Drug treatment


Overview of Systematic Reviews and Meta-analyses on Systemic Adverse Events Associated With Intravitreal Anti-Vascular Endothelial Growth Factor Medication Use.

Thulliez M, Angoulvant D, Pisella PJ, Bejan-Angoulvant T.

IMPORTANCE: The systemic safety of intravitreal anti-vascular endothelial growth factor (anti-VEGF) medications is still a matter of debate.

OBJECTIVE: This overview of systematic reviews evaluates systemic adverse events associated with intravitreal anti-VEGF treatments in patients with neovascular age-related macular degeneration, diabetic macular edema, or retinal vein occlusion.

DESIGN, EVIDENCE, AND REPORTING: This systematic search of PubMed and the Cochrane Central Register of Controlled Trials database includes meta-analyses and systematic reviews. We describe the summary measures of association between anti-VEGF treatments and outcomes reported in each systematic review.

MAIN OUTCOMES AND MEASURES: The quality of the systematic reviews was assessed with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and A Measurement Tool to Assess Systematic Reviews (AMSTAR) checklist, version 1.

FINDINGS: We retrieved 21 systematic reviews published between January 1, 2011, and June 30, 2016. Of these, 11 analyzed systemic adverse events as the primary outcome. The median (interquartile range) PRISMA and AMSTAR scores were 23 of 27 (15-27) and 8 of 11 (5-11), respectively, but 5 reviews (25%) scored below 20 and 7, respectively. All reviews used an objective scale to assess methodological risk of bias in their included studies, the Cochrane Risk of Bias Tool being the most commonly used (16 reviews [76%]). Anti-VEGF treatments did not increase the risk of systemic adverse events when compared with control regimens; similarly, there was no increase in systematic adverse events when treatment was given on a monthly schedule vs an as-needed regimen. Compared with ranibizumab, bevacizumab did not appear to be associated with an increase in the risk of systemic adverse events in the most recent and exhaustive reviews. Compared with control treatments, ranibizumab may be associated with an increase in the risk of nonocular hemorrhage in patients with age-related macular degeneration.

CONCLUSIONS AND RELEVANCE: This overview of reviews and meta-analyses suggest that anti-VEGF treatments do not increase the risk of systemic adverse events, but that caution might be advisable in older patients with age-related macular degeneration who may be at higher risk of hemorrhagic events when receiving ranibizumab.

PMID: 29566105 DOI: 10.1001/jamaophthalmol.2018.0002
Age, sex, and type of medication predict the effect of anti-VEGF treatment on central retinal thickness in wet age-related macular degeneration.

Bek T, Klug SE.

PURPOSE: Randomized clinical trials studying the effects of VEGF inhibition on wet age-related macular degeneration (wAMD) are designed so that the effects of individually varying risk factors on the treatment response are eliminated. The influence of these risk factors can be studied in large data sets from real-life experience.

PATIENTS AND METHODS: All 2,255 patients diagnosed with wAMD requiring anti-VEGF treatment in at least one eye over more than 9 years in a defined Danish population with 0.9 million inhabitants were studied. The predictive value of eye laterality, sex, current smoking status, type of anti-VEGF compound, membrane position, membrane type, leakage area, number of injections, number of visits, age, time to follow-up, visual acuity, and central retinal thickness (CRT) at baseline on change in CRT after three monthly injections with anti-VEGF compound followed by treatment pro re nata for up to 12 months was assessed.

RESULTS: After 12 months, 67 patients had died, 903 had had stable CRT for at least 6 months, and 1,285 patients had not achieved stable CRT. The reduction in CRT was \(-84.8 \pm 118.3 \mu m\), whereas the increase in visual acuity was \(2.2 \pm 14.7\) Early Treatment Diabetic Retinopathy Study letters. The risk factors included contributed to 64% of the variation in CRT reduction. High age and high CRT at baseline predicted high CRT reduction, whereas more injections, treatment with ranibizumab, and male sex predicted a low CRT reduction.

CONCLUSION: Age, sex, and type of anti-VEGF medication can be used to plan treatment and inform patients about the expected response of anti-VEGF treatment in wAMD.

PMID: 29563771 PMCID: PMC5848666 DOI: 10.2147/OPTH.S158760


Systemic safety following intravitreal injections of anti-VEGF [Article in French]

Bailiff S, Levy B, Girmens JF, Dumas S, Tadayoni R.

Abstract: The goal of this manuscript is to assess data suggesting that intravitreal injection of anti-vascular endothelial growth factors (anti-VEGFs) could result in systemic adverse events (AEs). The class-specific systemic AEs should be similar to those encountered in cancer trials. The most frequent AE observed in oncology, hypertension and proteinuria, should thus be the most common expected in ophthalmology, but their severity should be lower because of the much lower doses of anti-VEGFs administered intravitreally. Such AEs have not been frequently reported in ophthalmology trials. In addition, pharmacokinetic and pharmacodynamic data describing systemic diffusion of anti-VEGFs should be interpreted with caution because of significant inconsistencies reported. Thus, safety data reported in ophthalmology trials and pharmacokinetic/pharmacodynamic data provide robust evidence that systemic events after intravitreal injection are very unlikely. Additional studies are needed to explore this issue further, as much remains to be understood about local and systemic side effects of anti-VEGFs.

PMID: 29567019 DOI: 10.1016/j.jfo.2017.11.006

36-Month Evaluation of Intravitreous Aflibercept Injection for Wet Age-Related Macular Degeneration in Patients Previously Treated With Ranibizumab or Bevacizumab.

Conti FF, Silva FQ, Srivastava SK, Ehlers JP, Schachat AP, Singh RP.

BACKGROUND AND OBJECTIVE: In the ASSESS study, patients with neovascular age-related macular degeneration transitioned from other anti-vascular endothelial growth factor therapies to intravitreous aflibercept (Eylea; Regeneron, Tarrytown, NY) injections (IAI). The purpose was to determine the 36-month outcomes following the change from a fixed 24-month IAI dosing regimen to a routine clinical practice regimen.

PATIENTS AND METHODS: Patients were treated with a fixed bimonthly regimen for the first 2 years. In the third year, patients were managed according to routine clinical practice.

RESULTS: A total of 18 patients completed the 36 months and were considered for statistical analyses. At 36 months, a nonsignificant decrease of -37.8 μm in central subfield thickness and a nonsignificant gain of 5.8 letters from baseline were observed.

CONCLUSION: Despite the significant visual and anatomical gains observed in the 2 years of fixed-dosing IAI, there was gradual decline in these improvements when patients were transitioned to a variable regimen.

PMID: 29554385 DOI: 10.3928/23258160-20180221-05


Switching Anti-Vascular Endothelial Growth Factors in Refractory Neovascular Age-Related Macular Degeneration.

Ashraf M, Banaee T, Silva FQ, Singh RP.

BACKGROUND AND OBJECTIVE: Anti-vascular endothelial growth factor (VEGF) therapy is the treatment of choice for cases with neovascular age-related macular degeneration (AMD). Switching to an alternate anti-VEGF has been suggested as a possible option for resistant cases. The purpose of this review is to evaluate whether the timing of switching affects treatment outcomes.

PATIENTS AND METHODS: A review of published literature was performed looking at all studies where patients with refractory neovascular AMD were switched to an alternative anti-VEGF. Studies were then stratified based on the timing of switching into early (< 12 previous injections) and late (> 12 previous injections).

RESULTS: A total of 38 studies were identified: 18 where patients were switched early and 20 where they were switched late. Both subgroups showed anatomic improvement after switching, with limited visual gains.

CONCLUSION: There are insufficient data to recommend early versus late switching. However, both groups showed a reduction of fluid on optical coherence tomography and visual gains in 25% to 30% of patients.

PMID: 29554383 DOI: 10.3928/23258160-20180221-03
INTRAVITREAL INJECTIONS OF ZIV-AFLIBERCEPT FOR THE TREATMENT OF A PATIENT WITH MACULAR EDEMA SECONDARY TO BRANCH RETINAL VEIN OCCLUSION.

Andrade GC, Dias JRO, Maia A, Farah ME, Mitne S, Rodrigues EB.

PURPOSE: To describe the visual, tomographic, and electoretinographic findings in a patient with macular edema secondary to branch retinal vein occlusion who was submitted to three consecutive intravitreal injections of ziv-aflibercept.

METHODS: The patient underwent a complete ophthalmic examination, as well as optical coherence tomography and full-field electoretinography at baseline and 90 days after the first injection.

RESULTS: The best-corrected visual acuity improved from 20/400 to 20/40, and the central retinal thickness decreased from 791 μm to 198 μm after three consecutive intravitreal injections of ziv-aflibercept. Full-field electoretinography showed an increase in cone amplitude and decrease in rod amplitude. No adverse side effects were observed after injections.

CONCLUSION: Intravitreal injections of ziv-aflibercept showed both effectiveness and safety in the treatment of a patient with macular edema secondary to branch retinal vein occlusion. The observed anatomic (by ophthalmic examination, optical coherence tomography) and functional (best-corrected visual acuity, full-field electoretinography) improvements and lack of serious adverse side effects demonstrates the potential of intravitreal injections of ziv-aflibercept for the treatment of macular edema secondary to branch retinal vein occlusion.

PMID: 29554051 DOI: 10.1097/ICB.0000000000000449

Int Ophthalmol. 2018 Mar 17. [Epub ahead of print]

THE SHORT-TERM EFFICACY OF INTRAVITREAL RANIBIZUMAB, AFLIBERCEPT AND DEXAMETHASONE IMPLANT IN THE TREATMENT OF MACULAR EDEMA DUE TO NON-ISCHEMIC CENTRAL RETINAL VEIN OCCLUSION.

Yucel OE, Birinci H, Sullu Y.

PURPOSE: To assess and compare the efficacy over 6 months of intravitreal ranibizumab (IR), aflibercept (IA) and dexamethasone implant (IDI) in eyes with macular edema (ME) secondary to non-ischemic central retinal vein occlusion (CRVO).

METHODS: This is a retrospective single-center study. Patients who received pro re nata treatment of IR 0.5 mg, IA 2 mg or IDI 0.7 mg (as Group 1, Group 2, and Group 3, respectively) for the treatment of ME due to non-ischemic CRVO were included in the study. Efficacy outcomes were considered as the changes in mean best-corrected visual acuity (BCVA) and central macular thickness (CMT) from baseline over 6 months.

RESULTS: Eighteen patients (Group 1) received IR, 16 patients received (Group 2) IA, and 24 patients (Group 3) received IDI. The mean numbers of injections were 2.56 ± 1.0, 2.68 ± 0.9, and 1.62 ± 0.5 in Group 1, 2, and 3, respectively (p = 0.000). In Groups 1 and 2, the mean BCVA values increased significantly after the treatment (p < 0.001). However, in Group 3, no increase in mean BCVA was statistically significant in any month (p = 0.061). The proportion of eyes gaining at least three lines in BCVA was 33.3% in Group 1, 43.8% in Group 2, and 33.3% in Group 3 (p = 0.762). In all groups, significant improvements were observed in CMT after treatment (p < 0.001). At month 6, the mean changes in CMT were -162.7 ± 186.5 μm in Group 1, -310.1 ± 345.9 μm in Group 2, and -193.8 ± 228.3 μm in Group 3, with no significant difference among groups (p = 0.474). Cataract formation and IOP increase were higher in the IDI group, but the differences were not statistically significant (p = 0.054 and p = 0.392, respectively).

CONCLUSIONS: IR and IA may be preferred treatment for ME due to non-ischemic CRVO as visual
improvement remains the primary ophthalmological objective. The most important advantages of IDI are its effect on CMT and the need for fewer injections. The increase in IOP and the formation of cataract may be observed more in IDI-treated eyes.

PMID: 29550932 DOI: 10.1007/s10792-018-0890-6

**Ophthalmic Res. 2018 Mar 22. [Epub ahead of print]**

**Spectral-Domain Optical Coherence Tomography-Driven Treat-and-Extend and Pro Re Nata Regimen in Patients with Macular Oedema due to Retinal Vein Occlusion: 24-Month Evaluation and Outcome Predictors.**

Guichard MM, Xavier AR, Türksever C, Pruente C, Hatz K.

***PURPOSE:*** To analyse the efficacy and outcome predictors of ranibizumab using a spectral-domain optical coherence tomography (SD-OCT)-driven treat-and-extend regimen (TER) versus SD-OCT-driven pro re nata regimen (PRN) in patients with cystoid macular oedema (CME) due to branch or central retinal vein occlusion (BRVO, CRVO).

***METHODS:*** Retrospective, consecutive case series. Evaluation included best corrected visual acuity (BCVA), morphological parameters on SD-OCT, and treatment frequency.

***RESULTS:*** From baseline to months 12, 18, and 24, BCVA improved by 16.6 ± 13.1, 15.5 ± 14.4, and 16.6 ± 15.8 letters, respectively, in TER (n = 45), compared to 11.3 ± 17.0, 11.0 ± 15.0, and 10 ± 20.5 letters in PRN (n = 31) (p = 0.152, p = 0.237, p = 0.172). The mean reduction in central retinal thickness was -261 ± 189, -272 ± 188, and -264 ± 158 μm, respectively, in TER, compared to -130 ± 196, -140 ± 210, and -166 ± 207 μm in PRN (p = 0.006, p = 0.017, p = 0.064). 59% (53%) of TER and 22% (17%) of PRN patients showed no intra- or subretinal fluid on SD-OCT at 12 (24) months. Using TER, the maximum recurrence-free treatment interval increased from 8.9 ± 2.3 weeks at 12 months to 9.8 ± 2.3 and 10.5 ± 2.7 weeks at 18 and 24 months, respectively. The number of injections was significantly higher in the TER than in the PRN group.

***CONCLUSIONS:*** In CME, due to BRVO/CRVO, TER provides better morphological outcome using more injections than PRN.

PMID: 29566387 DOI: 10.1159/000487489


**Cost Evaluation of Laser versus Intravitreal Aflibercept for Proliferative Diabetic Retinopathy.**

Yannuzzi NA, Sridhar J, Chang JS, Lin J, Kuriyan AE, Smiddy WE.

PMID: 29571831 DOI: 10.1016/j.ophtha.2018.02.019


**Preexisting epiretinal membrane is associated with pseudophakic cystoid macular edema.**


***PURPOSE:*** The purpose of the present study was to evaluate whether preexisting epiretinal membrane (ERM) is a significant risk factor for developing pseudophakic cystoid macular edema (PCME).

***METHODS:*** Two hundred four consecutive eyes and 153 consecutive eyes without preexisting epiretinal
membranes were retrospectively compared regarding PCME development following phacoemulsification with posterior chamber lens implantation. Patients with vascular retinal diseases, uveitis, trauma, neovascular macular degeneration, chronic inflammatory conditions, diabetic retinopathy, endophthalmitis, eventful cataract surgery, and combination of cataract surgery and vitrectomy during the observation period were excluded. Macular examination was performed using spectral-domain optical coherence tomography (SD-OCT) before as well as at 4, 8, 12, 16, 24, and 36 weeks after cataract surgery. Univariate and multivariate logistic regression analyses were calculated.

RESULTS: PCME occurred in 32 of 204 eyes with preexisting ERM (15.7%), whereas 9 of 153 eyes without preexisting ERM (5.9%) developed PCME. The risk of PCME was significantly increased in eyes with ERM ($p = 0.007$). By multivariate logistic regression analysis, factors predictive of PCME included the history of previous pars plana vitrectomy for retinal detachment (odds ratio (OR) 3.619 [95% confidence interval (CI) 1.242 to 10.258]; $p = 0.016$) as well as the preexistence of ERM (OR 3.885 [95% CI 1.162 to 17.762]; $p = 0.04$).

CONCLUSION: Preexisting ERM seems to be associated with an increased risk of PCME following cataract surgery. Therefore, this risk should be considered in surgery planning, preoperative medication, and follow-up care after surgery.

PMID: 29564551 DOI: 10.1007/s00417-018-3954-4


The efficacy of conbercept or ranibizumab intravitreal injection combined with laser therapy for Coats' disease.

Zhang L, Ke Y, Wang W, Shi X, Hei K, Li X.

PURPOSE: The current treatment approaches for Coats' disease by intravitreal injection of anti-vascular endothelial growth factor (VEGF) agents (ranibizumab or conbercept) combined with laser therapy were evaluated for the efficacy during the treatment.

METHODS: The medical records of 28 patients diagnosed with Coats' disease followed by the treatment with intravitreal injection of anti-VEGF agents and laser therapies at Tianjin Medical University Eye Hospital and Hebei Eye Hospital during July 2012 and October 2017 were reviewed retrospectively. Clinical outcomes were recorded with a minimum follow-up of 6 months. The patients were divided into ranibizumab - and conbercept-treated groups, as well as based on age: pediatric and adult groups.

RESULT: Twenty-eight patients were involved in this study. The average number of the injections was 2.82 ± 0.98. Laser photoagulation was conducted in all patients, and the average number of lasers was 2.63 ± 0.74. The average follow-up period was 24.29 ± 9.85 months. Fourteen patients (50%) were stable, 12 (43%) patients were improved, and 2 patients (7%) showed recurred subretinal fluid and exudation. The final best corrected visual acuity (BCVA) increased markedly after intravitreal injection of ranibizumab or conbercept combined with laser therapy ($p = 0.029$, $p = 0.009$, respectively). The number of injections and lasers between conbercept and ranibizumab groups did not vary significantly ($p = 0.160$, $p = 0.573$, respectively). Nine patients (60%) in the ranibizumab-treated group and five (38%) in the conbercept-treated group reached a stable phase, and five (33%) and seven (54%) patients got the vision improved after treated with ranibizumab or conbercept, respectively. In pediatric and adult groups, the initial and final BCVA differed significantly ($p = 0.03$, $p = 0.008$, respectively). However, the injection number was remarkably different ($p = 0.02$), while the laser numbers did not have any markedly difference ($p = 0.38$).

CONCLUSION: Intravitreal injection of ranibizumab or conbercept combined with laser therapy is an effective therapeutic option in Coats' disease. Moreover, the intravitreal injection of ranibizumab or conbercept had no significant adverse effects and appeared to offer visual improvement in Coats' disease.

PMID: 29549425 DOI: 10.1007/s00417-018-3949-1

The Relationship Between Nonsteroidal Anti-inflammatory Drug Use and Age-related Macular Degeneration.

Pekel G, Pekel E.

PMID: 29548554 DOI: 10.1016/j.ajo.2018.02.011


PURPOSE: To evaluate outcomes and predictive factors of visual acuity (VA) change after cataract surgery in patients being treated for neovascular age-related macular degeneration (nAMD).

DESIGN: Retrospective, matched case-control study.

METHODS: We studied eyes undergoing cataract surgery that had been tracked since they first started treatment for nAMD. These eyes were compared with a cohort of unoperated phakic eyes being treated for nAMD (three per case) matched for treatment duration before cataract surgery, baseline VA, age and length of follow-up.

RESULTS: We included 124 patients that had cataract surgery and 372 matched controls. The mean (95% CI) VA gained was 10.6 letters (7.8, 13.2; P < 0.001) 12 months following surgery; 26.0% had gained ≥ 3 lines and 1.6% had lost ≥ 3 lines of VA. Visual acuity (mean [SD]) 12 months after surgery was higher in eyes that had cataract extraction compared with controls (65.8 [17.1] vs. 61.3 [20.8] letters respectively, P = 0.018). The proportion of visits where the choroidal neovascular (CNV) lesion was graded active and the mean number of injections were similar before and after surgery (P = 0.506 and P = 0.316, respectively), while both decreased in the control group, suggesting that surgery modestly increased the level of activity of the CNV lesion. Mean [SD] VA prior to surgery was lower in eyes that gained ≥15 letters compared with eyes that gained 0-14 letters (40.2 [21.4] vs. 62.1 [15.1], P < 0.001). Patients undergoing cataract surgery within the first 6 months of anti-VEGF therapy were more likely to lose rather than gain vision (20.8% lost vision vs. 12.8% and 4.4% gaining ≥15 or 0-14 letters respectively, P = 0.023). Age, receiving an injection at least 2 weeks before surgery, and the CNV lesion type had no discernible association with VA outcomes.

CONCLUSIONS: We found evidence of a modest effect of cataract surgery on CNV lesion activity in eyes being treated for nAMD. Despite this, visual outcomes were reassuringly good. Cataract surgery within 6 months of starting treatment for nAMD should be avoided if possible.

PMID: 29550186 DOI: 10.1016/j.ajo.2018.03.012

Other treatment and diagnosis


Early OCT angiography changes of type 1 CNV in exudative AMD treated with anti-VEGF.

Pilotto E, Frizziero L, Daniele AR et al
AIMS: To investigate, with optical coherence tomography angiography (OCTA), short-term changes of type 1 choroidal neovascularisation (CNV), secondary to exudative age-related macular degeneration, after anti-vascular endothelial growth factor (VEGF) treatment.

METHODS: Patients affected by type 1 CNV treated with intravitreal anti-VEGF were consecutively enrolled. All patients underwent OCTA examination before and 48 hours after anti-VEGF treatment. Quantitative and qualitative vascular and morphological macular changes were evaluated.

RESULTS: Sixteen eyes were included (11 treated with aflibercept and 5 with ranibizumab). Both CNV mean area and pigment epithelium detachment significantly reduced (p=0.0004 and p=0.0007, respectively) after treatment. Cystoid macular oedema (four eyes) decreased in all cases. Neuretinal detachment (13 eyes) decreased in 85% of cases (11 eyes). Fine CNV vessels density decreased in 75% (12 eyes), whereas larger CNV vessels density remained stable in 66.7% (10 eyes), choroidal flow void signal (7 eyes at baseline) increased in 42.9% (3 eyes) of them and remained stable in 57.1% (4 eyes). Interoperator reproducibility for OCT examination was good for all measurements (intraclass correlation coefficient>0.65).

CONCLUSION: Early remodelling of type 1 CNV network after treatment may be non-invasively and reproducibly analysed by means of OCTA. Choroidal perfusion impairment, choroidal flow void signal, surrounding CNV may change during treatment.

PMID: 29567794 DOI: 10.1136/bjophthalmol-2017-311752


Polarization Variability in Age-related Macular Degeneration.

VanNasdale DA, Elsner AE, Malinovsky VE, Peabody TD, Kohne KD, Haggerty BP, Clark CA.

SIGNIFICANCE: Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss. Complementary imaging techniques can be used to better characterize and quantify pathological changes associated with AMD. By assessing specific light-tissue interactions, polarization-sensitive imaging can be used to detect tissue disruption early in the disease process.

PURPOSE: The aim of this study was to compare variability in central macular polarization properties in patients with nonexudative AMD and age-matched control subjects.

METHODS: A scanning laser polarimeter (GDx, LDT/CZM) was used to acquire 15 × 15-degree macular images in 10 subjects diagnosed with nonexudative AMD and 10 age-matched control subjects. The coefficient of variation (COV, SD/mean) was used to quantify variability in pixel intensity in the central 3.3° of the macula for custom images emphasizing multiply scattered light (the depolarized light image) and polarization-retaining light (the maximum of the parallel detector image). The intensity COV was compared across subject categories using paired t tests for each image type.

RESULTS: The COV in the central macula was significantly higher in the AMD subject group (average, 0.221; 95% confidence interval [CI], 0.157 to 0.265) when compared with matched control subjects (average 0.120; 95% CI, 0.107 to 0.133) in the depolarized light image (P = .01). The COV in the maximum of the parallel detector image was not statistically different between the two subject groups (AMD average, 0.162 [95% CI, 0.138 to 0.185]; control average, 0.137 [95% CI, 0.115 to 0.158]; P = .21).

CONCLUSIONS: Variability in multiply scattered light is higher than that of light that is more polarization preserving in patients with nonexudative AMD. Multiple scattering may act as an early indicator representing disruption in the macula in early AMD.

PMID: 29561503 DOI: 10.1097/OPX.0000000000001197

Local Progression Kinetics of Geographic Atrophy in Age-Related Macular Degeneration Are Associated With Atrophy Border Morphology.


PURPOSE: To assess the impact of distinct atrophy border characteristics based on spectral-domain optical coherence tomography (SD-OCT) imaging on local atrophy progression.

METHODS: Patients with geographic atrophy (GA) secondary to AMD were recruited in the context of the Longitudinal Fundus Autofluorescence in Age-related Macular Degeneration and Directional Spread in Geographic Atrophy studies (NCT00393692, NCT02051998). Horizontal and vertical SD-OCT scans were acquired at sequential visits using a device allowing for anatomically accurate registration of follow-up to baseline scans. For quantification of local atrophy progression, the lateral spread of GA (LSGA) was measured. Further, border types were independently graded. Comparison of LSGA between the different border types was performed using linear mixed-effects models.

RESULTS: Seventy-two eyes of 49 patients (27 female) aged 74.0 years (Inter quartile range [IQR], 68.1-79.0) were included into this analysis. A total of 258 border sections were analyzed longitudinally over a median period of 1.2 years (IQR, 0.9-1.6). At baseline, 17.1% borders were classified as 'regular', 47.7% as 'irregular', and 35.3% as 'splitting'. Sixty-two percent of the eyes exhibited more than one border type. LSGA was slowest in 'regular' borders (62.85 ± 25.29 μm/y), followed by 'irregular' borders (91.15 ± 15.05 μm/y) and fastest in 'splitting' borders (183.15 ± 18.17 μm/y). Differences between the 'splitting' and each other border type were statistically significant (P < 0.001).

CONCLUSIONS: The results indicate that SD-OCT-based assessment of local GA border morphology can serve as a predictor for local atrophy progression. These observations help to better understand the natural history and potential pathogenetic factors of GA development and progression.

PMID: 29558533 DOI: 10.1167/iovs.17-23203


Multimodal Imaging Patterns for Development of Central Atrophy Secondary to Age-Related Macular Degeneration.

Thiele S, Pfau M, Larsen PP, Fleckenstein M, Holz FG, Schmitz-Valckenberg S.

PURPOSE: To evaluate the development of central atrophy in eyes with age-related macular degeneration (AMD).

METHODS: Six-year longitudinal multimodal retinal imaging data (MODIAMD study) from 98 eyes of 98 subjects with non-late-stage AMD in the study eye at baseline were analyzed for the presence of central atrophy at each annual follow-up visit. Development, manifestation, and further progression of complete retinal pigment epithelium and outer retinal atrophy (cRORA) by multimodal imaging data were compared with atrophy detection based on color fundus photography only.

RESULTS: Seventeen study eyes with development of central cRORA within 6 years (cumulative rate: 17.4%) were identified based on multimodal imaging. In 10 (60%) of these eyes, presence of central manifest atrophy was initially not detectable by color fundus photography. In six (35%) eyes, central cRORA occurred by the spread of existing paracentral atrophy toward the fovea. Drusen-associated atrophy development was noted in eight eyes. In two eyes, atrophy development was associated with refractile deposits, while only pigmentary changes in absence of large drusen or refractile deposits were detectable before atrophy occurrence in one eye.
CONCLUSIONS: The earlier and more precise detection of central cRORA by multimodal imaging as compared to atrophy detection solely based on color fundus photography allows for more accurate detection and identification of different pathways for atrophy development. In accordance with previous clinical and histopathologic reports, the results confirm that different precursor lesions may independently proceed to central cRORA in AMD.

PMID: 29558532 DOI: 10.1167/iovs.17-23315


Clinical applications of optical coherence tomography angiography: What we have learnt in the first 3 years.

Cohen SY, Miere A, Nghiem-Buffet S, Fajnkuchen F, Souied EH, Mrejen S.

Abstract: A review of the literature from 2014 to 2016 was conducted, focusing on the results of optical coherence tomography angiography in different chorioretinal diseases. In only 3 years, optical coherence tomography angiography has been shown to be an effective tool for diagnosing choroidal neovascularization complicating age-related macular degeneration, pathologic myopia, and inflammatory conditions. The technique has sometimes been considered superior to conventional multimodal imaging, for example, in choroidal neovascularization associated with chronic central serous chorioretinopathy or multifocal choroiditis. In retinal vascular diseases, optical coherence tomography angiography has helped to understand the condition described as paracentral acute middle maculopathy and has been considered highly effective for the analysis of retinal vascular macular changes secondary to retinal vein occlusion or macular telangiectasia. Changes in the foveal avascular zone, also reported in diabetic maculopathy, have been shown to occur before any angiographic signs. A reduction in capillary vascular density has been reported in the fovea of eyes with malignant melanoma, but not in eyes with choroidal nevus. However, optical coherence tomography angiography is a recent technique that probably needs refinements and further studies. Nevertheless, the first 3 years of optical coherence tomography angiography use suggest its clinical relevance and useful applications in daily clinical practice.

PMID: 29554812 DOI: 10.1177/1120672117753704

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

COMPARISON OF RETINAL PATHOLOGY VISUALIZATION IN MULTISPECTRAL SCANNING LASER IMAGING.

Meshi A, Lin T, Dans K, Chen KC, Amador M, Hasenstab K, Muftuoglu IK, Nudleman E, Chao D, Bartsch DU, Freeman WR.

PURPOSE: To compare retinal pathology visualization in multispectral scanning laser ophthalmoscope imaging between the Spectralis and Optos devices.

METHODS: This retrospective cross-sectional study included 42 eyes from 30 patients with age-related macular degeneration (19 eyes), diabetic retinopathy (10 eyes), and epiretinal membrane (13 eyes). All patients underwent retinal imaging with a color fundus camera (broad-spectrum white light), the Spectralis HRA-2 system (3-color monochromatic lasers), and the Optos P200 system (2-color monochromatic lasers). The Optos image was cropped to a similar size as the Spectralis image. Seven masked graders marked retinal pathologies in each image within a 5 × 5 grid that included the macula.

RESULTS: The average area with detected retinal pathology in all eyes was larger in the Spectralis images compared with Optos images (32.4% larger, P < 0.0001), mainly because of better visualization of epiretinal membrane and retinal hemorrhage. The average detection rate of age-related macular degeneration and diabetic retinopathy pathologies was similar across the three modalities, whereas epiretinal membrane
detection rate was significantly higher in the Spectralis images.

CONCLUSION: Spectralis tricolor multispectral scanning laser ophthalmoscope imaging had higher rate of pathology detection primarily because of better epiretinal membrane and retinal hemorrhage visualization compared with Optos bicolor multispectral scanning laser ophthalmoscope imaging.

PMID: 29554078 DOI: 10.1097/IAE.000000000002156


Successful single treatment with ziv-aflibercept for existing corneal neovascularization following ocular chemical insult in the rabbit model.


PURPOSE: To evaluate the efficacy of ziv-aflibercept as a treatment for established corneal neovascularization (NV) and to compare its efficacy to that of bevacizumab following ocular chemical insult of sulfur mustard (SM) in the rabbit model.

METHODS: Chemical SM burn was induced in the right eye of NZW rabbits by vapor exposure. Ziv-aflibercept (2 mg) was applied once to neovascularized eyes by subconjunctival injection while subconjunctival bevacizumab (5 mg) was administered twice a week, for 3 weeks. Non-treated exposed eyes served as a control. A clinical follow-up employed by slit-lamp microscope, was performed up to 12 weeks following exposure and digital photographs of the cornea were taken for measurement of blood vessels length using the image analysis software. Eyes were taken for histological evaluation 2, 4 and 8 weeks following treatment for general morphology and for visualization of NV, using H&E and Masson Trichrome stainings, while conjunctival goblet cell density was determined by PAS staining.

RESULTS: Corneal NV developed, starting as early as two weeks after exposure. A single subconjunctival treatment of ziv-aflibercept at 4 weeks post exposure, significantly reduced the extent of existing NV already one week following injection, an effect which lasted for at least 8 weeks following treatment, while NV in the non-treated exposed eyes continued to advance. The extensive reduction in corneal NV in the ziv-aflibercept treated group was confirmed by histological evaluation. Bevacizumab multiple treatment showed a benefit in NV reduction, but to a lesser extent compared to the ziv-aflibercept treatment. Finally, ziv-aflibercept increased the density of conjunctival goblet cells as compared to the exposed non-treated group.

CONCLUSIONS: Subconjunctival ziv-aflibercept single treatment presented a highly efficient long-term therapeutic benefit in reducing existing corneal NV, following ocular sulfur mustard exposure. These findings show the robust anti-angiogenic efficacy of ziv-aflibercept and demonstrate the advantage of this treatment over the other anti-angiogenic therapies in ameliorating corneal NV and protecting the ocular surface.

PMID: 29548928 DOI: 10.1016/j.exer.2018.03.010

Eye (Lond). 2018 Mar 20. [Epub ahead of print]

'Statins in retinal disease'.

Al-Janabi A, Lightman S, Tomkins-Netzer O.

Abstract: Statins are known for their blood cholesterol-lowering effect and are widely used in patients with cardiovascular and metabolic diseases. Research over the past three decades shows that statins have diverse effects on different pathophysiological pathways involved in angiogenesis, inflammation, apoptosis,
and anti-oxidation, leading to new therapeutic options. Recently, statins have attracted considerable attention for their immunomodulatory effect. Since immune reactivity has been implicated in a number of retinal diseases, such as uveitis, age-related macular degeneration (AMD) and diabetic retinopathy, there is now a growing body of evidence supporting the beneficial effects of statins in these retinopathies. This review evaluates the relationship between statins and the pathophysiological basis of these diseases, focusing on their potential role in treatment. A PubMed database search and literature review was conducted. Among AMD patients, there is inconsistent evidence regarding protection against development of early AMD or delaying disease progression; though they have been found to reduce the risk of developing choroidal neovascular membranes (CNV). In patients with retinal vein occlusion, there was no evidence to support a therapeutic benefit or a protective role with statins. In patients with diabetic retinopathy, statins demonstrate a reduction in disease progression and improved resolution of diabetic macular oedema (DMO). Among patients with uveitis, statins have a protective effect by reducing the likelihood of uveitis development.

PMID: 29556012 DOI: 10.1038/s41433-018-0066-7


Automatic diagnosis of abnormal macula in retinal optical coherence tomography images using wavelet-based convolutional neural network features and random forests classifier.

Rasti R, Mehridehnavi A, Rabbani H, Hajizadeh F.

Abstract: The present research intends to propose a fully automatic algorithm for the classification of three-dimensional (3-D) optical coherence tomography (OCT) scans of patients suffering from abnormal macula from normal candidates. The method proposed does not require any denoising, segmentation, retinal alignment processes to assess the intraretinal layers, as well as abnormalities or lesion structures. To classify abnormal cases from the control group, a two-stage scheme was utilized, which consists of automatic subsystems for adaptive feature learning and diagnostic scoring. In the first stage, a wavelet-based convolutional neural network (CNN) model was introduced and exploited to generate B-scan representative CNN codes in the spatial-frequency domain, and the cumulative features of 3-D volumes were extracted. In the second stage, the presence of abnormalities in 3-D OCTs was scored over the extracted features. Two different retinal SD-OCT datasets are used for evaluation of the algorithm based on the unbiased fivefold cross-validation (CV) approach. The first set constitutes 3-D OCT images of 30 normal subjects and 30 diabetic macular edema (DME) patients captured from the Topcon device. The second publicly available set consists of 45 subjects with a distribution of 15 patients in age-related macular degeneration, DME, and normal classes from the Heidelberg device. With the application of the algorithm on overall OCT volumes and 10 repetitions of the fivefold CV, the proposed scheme obtained an average precision of 99.33% on dataset1 as a two-class classification problem and 98.67% on dataset2 as a three-class classification task.

PMID: 29564864 DOI: 10.1117/1.JBO.23.3.035005

Pathogenesis

Int Ophthalmol. 2018 Mar 23. [Epub ahead of print]

Elevated lipocalin-2 level in aqueous humor of patients with central retinal vein occlusion.

Koban Y, Sahin S, Boy F, Kara F.

PURPOSE: To assess the concentrations of lipocalin-2 (LCN2) in the serum and the aqueous humor of patients with central retinal vein occlusion (CRVO).
METHODS: The concentrations of LCN2 in the serum and aqueous humor of 16 cataract patients and 16 patients with CRVO with macular edema were compared. Collection of aqueous samples was conducted in the operating theater under sterile conditions and just prior to intravitreal ranibizumab injection or cataract surgery. LCN2 levels in serum and aqueous humor samples were measured using a commercial kit (human lipocalin-2/NGAL PicoKine ELISA Kit, MyBioSource Inc., USA; Catalog No: MBS175829) based on standard sandwich enzyme-linked immunosorbent assay technology.

RESULTS: The concentrations of LCN2 in the aqueous humors of the CRVO group were higher than those of the control group (p = 0.021). There was no significant difference in serum LCN2 level between the two groups (p = 0.463).

CONCLUSIONS: Concentrations of LCN2 in aqueous humor are increased in CRVO. LCN2 may be part of a pro-catabolic phenotype, and it may play an important role in the dreaded complications of CRVO, such as macular edema, macular ischemia, and neovascularization, which lead to blindness.

PMID: 29572586 DOI: 10.1007/s10792-018-0894-2

**Methods Mol Biol. 2018;1753:317-330.**

**Analysis of Retinal Vascular Plexuses and Interplexus Connections.**

Simmons AB, Fuerst PG.

Abstract: The retina is a highly organized neural tissue consisting of three neural layers and two synaptic layers. Blood vessels that nourish the mouse and human neural retina mirror this organization consisting of three plexus layers, or plexuses, that run parallel within the retina, connected by interplexus vessels to create a closed vascular network. Here, we describe a methodology to describe this organization that can be used to interrogate factors mediating retinal vessel patterning including: coverage of the vascular plexuses, branching and orientation of the interplexus connections, and digital reconstruction of the retinal vasculature to measure vessel length and density. The methodology focuses on the mouse retina, but can easily be adapted to study retinal vessels of other species.

PMID: 29564799 DOI: 10.1007/978-1-4939-7720-8_22

**Neural Regen Res. 2018 Feb;13(2):207-210.**

**Dyslipidemia modulates Müller glial sensing and transduction of ambient information.**

Lakk M, Vazquez-Chona F, Yarishkin O, Križaj D.

Abstract: Unesterified cholesterol controls the fluidity, permeability and electrical properties of eukaryotic cell membranes. Consequently, cholesterol levels in the retina and the brain are tightly regulated whereas depletion or oversupply caused by diet or heredity contribute to neurodegenerative diseases and vision loss. Astroglia play a central role in the biosynthesis, uptake and transport of cholesterol and also drive inflammatory signaling under hypercholesterolemic conditions associated with high-fat diet (diabetes) and neurodegenerative disease. A growing body of evidence shows that unesterified membrane cholesterol modulates the ability of glia to sense and transduce ambient information. Cholesterol-dependence of Müller glia - which function as retinal sentinels for metabolic, mechanical, osmotic and inflammatory signals - is mediated in part by transient receptor potential V4 (TRPV4) channels. Cholesterol supplementation facilitates, whereas depletion suppresses, TRPV4-mediated transduction of temperature and lipid agonists in Müller cells. Acute effects of cholesterol supplementation/depletion on plasma membrane ion channels and calcium homeostasis differ markedly from the effects of chronic dyslipidemia, possibly due to differential modulation of modality-dependent energy barriers associated with the functionality of polymodal channels embedded within lipid rafts. Understanding of cholesterol-dependence of TRP channels is thus providing insight into dyslipidemic pathologies associated with diabetic retinopathy, glaucoma and macular
Degeneration.

PMID: 29557361 DOI: 10.4103/1673-5374.226383


Smith JR, David LL, Appukuttan B, Wilmarth PA.

Abstract: Diseases that involve retinal or choroidal vascular endothelial cells are leading causes of vision loss: age-related macular degeneration, retinal ischemic vasculopathies and non-infectious posterior uveitis. Proteins differentially expressed by these endothelial cell populations are potential drug targets. We used deep proteomic profiling to define the molecular phenotype of human retinal and choroidal endothelial cells at the protein level. Methods Retinal and choroidal vascular endothelial cells were separately isolated from five human eye pairs by selection on CD31. Total protein was extracted and digested, and peptide fractions were analyzed by reverse-phase liquid chromatography tandem mass spectrometry. Peptide sequences were assigned to fragment ion spectra, and proteins were inferred from openly accessible protein databases. Protein abundance was determined by spectral counting. Publically available software packages were used to identify proteins that were differentially expressed between human retinal and choroidal endothelial cells, and to classify proteins that were highly abundant in each endothelial cell population. Results Human retinal and/or choroidal vascular endothelial cells expressed 5,042 non-redundant proteins. Setting the differential expression false discovery rate at 0.05, 498 proteins (14.4%) of 3,454 quantifiable proteins with minimum mean spectral counts of 2.5 were differentially abundant in the two cell populations. Retinal and choroidal endothelial cells were enriched in angiogenic proteins, and retinal endothelial cells were also enriched in immunologic proteins. Conclusions This work describes the different protein expression profiles of human retinal and choroidal vascular endothelial cells, and provides multiple candidates for further study as novel treatments or drug targets for posterior eye diseases.

PMID: 29559410 DOI: 10.1016/j.ajo.2018.03.020

Arch Pharm Res. 2018 Mar 19. [Epub ahead of print]

Causes of hyperhomocysteinemia and its pathological significance.

Kim J, Kim H, Roh H, Kwon Y.

Abstract: In the last 10 years, homocysteine has been regarded as a marker of cardiovascular disease and a definite risk factor for many other diseases. Homocysteine is biosynthesized from methionine through multiple steps and then goes through one of two major metabolic pathways: remethylation and transsulfuration. Hyperhomocysteinemia is a state in which too much homocysteine is present in the body. The main cause of hyperhomocysteinemia is a dysfunction of enzymes and cofactors associated with the process of homocysteine biosynthesis. Other causes include excessive methionine intake, certain diseases and side effects of some drugs. Hyperhomocysteinemia is a trigger for many diseases, such as atherosclerosis, congestive heart failure, age-related macular degeneration, Alzheimer's disease and hearing loss. There are many studies showing a positive relationship between homocysteine level and various symptoms. We speculate that a high level of homocysteine can be the sole reason or an aggravating factor in numerous diseases for which causal links are not fully understood.

PMID: 29552692 DOI: 10.1007/s12272-018-1016-4
Gonadal Hormones and Retinal Disorders: A Review.

Nuzzi R, Scalabrin S, Becco A, Panzica G.

AIM: Gonadal hormones are essential for reproductive function, but can act on neural and other organ systems, and are probably the cause of the large majority of known sex differences in function and disease. The aim of this review is to provide evidence for this hypothesis in relation to eye disorders and to retinopathies in particular.

METHODS: Epidemiological studies and research articles were reviewed.

RESULTS: Analysis of the biological basis for a relationship between eye diseases and hormones showed that estrogen, androgen, and progesterone receptors are present throughout the eye and that these steroids are locally produced in ocular tissues. Sex hormones can have a neuroprotective action on the retina and modulate ocular blood flow. There are differences between the male and the female retina; moreover, sex hormones can influence the development (or not) of certain disorders. For example, exposure to endogenous estrogens, depending on age at menarche and menopause and number of pregnancies, and exposure to exogenous estrogens, as in hormone replacement therapy and use of oral contraceptives, appear to protect against age-related macular degeneration (both drusenoid and neurovascular types), whereas exogenous testosterone therapy is a risk factor for central serous chorioretinopathy. Macular hole is more common among women than men, particularly in postmenopausal women probably owing to the sudden drop in estrogen production in later middle age. Progestin therapy appears to ameliorate the course of retinitis pigmentosa. Diabetic retinopathy, a complication of diabetes, may be more common among men than women.

CONCLUSION: We observed a correlation between many retinopathies and sex, probably as a result of the protective effect some gonadal hormones may exert against the development of certain disorders. This may have ramifications for the use of hormone therapy in the treatment of eye disease and of retinal disorders in particular.

PMID: 29551993 PMCID: PMC5840201 DOI: 10.3389/fendo.2018.00066
CONCLUSIONS: Our results indicate that chronic TNF-α-exposure is sufficient to alter RPE morphology and impede cardinal features that define the differentiated state of RPE cells with striking similarities to the alterations that are observed with age in neurodegenerative diseases such as age-related macular degeneration.

PMID: 29548329 PMCID: PMC5857126 DOI: 10.1186/s12974-018-1106-8

Epidemiology


Cognitive Function and Ophthalmological Diseases: The Beijing Eye Study.

Jonas JB, Wei WB, Zhu LP, Xu L, Wang YX.

Abstract: To examine associations between cognitive function and ophthalmological parameters, the population-based Beijing Eye Study examined ophthalmologically and physically 3127 individuals (mean age: 64.2 ± 9.8 years). Using the mini-mental state examination, cognitive function was assessed as cognitive function score (CFS). Mean CFS was 26.3 ± 3.7 (median: 27; range: 2-30). Prevalence of mild (CFS: 23-19), moderate (CFS: 18-10) and severe cognitive dysfunction was 9.6% (95% confidence interval (CI): 8.5, 10.6), 3.2% (95% CI: 2.6, 3.9) and 0.6% (95% CI: 0.4,0.9), respectively. In multivariate analysis, better cognition (i.e., higher CFS) was significantly associated with better best corrected visual acuity (r² = 0.38), smaller amount of undercorrected visual acuity, lower prevalence of primary angle-closure glaucoma, and thicker subfoveal choroidal thickness. Prevalence of age-related macular degeneration, open-angle glaucoma, diabetic retinopathy, any type of cataract, retinal vein occlusions or pseudoexfoliation was not significantly correlated with CFS. Though the causal relationship is unclear, the associations of lower cognitive function with undercorrected visual acuity suggest the need for earlier and more regular refraction testing in the elderly so that providing adequate glasses to the elderly can be provided and vision-associated cognitive decline can be reduced. Associations of cognitive function with primary angle-closure glaucoma and leptochoroid should be further explored.

PMID: 29556090 PMCID: PMC5859266 DOI: 10.1038/s41598-018-23314-5


Appointment Compliance in Patients With Diabetic Macular Edema and Exudative Macular Degeneration.


BACKGROUND AND OBJECTIVE: The purpose of this study is to compare cancellation and no-show rates in patients with diabetic macular edema (DME) and exudative macular degeneration (wet AMD).

PATIENTS AND METHODS: An anonymous survey was sent to 1,726 retina specialists inquiring as to the number of appointments their patients with DME and wet AMD attended, cancelled, or did not show up for in 2014 and 2015.

RESULTS: Data were obtained on 109,599 appointments. Patients with DME in the U.S. had a 1.591-times increased odds of cancelling or no-showing to their appointments than patients with wet AMD (P < .0001). Patients with DME in Europe had a 1.918-times increased odds of cancelling or no showing to their appointments than patients with wet AMD (P < .0001).

CONCLUSION: Patients with DME in the U.S. and Europe cancelled and no-showed to their appointments significantly more often than patients with wet AMD. These findings can be taken into consideration when
establishing treatment plans for patients with DME. [Ophthalmic Surg Lasers Imaging Retina. 2018;49:186-190.].

PMID: 29554386 DOI: 10.3928/23258160-20180221-060

Psychiatry Res. 2018 Mar 6;263:158-161. [Epub ahead of print]

A pilot study assessing retinal pathology in psychosis using optical coherence tomography: Choroidal and macular thickness.

Joe P, Ahmad M, Riley G, Weissman J, Smith RT, Malaspina D.

Abstract: Mounting evidence supports a genetic-vascular-inflammatory etiology of schizophrenia. The retina provides an indirect assessment of inflammation and degeneration in the brain. In particular, the use of spectral domain optical coherence tomography (SD-OCT) has emerged as a powerful tool for examining single retinal nerve cell layers and the choroid, the vascular layer supplying the outer retina. In this study, choroidal and macular thicknesses were measured in six patients with psychosis with either schizophrenia or bipolar disorder, and in 18 age- and sex-matched healthy controls. Mean choroidal thickness was reduced in psychosis, though not significantly so. There was a statistically significant decrease in macular thickness in psychosis patients predominantly affecting the inner layers of the macula. Significant macular thinning may signal vascular, inflammatory, or degenerative processes that may also be occurring in the brain. This is one of the first studies to examine choroidal thickness in psychosis. Further studies are needed to determine whether the retinal changes in psychosis are correlated with microvascular dysfunction, neuroinflammation, and neurodegeneration.

PMID: 29567341 DOI: 10.1016/j.psychres.2018.03.011

Genetics and gene therapy


Polymorphisms in Selected Genes and Their Association with Age-Related Macular Degeneration in a Chinese Population.

Huang Q, Xiang Y.

Abstract: BACKGROUND Increasing evidence shows that polymorphisms in a number of genes can influence age-related macular degeneration (AMD) risk. This study aimed to investigate the association of CX3CR1 839C/T, CX3CR1 745G/A, PLEKHA1 958A/G, VEGFA +674C/T, and VEGFA +936C/T polymorphisms with AMD risk among Chinese. MATERIAL AND METHODS The polymorphisms were genotyped on 827 AMD patients and 827 controls, and the odds ratios (ORs) were calculated under allele, additive, recessive, and dominant genetic models. Logistic regression analysis was performed to control for potential confounders (age, sex, and smoking status). RESULTS We showed that all the 5 polymorphisms showed a significant association with AMD risk under the additive model (for homozygous mutant genotype) and at least 1 other genetic model, both before and after adjustment for the potential confounders. PLEKHA1 958A/G polymorphism was associated with a decreased AMD risk (additive model: aOR=0.722, 95% CI=0.450-0.979, P=0.019; allele model: aOR=0.883, 95% CI=0.736-0.992, P=0.014), while all other polymorphisms were associated with an increased AMD risk (CX3CR1 839C/T, additive model: aOR=2.682, 95% CI=1.199-5.709, P=0.022, recessive model: aOR=2.729, 95% CI=1.141-6.048, P=0.010; CX3CR1 745G/A, additive model: aOR=2.641, 95% CI=1.231-6.012, P=0.020, recessive model: aOR=2.340, 95% CI=1.227-5.993, P=0.011; VEGFA +674C/T, additive model: aOR=1.601, 95% CI=1.253-2.179, P<0.001, dominant model: aOR=1.287, 95% CI=1.058-1.570, P<0.001, allele model: OR=1.220, 95% CI=1.118-1.427, P<0.001; VEGFA +936C/T, additive model: aOR=1.509, 95% CI=1.105-2.311, P<0.001, recessive model: aOR=1.432, 95% CI=1.027-2.192, P=0.009, dominant model: aOR=1.207, 95%
CI=1.031-1.514, P0.001, allele model: aOR=1.216, 95% CI=1.062-1.408, P<0.001). CONCLUSIONS We conclude that the 5 polymorphisms could serve as biomarkers for AMD susceptibility.

PMID: 29565837


Epigenetic modifications in hyperhomocysteinemia: potential role in diabetic retinopathy and age-related macular degeneration.

Elmasry K, Mohamed R, Sharma I, Elsherbiny NM, Liu Y, Al-Shabrawey M, Tawfik A.

Abstract: To study Hyperhomocysteinemia (HHcy)-induced epigenetic modifications as potential mechanisms of blood retinal barrier (BRB) dysfunction, retinas isolated from three-week-old mice with elevated level of Homocysteine (Hcy) due to lack of the enzyme cystathionine β-synthase (cbs-/-, cbs+/-, and cbs+/+), human retinal endothelial cells (HRECs), and human retinal pigmented epithelial cells (ARPE-19) treated with or without Hcy were evaluated for (1) histone deacetylases (HDAC), (2) DNA methylation (DNMT), and (3) miRNA analysis. Differentially expressed miRNAs in mice with HHcy were further compared with miRNA analysis of diabetic mice retinas (STZ) and miRNAs within the exosomes released from Hcy-treated RPEs. Differentially expressed miRNAs were further evaluated for predicted target genes and associated pathways using Ingenuity Pathway Analysis. HHcy significantly increased HDAC and DNMT activity in HRECs, ARPE-19, and cbs mice retinas, whereas inhibition of HDAC and DNMT decreased Hcy-induced BRB dysfunction. MiRNA profiling detected 127 miRNAs in cbs+/+ and 39 miRNAs in cbs-/- mice retinas, which were significantly differentially expressed compared to cbs+/+. MiRNA pathway analysis showed their involvement in HDAC and DNMT activation, endoplasmic reticulum (ER), and oxidative stresses, inflammation, hypoxia, and angiogenesis pathways. Hcy-induced epigenetic modifications may be involved in retinopathies associated with HHcy, such as age-related macular degeneration and diabetic retinopathy.

PMID: 29560091 PMCID: PMC5849155 DOI: 10.18632/oncotarget.24333


DJ-1 in Ocular Diseases: A Review.

Liu C, Liu X, Qi J, Pant OP, Lu CW, Hao J.

Abstract: Protein deglycase DJ-1 (Parkinson disease protein 7) is a 20 kDa protein encoded by PARK7 gene. It is also known as a redox-sensitive chaperone and sensor that protect cells against oxidative stress-induced cell death in many human diseases. Though increasing evidence implicates that DJ-1 may also participate in ocular diseases, the overview of DJ-1 in ocular diseases remains elusive. In this review, we discuss the role as well as the underlying molecular mechanisms of DJ-1 in ocular diseases, including Fuchs endothelial corneal dystrophy (FECD), age-related macular degeneration (AMD), cataracts, and ocular neurodegenerative diseases, highlighting that DJ-1 may serve as a very striking therapeutic target for ocular diseases.

PMID: 29559831 PMCID: PMC5859765 DOI: 10.7150/ijms.23428


N-Terminomics identifies HtrA1 cleavage of thrombospondin-1 with generation of a proangiogenic fragment in the polarized retinal pigment epithelial cell model of age-related macular degeneration.

Chen CY, Melo E, Jakob P et al
Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population. Variants in the HTRA1-ARMS2 locus have been linked to increased AMD risk. In the present study we investigated the impact of elevated HtrA1 levels on the retina pigment epithelial (RPE) secretome using a polarized culture system. Upregulation of HtrA1 alters the abundance of key proteins involved in angiogenesis and extracellular matrix remodeling. Thrombospondin-1, an angiogenesis modulator, was identified as a substrate for HtrA1 using terminal amine isotope labeling of substrates in conjunction with HtrA1 specificity profiling. HtrA1 cleavage of thrombospondin-1 was further corroborated by in vitro cleavage assays and targeted proteomics together with small molecule inhibition of HtrA1. While thrombospondin-1 is anti-angiogenic, the proteolytically released N-terminal fragment promotes the formation of tube-like structure by endothelial cells. Taken together, our findings suggest a mechanism by which increased levels of HtrA1 may contribute to AMD pathogenesis. The proteomic data has been deposited to the ProteomeXchange Consortium via the PRIDE partner repository with the data set identifier. For quantitative secretome analysis, project accession: PXD007691, username: reviewer45093@ebi.ac.uk, password: 1FuPs6Yq. For TAILS analysis, project accession: PXD007139, username: reviewer76731@ebi.ac.uk, password: sNbMp7xK.

PMID: 29572155 DOI: 10.1016/j.matbio.2018.03.013

Stem cells


Over-expression of CNTF in bone marrow mesenchymal stem cells protects RPE cells from short-wavelength, blue-light injury.

Lin W, Xu G.

Abstract: Increasing evidence has demonstrated that excessive blue-light (BL) with high photochemical energy and phototoxicity could induce apoptosis in retinal pigment epithelium (RPE) cells. RPE apoptosis leads to retina damage and further aggravate age-related macular degeneration (ARMD). Because of their neuroprotective, plasticity, and immunomodulatory ability, bone marrow mesenchymal stem cells (BMSCs) are recognized for retinal neuroprotection. RPE cells possess ciliary neurotrophic factor (CNTF) receptor complexes and can respond to CNTF; hence, we investigated the effects of BMSCs over-expressing CNTF on BL-injured RPE cells. BL-injured RPE cells were co-cultured with CNTF-BMSCs and GFP-BMSCs for 24 and 48 h. Superoxide dismutase and malondialdehyde assays were conducted to examine the effects of CNTF-BMSCs on the oxidative stress of RPE cells. VEGF protein secretion by RPE was determined by ELISA, and western blotting analysis was used to determine apoptotic protein expression and autophagic flux. Immunofluorescence was used to demonstrate the relationship between autophagy and apoptosis. We found that CNTF-BMSCs enhanced antioxidant capacity, decreased VEGF secretion, promoted autophagic flux, and inhibited apoptosis in BL-injured RPE cells, compared to GFP-BMSCs. Our findings suggest that CNTF over-expression enhances the protective effects of BMSCs on RPE cells, thus indicating subretinal-transplantation of CNTF-BMSCs may be a promising therapy for BL-injured retina.

PMID: 29564604 DOI: 10.1007/s11626-018-0243-9


Regenerative Therapy by Suprachoroidal Cell Autograft in Dry Age-related Macular Degeneration: Preliminary In Vivo Report.

Limoli PG, Vingolo EM, Limoli C, Scalinci SZ, Nebbioso M.

Abstract: This study is aimed at examining whether a suprachoroidal graft of autologous cells can improve best corrected visual acuity (BCVA) and responses to microperimetry (MY) in eyes affected by dry Age-
related Macular Degeneration (AMD) over time through the production and secretion of growth factors (GFs) on surrounding tissue. Patients were randomly assigned to each study group. All patients were diagnosed with dry AMD and with BCVA equal to or greater than 1 logarithm of the minimum angle of resolution (logMAR). A suprachoroidal autologous graft by Limoli Retinal Restoration Technique (LRRT) was carried out on group A, which included 11 eyes from 11 patients. The technique was performed by implanting adipocytes, adipose-derived stem cells obtained from the stromal vascular fraction, and platelets from platelet-rich plasma in the suprachoroidal space. Conversely, group B, including 14 eyes of 14 patients, was used as a control group. For each patient, diagnosis was verified by confocal scanning laser ophthalmoscope and spectral domain-optical coherence tomography (SD-OCT). In group A, BCVA improved by 0.581 to 0.504 at 90 days and to 0.376 logMAR at 180 days (+32.20%) postoperatively. Furthermore, MY test increased by 11.44 dB to 12.59 dB at 180 days. The different cell types grafted behind the choroid were able to ensure constant GF secretion in the choroidal flow. Consequently, the results indicate that visual acuity (VA) in the grafted group can increase more than in the control group after six months.

PMID: 29553543 DOI: 10.3791/56469