retina specialists and ophthalmic medical personnel.

Methods: In a simulated-use summative usability study, retina specialists (n=15) and ophthalmic medical personnel (n=15) prepared the ranibizumab PFS and performed injections into a model eye. In an actual-use formative usability study (ClinicalTrials.gov identifier: NCT02698566), three assistants and three retina specialists prepared the PFS and performed intravitreal injections, respectively, in study eyes of patients with retinal diseases (n=35).

Main Outcome Measures: Twelve tasks specific to the unpacking, preparing, and properly administering the PFS for intravitreal injection were evaluated by a study assessor. Task performances were evaluated for use errors, close calls, and operational difficulties. Post-injection subjective user evaluations were performed to assess ease of use.

Results: All participants successfully performed all essential and safety-critical tasks without use error in both the simulated-use and actual-use human factors usability studies. The majority of participants rated the tasks required to use the ranibizumab PFS as "Easy" or "Very Easy."

Conclusions: Both the simulated-use and actual-use usability studies yielded consistent data, showing that healthcare professionals are able to use the ranibizumab PFS by successfully performing all critical tasks involved in preparing and delivering an intravitreal injection. The simulated-use usability testing was sufficiently realistic and representative of real world use, and was appropriate and preferred over actual-use
usability testing for proper evaluation of the product user interface.

PMID: 29853609 DOI: 10.5731/pdajpst.2017.008342


A novel model of persistent retinal neovascularization for the development of sustained anti-VEGF therapies.

Li Y, Busoy JM, Zaman BAA, Woon QTS, Tan GSW, Amutha Barathi V, Cheung N, Wei JJ, Hunziker W, Hong W, Wong TY, Cheung CMG.

Abstract: Anti-vascular endothelial growth factor (VEGF) therapies lead to a major breakthrough in treatment of neovascular retinal diseases such as age-related macular degeneration or diabetic retinopathy. Current management of these conditions require regular and frequent intravitreal injections to prevent disease recurrence once the effect of the injected drug wears off. This has led to a pressing clinical need of developing sustained release formulations or therapies with longer duration. A major drawback in developing such therapies is that the currently available animal models show spontaneous regression of vascular leakage. They therefore not only fail to recapitulate retinal vascular disease in humans, but also prevent to discern if regression is due to prolonged therapeutic effect or simply reflects spontaneous healing. Here, we described the development of a novel rabbit model of persistent retinal neovascularization (PRNV). Retinal Müller glial are essential for maintaining the integrity of the blood-retinal barrier. Intravitreal injection of DL-alpha-aminoadipic acid (DL-AAA), a selective retinal glial (Müller) cell toxin, results in persistent vascular leakage for up to 48 weeks. We demonstrated that VEGF concentrations were significantly increased in vitreous suggesting VEGF plays a significant role in mediating the leakage observed. Intravitreal administration of anti-VEGF drugs (e.g. bevacizumab, ranibizumab and aflibercept) suppresses vascular leakage for 8-10 weeks, before recurrence of leakage to pre-treatment levels. All three anti-VEGF drugs are very effective in reducing angiographic leakage in PRNV model, and aflibercept demonstrated a longer duration of action compared with the others, reminiscent of what is observed with these drugs in human in the clinical setting. Therefore, this model provides a unique tool to evaluate novel anti-VEGF formulations and therapies with respect to their duration of action in comparison to the currently used drugs.

PMID: 29852133 DOI: 10.1016/j.exer.2018.05.027


Treatment Efficacy and Compliance in Patients with Diabetic Macular Edema Treated with Ranibizumab in a Real-Life Setting.

Best AL, Fajnkuchen F, Nghiem-Buffet S, Grenet T, Quentel G, Delahaye-Mazza C, Cohen SY, Giocanti-Aurégan A.

Purpose: To assess real-life efficacy of ranibizumab and treatment compliance of patients with vision loss secondary to diabetic macular edema (DME).

Methods: A retrospective study was conducted in DME patients treated with ranibizumab. Patients were monitored every 4 weeks for visual acuity (VA) and central retinal thickness (CRT) by SD-OCT. All patients received a loading dose of 3 monthly injections followed by retreatments on an as-needed basis. The primary endpoint was the change in VA at M12. Patient compliance to the follow-up and the correlation between the injection number and VA were also investigated. Compliance was compared to that of neovascular age-related macular degeneration (nAMD) patients.

Results: Seventy-two eyes of 55 consecutive DME patients were included. At baseline, the mean VA was 56.5 letters and CRT was 470 μm. At M12, the mean VA was 63.4 letters (p < 0.0001), 31.1% of patients
had a VA > 70 letters, the mean VA change was +6.9 letters, and the mean CRT was 361.9 μm (p = 0.0001) after a mean number of 5.33 intravitreal injections. In patients who received ≥7 injections, the VA gain and final VA were significantly higher than in patients who received <7 injections. At M12, 25.45% of DME patients were lost to follow-up versus 16.8% of nAMD patients (n = 55).

**Conclusion:** Our study confirms the real-life efficacy of ranibizumab in DME at M12 and the need for a large number of injections to achieve better visual outcomes. We also showed a trend to a lower compliance in diabetic versus nAMD patients.

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**J Ophthalmol. 2018 Apr 19;2018:4171628. eCollection 2018.**

**Comparison of Intravitreal Aflibercept and Ranibizumab following Initial Treatment with Ranibizumab in Persistent Diabetic Macular Edema.**

Demircan A, Alkin Z, Yesilkaya C, Demir G, Kemer B.

**Purpose:** To compare the visual and anatomic outcomes in patients with persistent diabetic macular edema (DME) who switched from ranibizumab to aflibercept with those who continued with previous ranibizumab therapy.

**Methods:** In this retrospective comparative study, medical records of consecutive patients with center-involved DME ≥ 350 μm who had at least three recent consecutive monthly ranibizumab injections followed by as-needed therapy with either aflibercept or ranibizumab were reviewed. Data were collected at presentation (preinjection), at the intermediary visit, and at the last visit (at the end of the follow-up period).

**Results:** Forty-three eyes of 43 patients were divided into two groups: the switch group (n = 20) and the ranibizumab group (n = 23). Though no significant improvement was found in the mean BCVA from the intermediary visit to the last visit, there was a difference in the mean CMT in the switch group and the ranibizumab group (p < 0.001 and p = 0.03, resp.). The mean CMT decreased after the intermediary visit by 188.6 ± 120.5 μm in the switch group and by 60.3 ± 117.1 μm in the ranibizumab group (p = 0.003).

**Conclusions:** Both aflibercept and ranibizumab decreased CMT in patients with persistent DME who showed a poor response to ranibizumab injections. However, switching to aflibercept provided only morphologic improvement.

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**Aflibercept Treatment Leads to Vascular Abnormalization of the Choroidal Neovascularization.**

Wyłęgała A, Wyłęgała F, Wyłęgała E.

**Abstract:** Recent studies do not support the hypothesis of vascular normalization in the eyes receiving various types of intravitreous antivascular endothelial growth factor (VEGF). This retrospective study considered 57 eyes of 32 patients with vascular age-related macular degeneration (AMD) undergoing aflibercept treatment. In this study, we measured the vessel density, Horton-Strahler (HS) ramification ratio (complexity), and the length ratio in 14 eyes with choroidal neovascularization treated with 3-5 Eylea injections, 17 eyes receiving 1-2 injections, and 14 treatment-naïve eyes to the use of swept source optical coherence tomography angiography (OCTA). Macular 6 × 6 mm scans were acquired using the DRI OCT Triton by a single trained technician. OCTA images were standardized, binarized, and skeletonized using ImageJ. Then, the HS analysis of the CNV was performed. Our data suggest that the vascular density significantly decreases after an anti-VEGF injection 36 and 93 versus 41 and 87 in treatment-naïve
patients. Moreover, CNV before the treatment and in a group with 3-5 injections was more complex than after receiving 1-2 injections. The branch length was not changed. Repeated anti-VEGF can lead to vascular abnormalization and further research is needed to confirm the results of this study.

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Intravitreal implantable magnetic micropump for on-demand VEGFR-targeted drug delivery.


Abstract: In this paper, we propose an intravitreal implantable magnetic micropump integrated with micro check valve capable of on-demand vascular endothelial growth factor receptor (VEGFR)-targeted drug delivery for the treatment of age-related macular degeneration, diabetic retinopathy and other eye pathologies characterized by ocular neoangiogenesis. Precise on-demand drug release is realized by the deflection of the magnetic membrane assembly according to the external magnetic field, and the membrane assembly consists of a thin elastic polydimethylsiloxane (PDMS) membrane and a cylindrical magnetic nanoparticle-PDMS composite block. Additionally, a micro check valve composed of two PDMS layers was integrated into the micropump to realize a diode-like one-directional drug delivery and prevent undesired drug diffusion. For specifically targeting VEGFR and suppression of VEGF-induced proliferation of microvascular endothelial cells, anti-Flt1 gold nanocomplexes are synthesized. In vitro and in vivo experiments and quantitative analysis are carried out in order to verify our proposed concept: precise drug release control according to the external magnetic field, targeting to microvascular endothelial cells, and efficient and on-demand drug delivery from the proposed micropump to the macular area of rabbit's eye.

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Treatment of Geographic Atrophy with Intravitreal Sirolimus: The Age-Related Eye Disease Study 2 Ancillary Study.

Gensler G, Clemons TE, Domalpally A et al.

Objective/Purpose: To evaluate efficacy and safety of monthly intravitreal injections of sirolimus, an immunosuppressive drug, for the treatment of age-related macular degeneration associated geographic atrophy (GA).

Design: Randomized, controlled, single-masked multi-center phase 2 clinical trial of intravitreal sirolimus vs. sham therapy in AREDS2 clinical centers.

Subjects: Participants with GA.

Methods: Participants eligible in one eye were randomly assigned to a monthly intravitreal injection of sirolimus (20 µL [440 µg]) or sham treatment while participants with two study eyes were assigned to a monthly intravitreal injection in a randomly-selected eye. Best-corrected visual acuities (BVCA), spectral domain optical coherence tomography (OCT), fundus color photography and fundus autofluorescence (FAF) images were obtained at baseline and every 6 months until visit month 24.

Main Outcome Measures: Rate of progression of GA (mm2/year) measured on color fundus photograph from baseline to 24 months. Secondary outcome measures include change in BVCA, worsening of vision by ≥3 lines, and changes in area of GA measured on FAF and OCT.

Results: 52 participants (mean age 79 years) were enrolled with 27 study eyes assigned to sirolimus from May 2012 to March 2014. The baseline median area of GA was 4.73 DA (12.01 mm2). The mean (standard
(deviation) growth rates of GA detected on color fundus photographs were 2.27 (2.17) mm² and 1.91 (2.27) mm² at month 12, and 4.94 (2.96) mm² and 5.72 (3.97) mm² at month 24, for the sirolimus and sham groups, respectively. There was no statistically significant difference in the GA growth rates between the two treatment groups (P=0.33). Median visual acuity changes and incidence of 15-letter loss from baseline were not different between the 2 treatment groups (p=0.19). The intervention was stopped early because of sterile endophthalmitis that occurred in 3 participants in the sirolimus group. Participants were followed for safety until the study was closed in May 2015 due to lack of efficacy.

**Conclusion:** Sirolimus did not result in different rates of GA growth in this phase 2 study. Immunosuppression may be important for some stages of the AMD process but may not necessarily be the main pathway for the development of GA.


**Ophthalmologica. 2018 May 25:1-5. [Epub ahead of print]**

**Aflibercept Treatment in Polypoidal Choroidal Vasculopathy: Results of a Prospective Study in a Caucasian Population.**


**Introduction:** Polypoidal choroidal vasculopathy (PCV) is a choroidal pathology characterized by frequent occurrences of subretinal hemorrhages and resistance to monotherapies such as ranibizumab or bevacizumab intravitreal injections (IVT). The purpose of this study is to evaluate both the anatomical and functional efficacy of aflibercept IVT as a monotherapy in PCV in a Caucasian population.

**Methods:** We conducted a prospective multicenter study in either treatment-naïve patients with PCV or PVC patients who had not been treated with anti-VEGF within the previous 3 months or with photodynamic therapy (PDT) within the previous 6 months. All patients had been treated with 3 initial monthly loading doses of aflibercept followed by a Q8 regimen for 28 weeks in total. All patients underwent a complete ophthalmic examination including the measurement of best-corrected visual acuity (BCVA) before each IVT and after 28 weeks as well as an optical coherent tomography (OCT) of the macula. At baseline and 28 weeks, the polypoidal dilations were analyzed with indocyanine green angiography.

**Results:** Thirty-four eyes of 34 patients were included in this study. All patients were followed for 28 weeks and received 5 aflibercept IVT. The mean baseline BCVA was 55 letters. After 28 weeks, significant +13 letters in BCVA and a regression of exudative signs on OCT in all patients were observed. In 62% of the cases, polyp disappearance was observed on indocyanine green angiography.

**Discussion:** In this study on a Caucasian population, we showed that aflibercept as a monotherapy provided both a significant visual gain and the regression of polypoidal dilations. Aflibercept use in monotherapy may contribute to reduce the hemorrhagic risk and atrophy linked to PDT.

PMID: 29804123 DOI: 10.1159/000488808


**Comparing Cytokine Kinetics between Ranibizumab and Aflibercept in Central Retinal Vein Occlusion with Macular Edema.**

Kotake O, Noma H, Yasuda K, Motohashi R, Goto H, Shimura M.

**Purpose:** To investigate dynamic changes in aqueous humor levels of vascular endothelial growth factor (VEGF), placental growth factor (PIGF), and inflammatory factors in patients receiving intravitreal
ranibizumab injection (IRI) or intravitreal aflibercept injection (IAI) to treat central retinal vein occlusion (CRVO) with macular edema.

Methods: In 22 CRVO patients scheduled to receive 3 doses of ranibizumab (11 eyes) or aflibercept (11 eyes) at monthly intervals, aqueous samples were collected at the time of intravitreal injection. The concentrations of VEGF, PIGF, soluble intercellular adhesion molecule-1, monocyte chemotactic protein (MCP)-1 (CCL2), platelet-derived growth factor-AA, interleukin (IL)-6, IL-8 (CXCL8), IL-12(p70) (IL12B), and IL-13 in aqueous samples were measured by the suspension array method.

Results: Visual acuity and foveal thickness improved significantly in both the IRI group and the IAI group. In addition, aqueous levels of VEGF and PIGF as well as MCP-1 and IL-6 decreased significantly over time in both groups. These parameters did not significantly differ between both groups.

Conclusions: In CRVO patients, both ranibizumab and aflibercept achieved similar improvement in clinical parameters and similar reductions in aqueous VEGF, PIGF, MCP-1, and IL-6 levels.

PMID: 29804112 DOI: 10.1159/000488494

JAMA Ophthalmol. 2018 May 2. [Epub ahead of print]

Efficacy and Safety of Lampalizumab for Geographic Atrophy Due to Age-Related Macular Degeneration: Chroma and Spectri Phase 3 Randomized Clinical Trials.


Importance: Geographic atrophy (GA) secondary to age-related macular degeneration is a leading cause of visual disability in older individuals. A phase 2 trial suggested that lampalizumab, a selective complement factor D inhibitor, reduced the rate of GA enlargement, warranting phase 3 trials.

Objective: To assess the safety and efficacy of lampalizumab vs sham procedure on enlargement of GA.

Design, Setting, and Participants: Two identically designed phase 3 double-masked, randomized, sham-controlled clinical trials, Chroma and Spectri, enrolled participants from August 28, 2014, to October 6, 2016, at 275 sites in 23 countries. Participants were aged 50 years or older, with bilateral GA and no prior or active choroidal neovascularization in either eye and GA lesions in the study eye measuring 2.54 to 17.78 mm2 with diffuse or banded fundus autofluorescence patterns.

Interventions: Participants were randomized 2:1:2:1 to receive 10 mg of intravitreal lampalizumab every 4 weeks, sham procedure every 4 weeks, 10 mg of lampalizumab every 6 weeks, or sham procedure every 6 weeks, through 96 weeks.

Main Outcomes and Measures: Safety and efficacy assessed as mean change from baseline in GA lesion area at week 48 from centrally read fundus autofluorescence images of the lampalizumab arms vs pooled sham arms, in the intent-to-treat population and by complement factor I-profile genetic biomarker.

Results: A total of 906 participants (553 women and 353 men; mean [SD] age, 78.1 [8.1] years) were enrolled in Chroma and 975 participants (578 women and 397 men; mean [SD] age, 77.9 [8.1] years) were enrolled in Spectri; 1733 of the 1881 participants (92.1%) completed the studies through 48 weeks. The adjusted mean increases in GA lesion area from baseline at week 48 were 1.93 to 2.09 mm2 across all groups in both studies. Differences in adjusted mean change in GA lesion area (lampalizumab minus sham) were -0.02 mm2 (95% CI, -0.21 to 0.16 mm2; P = .80) for lampalizumab every 4 weeks in Chroma, 0.16 mm2 (95% CI, 0.00-0.31 mm2; P = .048) for lampalizumab every 4 weeks in Spectri, 0.05 mm2 (95% CI, -0.13 to 0.24 mm2; P = .59) for lampalizumab every 6 weeks in Chroma, and 0.09 mm2 (95% CI, -0.07 to 0.24 mm2; P = .27) for lampalizumab every 6 weeks in Spectri. No benefit of lampalizumab was observed across prespecified subgroups, including by complement factor I-profile biomarker. Endophthalmitis occurred after 5 of 12 447 injections (0.04%) or in 5 of 1252 treated participants (0.4%) through week 48.
Conclusions and Relevance: In Chroma and Spectri, the largest studies of GA conducted to date, lampalizumab did not reduce GA enlargement vs sham during 48 weeks of treatment. Results highlight the substantial and consistent enlargement of GA, at a mean of approximately 2 mm² per year.

Trial Registration: ClinicalTrials.gov Identifier: NCT02247479 and NCT02247531.

PMID: 29801123 DOI: 10.1001/jamaophthalmol.2018.1544

JAMA Ophthalmol. 2018 May 2. [Epub ahead of print]

Efficacy and Safety of Intravitreal Aflibercept for Polypoidal Choroidal Vasculopathy in the PLANET Study: A Randomized Clinical Trial.


Importance: Polypoidal choroidal vasculopathy (PCV) is common in Asian populations, but an optimal treatment approach remains to be confirmed.

Objective: To evaluate intravitreal aflibercept injection (IAI) in participants with PCV and compare IAI monotherapy with IAI plus rescue photodynamic therapy (PDT).

Design, Setting, and Participants: This 96-week, double-masked, sham-controlled phase 3b/4 randomized clinical trial was conducted at multiple centers in Australia, Germany, Hong Kong, Hungary, Japan, Singapore, South Korea, and Taiwan from May 2014 to August 2016, and included adults 50 years or older with symptomatic macular PCV and a best-corrected visual acuity of 73 to 24 Early Treatment Diabetic Retinopathy Study letters (20/40-20/320 Snellen equivalent).

Interventions: Participants received 2 mg of IAI at weeks 0, 4, and 8. At week 12, participants with a suboptimal response were randomized 1:1 to receive IAI plus sham PDT (IAI monotherapy) or a "rescue" of IAI plus rescue PDT (IAI/PDT). Participants who did not qualify for rescue received IAI every 8 weeks; those qualifying for rescue received IAI every 4 weeks plus sham/active PDT. When the rescue criteria were no longer met, injection intervals were gradually extended to 8 weeks.

Main Outcomes and Measures: Noninferiority of IAI monotherapy to IAI/PDT for mean change in best-corrected visual acuity from baseline to week 52 (95% CI of the difference entirely above -5 letters).

Results: Of the 318 participants, the mean (SD) age was 70.6 (8.2) years, 96 (30.2%) were women, and 152 (47.8%) were Japanese. Monotherapy with IAI was noninferior to IAI/PDT for the primary end point (+10.7 vs +10.8 letters, respectively; 95% CI, -2.9 to 1.6; P = .55), with few participants requiring rescue therapy (19 [12.1%] vs 23 [14.3%], respectively). Participants in both treatment groups had similar reductions in central subfield thickness from baseline to week 52 (-137.7 μm [IAI monotherapy] vs -143.5 μm [IAI/PDT]). At week 52, 49 (38.9%) and 60 participants (44.8%) had no polypoidal lesions observed on indocyanine green angiography in the IAI monotherapy and IAI/PDT groups, respectively. Furthermore, 116 (81.7%) and 136 (88.9%), respectively, had no polypoidal lesions with leakage. The most frequent ocular adverse events were conjunctival hemorrhage (IAI monotherapy, 8 [5.1%]) and dry eye (IAI/PDT, 9 [5.6%]).

Conclusions and Relevance: Improvement in visual and/or functional outcomes was achieved in more than 85% of participants who were treated with IAI monotherapy, with no signs of leakage from polypoidal lesions in more than 80%. As fewer than 15% met the criteria of a suboptimal response to receive PDT, the potential benefit of adding PDT cannot be determined.

Trial Registration: clinicaltrials.gov Identifier: NCT02120950.

PMID: 29801063 DOI: 10.1001/jamaophthalmol.2018.1804
Outcomes of Anti-Vascular Endothelial Growth Factor Treatment for Choroidal Neovascularization in Fellow Eyes of Previously Treated Patients with Neovascular Age-Related Macular Degeneration.

Stem MS, Moinuddin O, Kline N, Thanos A, Rao P, Williams GA, Hassan TS.

Importance: Neovascular age-related macular degeneration (nvAMD) is a leading cause of vision loss. The optimal screening protocol to detect choroidal neovascularization (CNV) in fellow eyes of patients undergoing treatment for unilateral CNV has not been determined.

Objective: To compare the visual outcomes of eyes with established, active nvAMD in index eyes with outcomes of fellow eyes that subsequently developed CNV during the management protocol.

Design, Setting, and Participants: In this retrospective single-center case series conducted at a private vitreoretinal practice, data were collected for all patients treated for bilateral nvAMD between October 1, 2015, and October 1, 2016, for whom we could determine the date of index eye and fellow eye conversion to nvAMD (n = 1600). Per institutional protocol, patients were screened for new CNV in the fellow eye at every office visit. Patients were excluded if they had a condition that could result in marked asymmetric vision loss.

Exposures: Development of nvAMD.

Main Outcomes and Measures: Visual acuity (VA) at the time of diagnosis of nvAMD and at equivalent time points following conversion to nvAMD for both index eyes and fellow eyes.

Results: A total of 264 patients met the inclusion criteria; 197 (74.6%) were women and 253 (95.8%) were white, and the mean (SD) age was 79.1 (8.2) years at time of index eye conversion to nvAMD and 80.6 (8.2) years at time of fellow eye conversion to nvAMD. Fellow eyes presented with better VA (mean VA, 20/50 [0.40 logMAR]) compared with index eyes (mean VA, 20/90 [0.67 logMAR]) at the time of conversion (difference, 14 letters [0.27 logMAR]; 95% CI, 10-17 [0.20-0.34]; P < .001). Index eyes did not achieve the same level of VA as fellow eyes after an equivalent postconversion follow-up of approximately 20 months (mean VA: index eye; 20/70 [0.56 logMAR]; fellow eye, 20/50 [0.40 logMAR]; difference, 8 letters [0.15 logMAR]; 95% CI, 4-11 [0.08-0.22]; P < .001). No difference was detected between the mean number of anti-vascular endothelial growth factor injections received by fellow eyes and index eyes (9.7 vs 10.0 injections, respectively).

Conclusions and Relevance: This retrospective study suggests that fellow eyes of previously treated patients with nvAMD may achieve better VA than their index eye counterparts after an equivalent amount of follow-up. This may be because the CNV was detected and treated earlier and at a better level of VA, although it is unknown whether the frequent office visits, VA measurements, or optical coherence tomography testing was responsible for the detection at a better level of VA.

PMID: 29800991 DOI: 10.1001/jamaophthalmol.2018.1534


A meta-analysis of the effect of a dexamethasone intravitreal implant versus intravitreal anti-vascular endothelial growth factor treatment for diabetic macular edema.

He Y, Ren XJ, Hu BJ, Lam WC, Li XR.

Background: This meta-analysis evaluated the effectiveness and safety of dexamethasone (DEX) implant and intravitreal anti-vascular endothelial growth factor (VEGF) treatment for diabetic macular edema (DME).

Methods: The PubMed, Embase, clinicaltrials.gov website and Cochrane Library databases were
comprehensively searched for studies comparing DEX implant with anti-VEGF in patients with DME. Best-corrected visual acuity (BCVA), central subfield thickness (CST) and adverse events were extracted from the final eligible studies. Review Manager (RevMan) 5.3 for Mac was used to analyze the data and GRADE profiler were used to access the quality of outcomes.

**Results:** Based on four randomized clinical trials assessing a total of 521 eyes, the DEX implant can achieve visual acuity improvement for DME at rates similar to those achieved via anti-VEGF treatment (mean difference [MD] = -0.43, P = 0.35), with superior anatomic outcomes at 6 months (MD = -86.71 μm, P = 0.02), while requiring fewer injections, in comparison to anti-VEGF treatment. Although the mean reduction in CST did not showed significant difference at 12 months (MD = -33.77 μm, P = 0.21), the significant in BCVA from baseline to 12 months supported the anti-VEGF treatment (MD = -3.26, P < 0.00001). No statistically significant differences in terms of the serious adverse events. However, use of the DEX implant has higher risk of intraocular pressure elevation and cataract than anti-VEGF treatment.

**Conclusion:** Compared with anti-VEGF, DEX implant improved anatomical outcomes significantly. However, this did not translate to improved visual acuity, which may be due to the progression of cataract. Therefore, the DEX implant may be recommended as a first choice for select cases, such as for pseudophakic eyes, anti-VEGF-resistant eyes, or patients reluctant to receive intravitreal injections frequently.

PMID: 29784048 DOI: 10.1186/s12886-018-0779-1

**Invest Ophthalmol Vis Sci. 2018 May 1;59(6):2659-2669.**

**A CCR2/5 Inhibitor, PF-04634817, is Inferior to Monthly Ranibizumab in the Treatment of Diabetic Macular Edema.**

Gale JD, Berger B, Gilbert S, Popa S, Sultan MB, Schachar RA, Girgenti D, Perros-Huguet C.

**Purpose:** Ligands for the proinflammatory C-C chemokine receptor types 2 and 5 (CCR2 and CCR5) are elevated in the eyes of patients with diabetic macular edema (DME). We evaluated the efficacy and safety of PF-04634817, an oral CCR2/5 dual antagonist, versus intravitreal ranibizumab, in adult subjects with DME.

**Methods:** In this phase II, randomized, placebo-controlled, double-masked study, eligible subjects (≥18 years of age) had type 1 or 2 diabetes and DME with best-corrected visual acuity (BCVA) of 20/32 or worse (letter score ≤ 78), and up to 20/320 or better (≥24 letter score), in the study eye. Subjects were assigned randomly 1:1 to once-daily (QD) oral PF-04634817 200 mg plus masked sham therapy as placebo or monthly intravitreal ranibizumab 0.3/0.5 mg plus QD oral placebo. The primary objective was to evaluate the efficacy of PF-04634817 compared with ranibizumab in change from baseline in BCVA after 12 weeks in a noninferiority design. Noninferiority was based on BCVA 80% confidence interval (CI): there had to be a less than three letter loss in the PF-04634817 arm compared with the ranibizumab arm.

**Results:** A total of 199 subjects were randomized. Least squares mean difference in change in BCVA from baseline to week 12 in the study eye for the PF-04634817 arm was -2.41 letters (80% CI: -3.91, -0.91; P = 0.04) compared with ranibizumab. PF-04634817 was well tolerated.

**Conclusions:** Treatment with oral CCR2/5 receptor dual antagonist PF-04634817 was associated with a modest improvement in BCVA, but did not meet the predefined noninferiority criteria compared with intravitreal ranibizumab.

PMID: 29847672 DOI: 10.1167/iovs.17-22731
Anti-vascular endothelial growth factor for neovascular age-related macular degeneration: a meta-analysis of randomized controlled trials.

Nguyen CL, Oh LJ, Wong E, Wei J, Chilov M.

Background: To evaluate the relative efficacy and safety of anti-vascular endothelial growth factor (anti-VEGF) agents for the treatment of neovascular age-related macular degeneration (AMD).

Methods: Systematic literature review identifying RCTs comparing anti-VEGF agents to another treatment published before June 2016. Efficacy assessed by mean change in best corrected visual acuity (BCVA) and central macular thickness (CMT) from baseline at up to 2 years followup. Safety assessed by proportions of patients with death, arteriothrombotic and venous thrombotic events, and at least one serious systemic adverse event at up to 2 years of follow-up.

Results: Fifteen RCTs selected for meta-analysis (8320 patients). Two trials compared pegaptanib, and three trials compared ranibizumab versus control. Eight trials compared bevacizumab with ranibizumab. Two trials compared aflibercept with ranibizumab. There were no significant differences between bevacizumab and ranibizumab for BCVA at 1 or 2 years (weighted mean difference = -0.57, 95% CI -1.55 to 0.41, \( P = 0.25 \)) and weighted mean difference = -0.76, 95% CI -2.25 to 0.73, \( P = 0.32 \), respectively). Ranibizumab was more effective in reducing CMT at 1 year (weighted mean difference = 4.49, 95% CI 1.13 to 7.84, \( P = 0.009 \)). Risk ratios comparing rates of serious systemic adverse events at 1 and 2 years were slightly out of favour for bevacizumab. Aflibercept compared with ranibizumab demonstrated similar mean change in BCVA, reduction in CMT, and safety at 1 year.

Conclusions: Bevacizumab and ranibizumab had equivalent efficacy for BCVA, while ranibizumab had greater reduction in CMT and less rate of serious systemic adverse events. Aflibercept and ranibizumab had comparable efficacy for BCVA and CMT. This provides information to balance comparable effects on vision and risk of adverse events between anti-VEGF agents.

PMID: 29843663 PMCID: PMC5975529 DOI: 10.1186/s12886-018-0785-3

Other treatment and diagnosis


Comparison of SD-Optical Coherence Tomography Angiography and Indocyanine Green Angiography in Type 1 and 2 Neovascular Age-related Macular Degeneration.


Purpose: The purpose of this study is to compare the ability of spectral domain optical coherence tomography angiography (SD-OCTA) and indocyanine green angiography (ICGA) to detect and measure lesion area in patients with type 1 and 2 choroidal neovascularization (CNV).

Methods: Types 1 and 2 neovascular AMD (nAMD) were included in this prospective and observational case series. ETDRS best-corrected visual acuity (BCVA), ophthalmic examination with funduscopy, OCTA (AngioVue), fluorescein angiography (FA), ICGA, and OCT (Spectralis) were performed. CNV measurements were done manually by two experienced graders using the systems’ innate region selection tools.

Results: Forty eyes of 39 consecutive patients with nAMD were included. Mean age was 77 ± 6.4 years, ETDRS BCVA was 67 ± 13 letters, and 11 eyes were treatment naïve. Nineteen CNV lesions were classified as type 1 and 21 as type 2. ICGA was able to identify CNV in all eyes. By contrast, OCTA
detected CNV in 95% of type 1 and 86% of type 2 nAMD eyes. Mean overall CNV area (CNV-A) was 2.8 ± 2.7 mm² in ICGA and 2.1 ± 2.7 mm² in OCTA. Both lesion types CNV-A appeared significantly smaller in OCTA compared with ICGA (P < 0.01). Bland-Altman plot revealed a mean difference (bias) between OCTA and ICGA CNV-A of 0.76 ± 1.74 mm². Intraclass correlation coefficient (ICC) for CNV-A was 0.91 and 0.93 for ICGA and OCTA, respectively. ICGA CNV-A in the four OCTA-negative eyes (median 4.7 mm²) was not significantly different from the 36 OCTA-positive eyes (median 1.7 mm²).

Conclusions: Type 1 and 2 CNV-A were significantly smaller in OCTA than in ICGA. OCTA was generally less successful in detecting CNV than ICGA in patients who were included into this study based on FA and OCT. However, OCTA detected all type 1 lesions except for one, indicating that the SD-OCTA signal is limited by detection limits of blood flow velocity rather than lesion type. Further efforts are needed pushing the limits of lowest detectable and fastest distinguishable flow until OCTA can deliver realistic qualitative and quantitative imaging of type 1 and 2 CNV for diagnosis and monitoring.

PMID: 29847645 DOI: 10.1167/iovs.17-22902

**J Ophthalmol. 2018 May 7;2018:9246384. eCollection 2018.**

**Evaluation of Vitrectomy with Planned Foveal Detachment as Surgical Treatment for Refractory Diabetic Macular Edema with or without Vitreomacular Interface Abnormality.**

**Abdel Hadi AM.**

**Purpose:** To evaluate the therapeutic efficacy of subretinal BSS injections done during vitrectomy for refractory diabetic macular edema (DME) resistant to other modes of treatment including previous vitrectomy.

**Materials and Methods:** A prospective, interventional noncomparative case series in which cases had refractory DME with a central macular thickness (CMT) ≥ 300 μm, despite previous anti-VEGF therapy (ranibizumab or bevacizumab with shifting to aflibercept). Some cases even received intravitreal triamcinolone acetone injection, before attempting this solution. The study included group 1, surgically naïve eyes, and group 2, cases with persistent edema despite a previous vitrectomy (7 eyes (25%)). The cases were also divided into group a, eyes with normal vitreomacular interface, and group b, with abnormal vitreomacular attachment (VMA) (6 (21.4%)). The 1ry endpoint for this study was the change in CMT after 9 -12 months from surgery. The 2ry endpoints were change in BCVA, recurrence of DME, and surgical complications.

**Results:** The study included 28 eyes, 6 (21.4%) of which suffered from edema recurrence. The mean recorded CMT was 496 ± 88.7 μm and 274.1 ± 31.6 μm preoperatively and postoperatively, respectively. In all eyes, the preoperative mean BCVA in decimal form was 0.2 ± 0.11, which improved significantly to 0.45 ± 0.2. In the end, the CMT of groups 1 and 2 measured 239 μm and 170.8 μm, respectively (p = 0.019). The preoperative BCVA in groups 1 and 2 was 0.16 ± 0.07 and 0.37 ± 0.14, respectively, which improved to a mean of 0.34 ± 0.09 and 0.7 ± 0.16 postoperatively, respectively (p = 0.185).

**Conclusion:** Vitrectomy with a planned foveal detachment technique was shown to be a promising solution for refractory DME cases with rapid edema resolution. CMT was shown to improve more in eyes where conventional vitrectomy was not attempted. Moreover, cases with VMA resistant to pharmacotherapy was shown to respond well to this technique. The study has been registered in Contact ClinicalTrials.gov PRS Identifier: NCT03345056.

PMID: 29854429 PMCID: PMC5964411 DOI: 10.1155/2018/9246384
Ocular Distribution and Pharmacodynamics of SF0166, a Topically Administered αvβ3 Integrin Antagonist, for the Treatment of Retinal Diseases.

Askew BC, Furuya T, Edwards DS.

Abstract: SF0166, a small molecule αvβ3 antagonist, has physiochemical properties that allow distribution to the posterior segment of the eye after topical administration in an ophthalmic solution. The pharmacodynamics and pharmacokinetics of SF0166 were evaluated in several cell lines, chick chorioallantoic membrane assays, and models of ocular neovascularization in mice and pigmented rabbits. SF0166 inhibited cellular adhesion to vitronectin across human, rat, rabbit, and dog cell lines with IC50 values of 7.6 pM to 76 nM. SF0166 inhibited integrin-ligand interactions at IC50 values of 0.6 nM to 13 nM for human αvβ3, αvβ6, and αvβ8. SF0166 significantly decreased neovascularization in the oxygen-induced retinopathy mouse model. SF0166 distributed to the choroid and retina after topical ocular administration in amounts that substantially exceeded the cellular IC50 for adhesion to vitronectin; drug concentrations were maintained for >12 hours. In the laser-induced choroidal neovascularization model, topical ocular administration of SF0166 decreased lesion area compared with vehicle and was comparable to a bevacizumab injection. In the vascular endothelial growth factor-induced early neovascularization and vascular leakage model, topical ocular application of SF0166 resulted in a dose-dependent reduction in vascular leakage; the highest ocular doses tested showed comparable activity to a bevacizumab injection. In summary, SF0166 was safe and efficacious in animal models of ocular neovascularization and Phase I/II clinical trials in patients with diabetic macular edema (NCT02914613) and neovascular age-related macular degeneration (NCT02914639) have recently completed.

PMID: 29853477 DOI: 10.1124/jpet.118.248427

Treatments for dry age-related macular degeneration and Stargardt disease: a systematic review.


Background: Age-related macular degeneration (AMD) is the leading cause of visual loss in older people. Advanced AMD takes two forms, neovascular (wet) and atrophic (dry). Stargardt disease (STGD) is the commonest form of inherited macular dystrophy.

Objective: To carry out a systematic review of treatments for dry AMD and STGD, and to identify emerging treatments where future NIHR research might be commissioned.

Design: Systematic review.

Methods: We searched MEDLINE, EMBASE, Web of Science and The Cochrane Library from 2005 to 13 July 2017 for reviews, journal articles and meeting abstracts. We looked for studies of interventions that aim to preserve or restore vision in people with dry AMD or STGD. The most important outcomes are those that matter to patients: visual acuity (VA), contrast sensitivity, reading speed, ability to drive, adverse effects of treatment, quality of life, progression of disease and patient preference. However, visual loss is a late event and intermediate predictors of future decline were accepted if there was good evidence that they are strong predictors of subsequent visual outcomes. These include changes detectable by investigation, but not necessarily noticed by people with AMD or STGD. ClinicalTrials.gov, the World Health Organization search portal and the UK Clinical Trials gateway were searched for ongoing and recently completed clinical trials.

Results: The titles and abstracts of 7948 articles were screened for inclusion. The full text of 398 articles were obtained for further screening and checking of references and 112 articles were included in the final report. Overall, there were disappointingly few good-quality studies (including of sufficient size and duration) reporting useful outcomes, particularly in STGD. However we did identify a number of promising research topics, including drug treatments, stem cells, new forms of laser treatment, and implantable...
intraocular lens telescopes. In many cases, research is already under way, funded by industry or governments.

Limitations: In AMD, the main limitation came from the poor quality of much of the evidence. Many studies used VA as their main outcome despite not having sufficient duration to observe changes. The evidence on treatments for STGD is sparse. Most studies tested interventions with no comparison group, were far too short term, and the quality of some studies was poor.

Future work: We think that the topics on which the Health Technology Assessment (HTA) and Efficacy Mechanism and Evaluation (EME) programmes might consider commissioning primary research are in STGD, a HTA trial of fenretinide (ReVision Therapeutics, San Diego, CA, USA), a visual cycle inhibitor, and EME research into the value of lutein and zeaxanthin supplements, using short-term measures of retinal function. In AMD, we suggest trials of fenretinide and of a potent statin. There is epidemiological evidence from the USA that the drug, levodopa, used for treating Parkinson's disease, may reduce the incidence of AMD. We suggest that similar research should be carried out using the large general practice databases in the UK. Ideally, future research should be at earlier stages in both diseases, before vision is impaired, using sensitive measures of macular function. This may require early detection of AMD by screening.

Study Registration: This study is registered as PROSPERO CRD42016038708.

Funding: The National Institute for Health Research HTA programme.

PMID: 29846169 DOI: 10.3310/hta22270


Outcomes of cataract surgery in patients with exudative age-related macular degeneration and macular fluid.


Purpose: The purpose of this study was to investigate whether having macular fluid on the OCT prior to cataract surgery adversely affected vision or anatomic outcomes after cataract surgery in patients with exudative AMD.

Design: Retrospective, cohort study.

Methods: We examined all patients who underwent cataract surgery and were receiving intravitreal anti-VEGF injections from January 1st, 2012 through December 31st, 2016. There were 81 eyes that underwent cataract surgery and had received at least one intravitreal anti-VEGF injection for a diagnosis of exudative AMD within 6 months prior to surgery. Data collected included the development of subretinal or intraretinal macular fluid, or subretinal hemorrhage in the 6 months following surgery, number of injections, best corrected visual acuity (BCVA), and central subfield thickness (CST).

Results: There was a significant improvement between pre- and post-operative BCVA when comparing all patients (p values <0.0001) and no significant difference in CST before and after surgery (p >0.05). There were 23 eyes with fluid on the pre-operative OCT. There were no differences in final BCVA or CST and no difference in the development of fluid post-operatively when compared to patients without fluid pre-operatively (all p values >0.05). These patients also saw a significant improvement in BCVA (p = 0.006).

Conclusion: In a real world setting, patients with both cataracts and wet AMD may safely undergo cataract surgery. Patients with stable pre-operative fluid on OCT should be considered for cataract surgery as these patients did well post-operatively with no worsening of their neovascular process.

PMID: 29802819 DOI: 10.1016/j.ajo.2018.05.014

Association of Anticholinergic Drug Use With Risk for Late Age-Related Macular Degeneration.


Importance: Amyloid-β is a major component of retinal drusen, the primary lesions of age-related macular degeneration (AMD), and autopsy and animal models suggested that anticholinergic drug (ACD) use increased brain amyloid-β deposition.

Objective: To investigate the association between exposure to ACDs and late AMD (features of neovascular AMD or geographic atrophy of the retinal pigment epithelium in at least 1 eye).

Design, Setting and Participants: A multicenter case-control study in 4 French ophthalmologic centers comprising 200 cases with late AMD and 200 controls enrolled from July 2016 to June 2017.

Exposures: Exposure to at least 3 months of ACDs started before AMD diagnosis was recorded during a specific interview. A dose-effect association with cumulative exposure duration and Anticholinergic Burden Score was explored. The association between ACD exposure and AMD was assessed by multivariate logistic regression analysis adjusted for age, sex, smoking status, family history of AMD, alcohol consumption, and use of anticoagulant and anti-inflammatory drugs. Odds ratios (ORs) and 95% confidence intervals were estimated.

Main Outcomes and Measures: Association between exposure to ACDs and late AMD.

Results: Among case participants, the mean (SD) age was 74.8 (9.2) years, 129 (64.5%) were women, 192 (96%) were white, 65 (32.5%) had geographic atrophy, 135 (67.5%) had neovascular AMD, 116 (58%) had unilateral AMD, and 84 (42%) had bilateral AMD. Among control participants, the mean (SD) age was 75.5 (7.2) years, with 116 (58%) women and 187 (93.5%) white participants. Twenty-six cases (13%) and 10 controls (5%) were exposed to ACDs throughout life for at least 3 months before AMD onset. Risk of AMD was increased with ever exposure to ACDs (adjusted OR [aOR], 2.84; 95% CI, 1.33-6.06; P = .007), high Anticholinergic Burden Score (≥3) (aOR, 6.42; 95% CI, 1.38-29.92; P = .02), and longest cumulative exposure to ACD (≥15 years) (aOR, 5.88; 95% CI, 1.22-28.31; P = .03).

Conclusions and Relevance: Risk of late AMD may be increased with at least 3 months’ use of ACDs. A dose-effect association was suggested by a greater association with prolonged use and high Anticholinergic Burden Score. Further studies, in particular those with longitudinal design, are needed to confirm this association.

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Pathogenesis


Cyanidin-3-glucoside Alleviates 4-Hydroxyhexenal-Induced NLRP3 Inflammasome Activation via JNK-c-Jun/AP-1 Pathway in Human Retinal Pigment Epithelial Cells.


Abstract: Recently, the NLRP3 inflammasome activation in the eyes has been known to be associated with the pathogenesis of age-related macular degeneration. The aim of this study was to investigate the protective effects of cyanidin-3-glucoside (C3G), an important anthocyanin with great potential for preventing eye diseases, against 4-hydroxyhexenal- (HHE-) induced inflammatory damages in human retinal pigment epithelial cells, ARPE-19. We noticed that C3G pretreatment to the ARPE-19 cells rescued HHE-induced antiproliferative effects. Cell apoptosis ratio induced by HHE was also decreased by C3G,
measured by flow cytometry. The activation of NLRP3 inflammasome induced by HHE was found with increases of caspase-1 activity, proinflammatory cytokine releases (IL-1β and IL-18), and NLRP3 inflammasome-related gene expressions (NLRP3, IL-1β, IL-18, and caspase-1). The C3G showed potent inhibitive effects on these NLRP3 inflammasome activation hallmarks induced by HHE. Moreover, we noticed that the C3G's pretreatment leads to a delayed and a decreased JNK activation in HHE-challenged ARPE-19 cells. Finally, using a luciferase reporter gene assay system, we demonstrated that HHE-induced activation protein-1 (AP-1) transcription activity was abolished by C3G pretreatment in a dose-dependent manner. Taken together, these data showed that HHE leads to inflammatory damages to ARPE-19 cells while C3G has great protective effects, highlighting future potential applications of C3G against AMD-associated inflammation.

PMID: 29854843 PMCID: PMC5952446 DOI: 10.1155/2018/5604610


Vascular Endothelial Growth Factor, Basic Fibroblast Growth Factor, and Pigment Epithelium-Derived Factor Expression in the Neovascular Iris in Retinal Diseases.

Miao H, Hou X, Hwang DK, Tao Y.

Objective: To determine the expression of cytokines in the iris of patients with neovascular glaucoma (NVG).

Methods: Patients with NVG associated with proliferative diabetic retinopathy (PDR, group 1) or central retinal vein occlusion (CRVO, group 2) who had undergone surgical treatment were enrolled. Patients with primary open-angle glaucoma requiring surgical treatment were included in the control group (group 3). All iris specimens were obtained during trabeculectomy, 7 days after intravitreal injections of ranibizumab. The messenger RNA (mRNA) and protein levels of three target cytokines-vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and pigment epithelium-derived factor (PEDF)-in the iris were analyzed and compared.

Results: We included 39 eyes from 39 patients (12, 15, and 12 in groups 1, 2, and 3, resp.). The protein and mRNA levels of PEDF were higher in two NVG groups. The protein levels, but not mRNA level, of bFGF were higher in the two NVG groups. The protein and mRNA levels of VEGF were similar in the three groups.

Conclusions: The protein level of bFGF increased in the irises of the NVG patients was not expressed by the iris itself, whereas PEDF may be expressed by the iris tissue in these patients.

PMID: 29850214 PMCID: PMC5925170 DOI: 10.1155/2018/8025951


Aster koraiensis Extract and Chlorogenic Acid Inhibit Retinal Angiogenesis in a Mouse Model of Oxygen-Induced Retinopathy.

Kim J, Lee YM, Jung W, Park SB, Kim CS, Kim JS.

Abstract: Aster koraiensis extract (AKE) is a standard dietary herbal supplement. Chlorogenic acid (CA) is the major compound present in AKE. Retinal neovascularization is a common pathophysiology of retinopathy of prematurity, diabetic retinopathy, and wet form age-related macular degeneration. In this study, we aimed to evaluate the effects of AKE and CA on retinal neovascularization in a mouse model of oxygen-induced retinopathy (OIR). Vascular endothelial growth factor- (VEGF-) induced tube formation was assayed in human vascular endothelial cells. Experimental retinal neovascularization was induced by exposing C57BL/6 mice to 75% oxygen on postnatal day 7 (P7) and then returning them to normal oxygen...
pressure on P12. AKE (25 and 50 mg/kg/day) and CA (25 and 50 mg/kg/day) were administered intraperitoneally for 5 days (P12-P16). Retinal flat mounts were prepared to measure the extent of retinal neovascularization at P17. The incubation of human vascular endothelial cells with AKE and CA (1-10 μg/mL) resulted in the inhibition of VEGF-mediated tube formation in a dose-dependent manner. The neovascular area was significantly smaller in AKE or CA-treated mice than in the vehicle-treated mice. These results suggest that AKE is a potent antiangiogenic agent and that its antiangiogenic activity may, in part, be attributable to the bioactive component CA.

PMID: 29849715 PMCID: PMC5937502 DOI: 10.1155/2018/6402650


Circulating levels of mannose-binding lectin (MBL) in age-related macular degeneration.


Purpose: To assess whether the serum levels of mannose-binding lectin of the lectin complement pathway are associated with age-related macular degeneration.

Methods: Patients with age-related macular degeneration and age-matched controls underwent full ophthalmologic examination and optical coherence tomography. Using a time-resolved immunofluorometric assay, blood samples were evaluated to determine the serum mannose-binding lectin levels.

Results: A total of 136 individuals were evaluated, including 68 patients with age-related macular degeneration (34 exudative and 34 nonexudative) and 68 age-matched controls. The median mannose-binding lectin level was 608 ng/mL (range, 30-3,415 ng/mL) in patients with age-related macular degeneration and 739 ng/mL (range, 30-6,039 ng/mL) in controls, with no difference between the groups. Additionally, the median mannose-binding lectin level was 476 ng/mL (range, 30-3,415 ng/mL) in exudative cases and 692 ng/mL (range, 30-2,587 ng/mL) in nonexudative cases.

Conclusions: Serum mannose-binding lectin levels were not associated with age-related macular degeneration or with the exudative and nonexudative forms of the disease.

PMID: 29846424 DOI: 10.5935/0004-2749.20180027


Esculetin protects human retinal pigment epithelial cells from lipopolysaccharide-induced inflammation and cell death.

Ozal SA, Turkekul K, Gurlu V, Guclu H, Erdogan S.

Purpose: Age-related macular degeneration (AMD) is the most common cause of visual loss. The dry AMD is characterized by retinal pigment epithelium (RPE) death and changes in AMD lead to severe loss of vision. Coumarin derived esculetin has a number of therapeutic and pharmacological effects such as anti-inflammatory and antioxidant with various mechanisms. The purpose of this study was to investigate the effects of esculetin treatment on lipopolysaccharide (LPS) - induced inflammation, oxidative stress and cell survival.

Material and methods: Human RPE cells (ARPE-19) were incubated for 24 - 72 h with 5 μg/ml LPS to induce inflammation and oxidative stress. Esculetin (5 μM) was used to protect the cells from LPS-induced damage. The cell viability was evaluated by quantitative MTT test. IL-6, IL-12 and vascular endothelial growth factor (VEGF) levels were determined by ELISA. IL-1β, tumor necrosis factor receptor (TNFR), TNF-related apoptosis-inducing ligand (TRAIL), catalase, glutathione peroxidase (GPx), superoxide dismutase 1 (CuZnSOD) and SOD2 (MnSOD) mRNA expressions were analyzed by RT-qPCR. Apoptosis was
monitored by cell-based cytometer. NF-kappa B (NF-κB) p65/RelA levels were determined by ELISA, and NF-κB protein expression and extracellular signal-regulated kinase (ERK1/2) phosphorylation were evaluated by Western blot analysis.

**Results:** Esculetin treatment significantly suppressed LPS-induced cell death mediated by apoptosis and necrosis in a concentration dependent manner. While LPS caused significant inflammation with cytokine increase in cells, esculetin reduced the expression of LPS-induced cytokines, VEGF, TNFR and TRAIL. Furthermore, exposure to LPS increased the expression of GPx and mitochondrial MnSOD, leading to oxidative stress in the cells. Esculetin treatment attenuated phosphorylation of ERK1/2 and NF-κB expression mediated by LPS.

**Conclusions:** These results suggest that esculetin may be an alternative treatment option for endotoxin-induced inflammation and oxidative stress, which therefore may inhibit the development of LPS-mediated AMD.

PMID: 29806490 DOI: 10.1080/02713683.2018.1481517


TGF-β concentrations and activity are down-regulated in the aqueous humor of patients with neovascular age-related macular degeneration.


**Abstract:** Controversy still exists regarding the role of the TGF-β in neovascular age-related macular degeneration (nAMD), a major cause of severe visual loss in the elderly in developed countries. Here, we measured the concentrations of active TGF-β1, TGF-β2, and TGF-β3 by ELISA in the aqueous humor of 20 patients affected by nAMD, who received 3 consecutive monthly intravitreal injections of anti-VEGF-A antibody. Samples were collected at baseline (before the first injection), month 1 (before the second injection), and month 2 (before the third injection). The same samples were used in a luciferase-based reporter assay to test the TGF-β pathway activation. Active TGF-β1 concentrations in the aqueous humor were below the minimum detectable dose. Active TGF-β2 concentrations were significantly lower at baseline and at month 1, compared to controls. No significant differences in active TGF-β3 concentration were found among the sample groups. Moreover, TGF-β pathway activation was significantly lower at baseline compared to controls. Our data corroborate an anti-angiogenic role for TGF-β2 in nAMD. This should be considered from the perspective of a therapy using TGF-β inhibitors.

PMID: 29795291 PMCID: PMC5966430 DOI: 10.1038/s41598-018-26442-0

**Epidemiology**


What Effect does Ethnicity have on the Response to Ranibizumab in the Treatment of Wet Age-Related Macular Degeneration?

Mohamed R, Gadhvi K, Mensah E.

**Aims:** To compare, in a single urban population, the visual outcomes of ranibizumab monotherapy in "White" (W) and "Non-White" (NW) patients with wet age-related macular degeneration (AMD).

**Procedures:** Prospective data was collected from 434 eyes of 217 patients with wet AMD patients receiving intravitreal ranibizumab. Baseline and monthly LogMAR visual acuities were obtained. All patients received treatment under a "treat and extend policy" consisting of three monthly injections of ranibizumab, followed...
Results: At 24 months, the percentage of eyes that maintained or improved vision was 91% in W patients and 83% in NW patients. Correspondingly, at 24 months, the percentage of visual loss was 9% for W patients and 17% of NW patients. We found that whilst W patients required fewer overall injections (14.1) they gained an average 4 LogMAR letters of visual acuity. However, NW patients required more injections (14.6) to gain 0.5 LogMAR letters of visual acuity over the same 24 months of treatment.

Conclusions: Individualised ranibizumab monotherapy is more effective in preserving vision for W compared to NW patients with wet AMD.

PMID: 29847823 DOI: 10.1159/000486403

**Medicine (Baltimore). 2018 May;97(21):e10422.**

*Therapeutic effects of various therapeutic strategies on non-exudative age-related macular degeneration: A PRISMA-compliant network meta-analysis of randomized controlled trials.*

Wei Y, Liao H, Ye J.

**Purpose:** Age-related macular degeneration (AMD) is a chronic progressive central retinal disease. Geographic atrophy (GA) is a late stage of dry AMD (DAMD) and is a slowly but inexorably progressive disease that causes irreversible blindness over time. We aimed to assess various therapeutic strategies for DAMD and GA treatment by network meta-analysis.

**Methods:** We searched PubMed, Embase, and the Cochrane Library to identify randomized controlled trials (RCTs) of atrophic AMD treatments published prior to December 16, 2017. Best-corrected visual acuity (BCVA) and change in GA area were evaluated to reflect therapeutic effects. A random-effects network meta-analysis, with a frequentist framework, was used to assess the effectiveness of therapeutic strategies for DAMD treatment.

**Results:** We included 22 articles that assessed 16 types of regimens and 2482 patients in our meta-analysis. The network meta-analysis results showed that zinc-monocysteine (98.1%) was the most likely to improve BCVA (logMAR), followed by alprostadil (84.0%), eculizumab (70.5%), and rheohemapheresis (67.3%). In BCVA (letters) outcomes, rheohemapheresis (99.6%), lampalizumab (69.5%), and the antioxidant complex (67.9%) showed marked benefits in visual function recovery. Regarding the outcome of GA area change, isopropyl unoprostone (IU) (88.6%) might have the best GA area reduction; however, there was no significant difference between IU and the blank control.

**Conclusions:** Zinc-monocysteine and rheohemapheresis showed significantly better effects on BCVA (logMAR) improvement, and compared with the blank control, rheohemapheresis and the antioxidant complex showed better effects on BCVA (letters) improvement. Other treatments have potential effects on DAMD, including alprostadil, eculizumab, and lampalizumab. However, there is no effective treatment for GA area reduction.

PMID: 29794727 DOI: 10.1097/MD.0000000000010422

**Cochrane Database Syst Rev. 2018 May 30;5:CD011140.**

*Implantable miniature telescope (IMT) for vision loss due to end-stage age-related macular degeneration.*

Gupta A1, Lam J, Custis P, Munz S, Fong D, Koster M.

**Background:** Age-related macular degeneration (AMD) causes progressive and irreversible damage to the retina, resulting in loss of central vision. AMD is the third leading cause of irreversible visual impairment...
Objective: To assess the effectiveness and safety of the IMT in improving visual acuity and quality of life in people with late or advanced AMD.

Search Methods: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2017, Issue 11); Ovid MEDLINE; Embase.com; PubMed; LILACS; AMED; Web of Science Conference Proceedings Citation Index-Science; OpenSIGLE; the metaRegister of Controlled Trials (mRCT) (last searched 27 June 2014); ClinicalTrials.gov; the ICTR and the US Food and Drug Administration (FDA) Medical Devices database. The date of the search was 2 November 2017, with the exception of mRCT which is no longer in service.

Selection Criteria: We planned to include randomized controlled trials (RCTs) and quasi-randomized trials that compared the IMT versus no IMT.

Data Collection and Analysis: Two review authors independently assessed all studies for inclusion, using standard methodological procedures expected by Cochrane.

Main Results: Our search yielded 1042 unique records. We removed irrelevant studies after screening titles and abstracts, and evaluated five full-text reports from four studies; three were non-randomized studies. There was one ongoing RCT that compared the OriLens intraocular telescope with standard low vision training in eyes with end-stage AMD. Results for this study are expected in 2020.

Authors’ Conclusions: We found no RCT or quasi-RCT and can draw no conclusion about the effectiveness and safety of the IMT in improving visual acuity in individuals with late or advanced AMD. Since the IMT is typically implanted monocularly based upon which eye has better best-corrected distance visual acuity, randomization between eyes within an individual may not be acceptable. Studies are needed that compare outcomes between individuals randomized to the device versus individuals not implanted, at least during study follow-up, who serve as controls.

PMID: 29847689 DOI: 10.1002/14651858.CD011140.pub2


Correlations between internal and external ocular factors and macular pigment optical density.

Tudosescu R, Alexandrescu CM, Istrate SL, Vrapciu AD, Ciuluvică RC, Voinea L.

Aim: To assess the relationship between the macular pigment optical density and blue-light issued by computers, glare sensitivity, with iris color, age, sex, or refractive errors.

Material and methods: 83 patients (166 eyes) were enrolled in a prospective observational study. They were divided into 2 groups: group 1 (study group) - computer using patients (time spent in front of the computer for minimum 8 hours per day, 5 days per week, 2 years) - 43 patients and group 2 (control group) - 40 patients. The following investigations were conducted in all the selected cases: visual acuity, refraction, biomicroscopy, measurement of the MPOD, glare sensitivity, assessment of eye color.

Results: 51.81% of the patients were included in group 1, while the rest, 48.19%, were in group 2. Thus, the MPOD had a mean value of (+/-SD) 0.42+/ -0.13 (t = -1.08, p = 0.28) in group 1, and 0.44+/- -0.16 on the LE. The results showed a MPOD mean value of 0.51+/ -0.16 in group 2 and 0.51+/ -0.16. (t = 0.49, p = 0.62) on the LE. 55.77% of the patients with light colored iris and 56.14% of those with dark iris had a low
MPOD.

Conclusions: The data from our study failed to illustrate a significant correlation between MPOD and blue-light issued by computers. Furthermore, a statistic significant relationship regarding iris color, refractive errors, glare, and MPOD was not observed.

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**Genetics and gene therapy**


**Gene therapy and genome surgery in the retina.**

DiCarlo JE, Mahajan VB, Tsang SH.

**Abstract:** Precision medicine seeks to treat disease with molecular specificity. Advances in genome sequence analysis, gene delivery, and genome surgery have allowed clinician-scientists to treat genetic conditions at the level of their pathology. As a result, progress in treating retinal disease using genetic tools has advanced tremendously over the past several decades. Breakthroughs in gene delivery vectors, both viral and nonviral, have allowed the delivery of genetic payloads in preclinical models of retinal disorders and have paved the way for numerous successful clinical trials. Moreover, the adaptation of CRISPR-Cas systems for genome engineering have enabled the correction of both recessive and dominant pathogenic alleles, expanding the disease-modifying power of gene therapies. Here, we highlight the translational progress of gene therapy and genome editing of several retinal disorders, including RPE65-, CEP290-, and GY2D-associated Leber congenital amaurosis, as well as choroideremia, achromatopsia, Mer tyrosine kinase- (MERTK-) and RPGR X-linked retinitis pigmentosa, Usher syndrome, neovascular age-related macular degeneration, X-linked retinoschisis, Stargardt disease, and Leber hereditary optic neuropathy.

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**Association of Genetic Variants with Response to Anti-Vascular Endothelial Growth Factor Therapy in Age-Related Macular Degeneration.**

Lorés-Motta L, Riaz M, Grunin M et al.

**Importance:** Visual acuity (VA) outcomes differ considerably among patients with neovascular age-related macular degeneration (nAMD) treated with anti-vascular endothelial growth factor (VEGF) drugs. Identification of pharmacogenetic associations may help clinicians understand the mechanisms underlying this variability as well as pave the way for personalized treatment in nAMD.

**Objective:** To identify genetic factors associated with variability in the response to anti-VEGF therapy for patients with nAMD.

**Design, Setting, and Participants:** In this multicenter genome-wide association study, 678 patients with nAMD with genome-wide genotyping data were included in the discovery phase; 1380 additional patients with nAMD were genotyped for selected common variants in the replication phase. All participants received 3 monthly injections of bevacizumab or ranibizumab. Clinical data were evaluated for inclusion/exclusion criteria from October 2014 to October 2015, followed by data analysis from October 2015 to February 2016. For replication cohort genotyping, clinical data collection and analysis (including meta-analysis) was performed from March 2016 to April 2017.

**Main Outcomes and Measures:** Change in VA after the loading dose of 3 monthly anti-VEGF injections
compared with baseline.

**Results:** Of the 2058 included patients, 1210 (58.8%) were women, and the mean (SD) age across all cohorts was 78 (7.4) years. Patients included in the discovery cohort and most of the patients in the replication cohorts were of European descent. The mean (SD) baseline VA was 51.3 (20.3) Early Treatment Diabetic Retinopathy Study (ETDRS) score letters, and the mean (SD) change in VA after the loading dose of 3 monthly injections was a gain of 5.1 (13.9) ETDRS score letters (ie, 1-line gain). Genome-wide single-variant analyses of common variants revealed 5 independent loci that reached a P value less than $10 \times 10^{-5}$. After replication and meta-analysis of the lead variants, rs12138564 located in the CCT3 gene remained nominally associated with a better treatment outcome (ETDRS letter gain, 1.7; $\beta$, 0.034; SE, 0.008; $P = 1.38 \times 10^{-5}$). Genome-wide gene-based optimal unified sequence kernel association test of rare variants showed genome-wide significant associations for the C10orf88 ($P = 4.22 \times 10^{-7}$) and UNC93B1 ($P = 6.09 \times 10^{-7}$) genes, in both cases leading to a worse treatment outcome. Patients carrying rare variants in the C10orf88 and UNC93B1 genes lost a mean (SD) VA of 30.6 (17.4) ETDRS score letters (ie, loss of 6.09 lines) and 26.5 (13.8) ETDRS score letters (ie, loss of 5.29 lines), respectively, after 3 months of anti-VEGF treatment.

**Conclusions and Relevance:** We propose that there is a limited contribution of common genetic variants to variability in nAMD treatment response. Our results suggest that rare protein-altering variants in the C10orf88 and UNC93B1 genes are associated with a worse response to anti-VEGF therapy in patients with nAMD, but these results require further validation in other cohorts.


The role of apolipoprotein E (rs7412 and rs429358) in age-related macular degeneration.


**Background:** Age-related macular degeneration (AMD) is the most common cause of incurable visual impairment in the developed countries. The main pathological change in AMD is the formation of drusen containing 40% of lipids, dominated by esterified cholesterol (EC) and phosphatidylcholine (PC), and protein. Haplotype $\varepsilon 4$ of apolipoprotein E (ApoE) acts as a ligand for the low-density lipoprotein receptor and is involved in the maintenance and repair of neuronal cell membranes.

**Purpose:** This study aimed to evaluate the association of AMD with ApoE gene polymorphism variants (rs7412 and rs429358).

**Methodology:** A total of 2133 subjects were enrolled in our research. The study group comprised patients with early AMD ($n = 413$) and exudative AMD ($n = 307$), and the control group enrolled randomly selected persons ($n = 1413$). The genotyping of ApoE (rs7412 and rs429358) was performed using the real-time polymerase chain reaction (PCR) method.

**Results:** Statistical analysis revealed that ApoE 4/2 genotype was less frequently observed in in older patients with exudative AMD compared to older healthy controls (0.4% vs. 4.0%, $p = 0.003$).

**Conclusion:** Our data demonstrated that ApoE 4/2 genotype was less frequently observed in old patients (65 years and more) with exudative AMD compared to old healthy controls. It leads to hypothesis on the protective effect of ApoE 4/2 to develop AMD in the elderly.

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Extremely hypomorphic and severe deep intronic variants in the ABCA4 locus result in varying Stargardt disease phenotypes.


Abstract: Autosomal recessive Stargardt disease (STGD1, MIM 248200) is caused by mutations in the ABCA4 gene. Complete sequencing of the ABCA4 locus in STGD1 patients identifies two expected disease-causing alleles in ~75% of patients and only one mutation in ~15% of patients. Recently, many possibly pathogenic variants in deep intronic sequences of ABCA4 have been identified in the latter group. We extended our analyses of deep intronic ABCA4 variants and determined that one of these, c.4253+43G>A (rs61754045), is present in 29/1155 (2.6%) of STGD1 patients. The variant is found at statistically significantly higher frequency in patients with only one pathogenic ABCA4 allele, 23/160 (14.38%), MAF=0.072, compared to MAF=0.013 in all STGD1 cases and MAF=0.006 in the matching general population (P<1x10-7). The variant, which is not predicted to have any effect on splicing, is the first reported intronic "extremely hypomorphic allele" in the ABCA4 locus; i.e., it is pathogenic only when in trans with a loss-of-function ABCA4 allele. It results in a distinct clinical phenotype characterized by late-onset of symptoms and foveal sparing. In ~70% of cases the variant was allelic with the c.6006-609T>A (rs575968112) variant, which was deemed non-pathogenic. Another rare deep intronic variant, c.5196+1056A>G (rs886044749), found in 5/834 (0.6%) of STGD1 cases is, conversely, a severe allele. This study determines pathogenicity for three non-coding variants in STGD1 patients of European descent accounting for ~3% of the disease. Defining disease-associated alleles in the non-coding sequences of the ABCA4 locus can be accomplished by integrated clinical and genetic analyses.

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Characterization of Rod Function Phenotypes Across a Range of Age-Related Macular Degeneration Severities and Subretinal Drusenoid Deposits.

Flynn OJ, Cukras CA, Jeffrey BG.

Purpose: To examine spatial changes in rod-mediated function in relationship to local structural changes across the central retina in eyes with a spectrum of age-related macular degeneration (AMD) disease severity.

Methods: Participants were categorized into five AMD severity groups based on fundus features. Scotopic thresholds were measured at 14 loci spanning ±18° along the vertical meridian from one eye of each of 42 participants (mean = 71.7 ± 9.9 years). Following a 30% bleach, dark adaptation was measured at eight loci (±12°). Rod intercept time (RIT) was defined from the time to detect a -3.1 log cd/m2 stimulus. RITslope was defined from the linear fit of RIT with decreasing retinal eccentricity. The presence of subretinal drusenoid deposits (SDD), ellipsoid (EZ) band disruption, and drusen at the test loci was evaluated using optical coherence tomography.

Results: Scotopic thresholds indicated greater rod function loss in the macula, which correlated with increasing AMD group severity. RITslope, which captures the spatial change in the rate of dark adaptation, increased with AMD severity (P < 0.0001). Three rod function phenotypes emerged: RF1, normal rod function; RF2, normal scotopic thresholds but slowed dark adaptation; and RF3, elevated scotopic thresholds with slowed dark adaptation. Dark adaptation was slowed at all loci with SDD or EZ band disruption, and at 32% of loci with no local structural changes.

Conclusions: Three rod function phenotypes were defined from combined measurement of scotopic threshold and dark adaptation. Spatial changes in dark adaptation across the macula were captured with
RITslope, which may be a useful outcome measure for functional studies of AMD.

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Correlating the Expression and Functional Activity of ABCA4 Disease Variants with the Phenotype of Patients with Stargardt Disease.


Purpose: Stargardt disease (STGD1), the most common early-onset recessive macular degeneration, is caused by mutations in the gene encoding the ATP-binding cassette transporter ABCA4. Although extensive genetic studies have identified more than 1000 mutations that cause STGD1 and related ABCA4-associated diseases, few studies have investigated the extent to which mutations affect the biochemical properties of ABCA4. The purpose of this study was to correlate the expression and functional activities of missense mutations in ABCA4 identified in a cohort of Canadian patients with their clinical phenotype.

Methods: Eleven patients from British Columbia were diagnosed with STGD1. The exons and exon-intron boundaries were sequenced to identify potential pathologic mutations in ABCA4. Missense mutations were expressed in HEK293T cells and their level of expression, retinoid substrate binding properties, and ATPase activities were measured and correlated with the phenotype of the STGD1 patients.

Results: Of the 11 STGD1 patients analyzed, 7 patients had two mutations in ABCA4, 3 patients had one detected mutation, and 1 patient had no mutations in the exons and flanking regions. Included in this cohort of patients was a severely affected 11-year-old child who was homozygous for the novel p.Ala1794Pro mutation. Expression and functional analysis of this variant and other disease-associated variants compared favorably with the phenotypes of this cohort of STGD1 patients.

Conclusions: Although many factors contribute to the phenotype of STGD1 patients, the expression and residual activity of ABCA4 mutants play a major role in determining the disease severity of STGD1 patients.

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CFH and VIPR2 as susceptibility loci in choroidal thickness and pachychoroid disease central serous chorioretinopathy.

Hosoda Y, Yoshikawa M, Miyake et al.

Abstract: Central serous chorioretinopathy (CSC) is a common disease affecting younger people and may lead to vision loss. CSC shares phenotypic overlap with age-related macular degeneration (AMD). As recent studies have revealed a characteristic increase of choroidal thickness in CSC, we conducted a genome-wide association study on choroidal thickness in 3,418 individuals followed by TaqMan assays in 2,692 subjects, and we identified two susceptibility loci: CFH rs800292, an established AMD susceptibility polymorphism, and VIPR2 rs3793217 (P = 2.05 × 10-10 and 6.75 × 10-8, respectively). Case-control studies using patients with CSC confirmed associations between both polymorphisms and CSC (P = 5.27 × 10-5 and 5.14 × 10-5, respectively). The CFH rs800292 G allele is reportedly a risk allele for AMD, whereas the A allele conferred risk for thicker choroid and CSC development. This study not only shows that susceptibility genes for CSC could be discovered using choroidal thickness as a defining variable but also, deepens the understanding of differences between CSC and AMD pathophysiology.

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Association of Single-Nucleotide Polymorphisms in Age-Related Macular Degeneration with Pseudodrusen: Secondary Analysis of Data From the Comparison of AMD Treatments Trials.

Lin LY, Zhou Q, Hagstrom S, Maguire MG, Daniel E, Grunwald JE, Martin DF, Ying GS; CATT Research Group.

Importance: Previous studies investigating the association of single-nucleotide polymorphisms (SNPs) that confer increased risk of age-related macular degeneration (AMD) with pseudodrusen have yielded conflicting results and have not evaluated other AMD SNPs or pseudodrusen subtypes.

Objective: To determine the association of SNPs in the complement factor H (CFH), age-related maculopathy susceptibility 2 (ARMS2), HtrA serine peptidase 1 (HTRA1), complement C2 (C2), complement C3 (C3), lipase C (LIPC), and complement factor B (CFB) genes with the presence of pseudodrusen and pseudodrusen subtypes (ie, dot, reticular, and confluent).

Design, Setting, and Participants: In this post hoc analysis of cross-sectional data from US participants in the Comparison of AMD Treatments Trials, genotyping was performed in 835 participants with TaqMan assays for the SNPs rs1061170 (Y402H variant in CFH), rs800292 (I62V variant in CFH), rs10490924 (A69S variant in ARMS2), rs11200638 (HTRA1), rs547154 (C2), rs2230199 (R102G variant in C3), rs10468017 (LIPC), and rs4151667 (L9H variant in CFB).

Main Outcomes and Measures: Presence and subtype of baseline pseudodrusen in either eye determined using color fundus photography, red-free images, and fluorescein angiograms.

Results: Among 835 participants enrolled for genotyping, 755 (90.4%) were evaluated for pseudodrusen. Of these, 471 (62.4%) were female and 750 (99.3%) were white, and the mean (SD) age was 78.3 (7.5) years. A total of 213 of 755 participants (28.2%) had pseudodrusen (107 [14.2%] had dot pseudodrusen, 180 [23.8%] had reticular pseudodrusen, and 102 [13.5%] had confluent pseudodrusen). After adjusting for age, sex, and smoking status, the ARMS2 risk allele T was associated with higher risk of pseudodrusen (odds ratio [OR], 1.93; 95% CI, 1.19-3.12) for TT vs GG (P = .04). A similar association was found for HTRA1 (OR, 2.04; 95% CI, 1.26-3.31) for AA vs GG (P = .03). The CFH Y402H risk allele C was associated with lower risk of pseudodrusen (OR, 0.61; 95% CI, 0.38-0.97) for CC vs TT but was not statistically significant after correcting for multiple comparison (P = .20). CFH Y402H, ARMS2, HTRA1, and C3 were significantly associated with reticular pseudodrusen.

Conclusions and Relevance: Among patients with neovascular AMD, the AMD risk alleles ARMS2 and HTRA1 were associated with an increased risk of pseudodrusen and the risk allele CFH Y402H was associated with lower risk of pseudodrusen, supporting findings from previous studies. Understanding the role of these SNPs in the development of pseudodrusen might improve our understanding of the pathogenesis of AMD and help develop future therapies.

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Stem cells


Smart Liposomal Drug Delivery for Treatment of Oxidative Stress Model in Human Embryonic Stem Cell-derived Retinal Pigment Epithelial Cells.

Behroozi F, Abdkhodaie MJ, Abandansari HS, Satarian L, Ashtiani MK, Jaafari MR, Baharvand H.

Abstract: Oxidative stress has been implicated in the progression of age-related macular degeneration (AMD). Treatment with antioxidants seems to delay progression of AMD. In this study, we suggested an antioxidant delivery system based on redox-sensitive liposome composed of phospholipids and a
diselenide centered alkyl chain. Dynamic light scattering assessment indicated that the liposomes had an average size of 140 nm with a polydispersity index below 0.2. The percentage of encapsulation efficiency of the liposomes was calculated by high-performance liquid chromatography. The carriers were loaded with N-acetyl cysteine as a model antioxidant drug. We demonstrated responsiveness of the nanocarrier and its efficiency in drug delivery in an oxidative stress model of human embryonic stem cell-derived retinal pigment epithelial (hESC-RPE) cells. The modeled cells treated with diselenide containing liposomes loaded with 10 mM NAC, showed a better therapeutic effect with a cell metabolic activity of 90%, which was significantly higher compared to insensitive liposomes or NAC treated groups (P<0.05). In addition, the expression of oxidative-sensitive gene markers in diselenide containing liposomes groups were improved. Our results demonstrated fabricated smart liposomes opens new opportunity for targeted treatment of retinal degeneration.

PMID: 29802900 DOI: 10.1016/j.ijpharm.2018.05.056

Diet, lifestyle and low vision


The Eye, Oxidative Damage and Polyunsaturated Fatty Acids.

Saccà SC, Cutolo CA, Ferrari D, Corazza P, Traverso CE.

Abstract: Polyunsaturated fatty acids (PUFA) are known to have numerous beneficial effects, owing to their anti-inflammatory and antioxidant properties. From a metabolic standpoint, the mitochondria play a fundamental role in cellular homeostasis, and oxidative stress can affect their functioning. Indeed, the mitochondria are the main source of ROS, and an imbalance between ROS and antioxidant defenses leads to oxidative stress. In addition, aging, the decline of cellular functions, and continual exposure to light underlie many diseases, particularly those of the eye. Long-term exposure to insults, such as UV light, visible light, ionizing radiation, chemotherapeutics, and environmental toxins, contribute to oxidative damage in ocular tissues and expose the aging eye to considerable risk of pathological consequences of oxidative stress. Ample antioxidant defenses responsible for scavenging free radicals are essential for redox homeostasis in the eye, indeed, eye tissues, starting from the tear film, which normally are exposed to high oxygen levels, have strong antioxidant defenses that are efficient for protecting against ROS-related injuries. On the contrary, instead, the trabecular meshwork is not directly exposed to light and its endothelial cells are poorly equipped with antioxidant defenses. All this makes the eye a target organ of oxidative damage. This review focuses on the role of the polyunsaturated fatty acids in the human eye, particularly in such pathologies as dry eye, glaucoma, and macular degeneration, in which dietary PUFA supplementation can be a valid therapeutic aid.

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Case Reports


Therapeutic Effect of Anti-VEGF for Age-Related Macular Degeneration in the Untreated Fellow Eye.

Isildak H, Schwartz SG, Flynn HW Jr.

Abstract: Intravitreal injections of antivascular endothelial growth factor (anti-VEGF) agents have been reported to occasionally produce a therapeutic effect in the uninjected fellow eye. Here, three patients with bilateral neovascular age-related macular degeneration are presented. In all three patients, unilateral anti-VEGF injection resulted in bilateral reduction of macular thickness as measured by spectral domain optical coherence tomography.
Genetic Background of a Recurrent Unusual Combined Form of Retinal Vein Occlusion: A Case Report.

Bucan K, Plestina Borjan I, Bucan I, Paradzik Simunovic M, Borjan I.

Abstract: The authors report a rare case of nonischemic branch retinal vein occlusion and nonischemic hemiretinal vein occlusion in a patient with impaired fibrinolysis. A 61-year-old woman presented to the Department of Ophthalmology, Clinical Hospital Center Split, Croatia, with acute blurring of vision in the right eye (RE) due to branch retinal vein occlusion. Ophthalmologic evaluation revealed a best corrected visual acuity (BCVA) of 0.02 in the RE and of 1.0 in the left eye. Ophthalmoscopy and fluorescein angiography of the RE demonstrated signs of nonischemic branch retinal vein occlusion. She was otherwise healthy and had no other ocular and systemic diseases. She was treated with 3 consecutive intravitreal applications of anti-vascular endothelial growth factor (anti-VEGF; bevacizumab) due to cystoid macular edema with full resolution of the intraretinal fluid and improvement of the BCVA to 0.9. After 8 months, she presented again with acute blurring of vision in the same (right) eye with a BCVA of 0.5. Ophthalmoscopy and fluorescein angiography of the RE indicated nonischemic hemiretinal vein occlusion. She was treated with a single intravitreal application of anti-VEGF (ranibizumab) due to macular edema. Full resolution of the intraretinal fluid and improvement of the BCVA to 0.9 were achieved. A laboratory workup was performed to rule out all known causes of retinal venous occlusive disease, which showed negative results. A molecular analysis showed the gene of thrombophilia - plasminogen activator inhibitor (PAI)-1 4G/5G polymorphism genotype - as the only risk factor for retinal venous occlusive disease in our patient.