Macular Atrophy in the HARBOR Study for Neovascular Age-Related Macular Degeneration.

Sadda SR, Tuomi LL, Ding B, Fung AE, Hopkins JJ.

PURPOSE: To evaluate macular atrophy (MA) presence in the 24-month HARBOR study (NCT00891735) for neovascular age-related macular degeneration (AMD).

DESIGN: Post hoc analysis of a phase 3 multicenter, prospective, randomized, double-masked, active treatment-controlled clinical trial.

PARTICIPANTS: Evaluable subjects (N = 1095) with subfoveal choroidal neovascularization (CNV) secondary to neovascular AMD treated with ranibizumab 0.5 mg or 2.0 mg monthly or pro re nata (PRN).

METHODS: Fluorescein angiograms (FAs) and color fundus photographs at baseline and months 3, 12, and 24 were retrospectively graded by masked graders for MA: well-defined areas of depigmentation with increased choroidal vessel visibility, diameter ≥250 μm, corresponding to flat areas of well-demarcated staining on FA, excluding atrophy associated with retinal pigment epithelium tears. Atrophy immediately within, adjacent, and nonadjacent to CNV lesions was included.

MAIN OUTCOME MEASURES: Macular atrophy incidence, best-corrected visual acuity (BCVA).

RESULTS: At baseline, MA was detected in 11.2% (123/1095) of study eyes. At month 24, 29.4% (229/778) of eyes without baseline atrophy had detectable MA. Eyes with and without baseline MA had significant mean BCVA gains from baseline at month 24 (letters [95% confidence interval]: +6.7 [4.1-9.3]; +9.1 [8.0-10.2], respectively). Among eyes with and without MA at month 24, mean month 24 BCVA was 62.0 [60.3-63.7] and 64.7 [63.2-66.3] letters, respectively. Baseline risk factors for month 24 MA presence included intraretinal cysts (hazard ratio [HR], 2.45 [1.76-3.42]) and fellow eye atrophy (HR, 2.02 [1.42-2.87]); subretinal fluid was associated with a lower MA risk (HR, 0.50 [0.33-0.74]). Ranibizumab dose was not associated with MA development. Monthly versus PRN treatment trended toward an association with MA (HR, 1.29 [0.99-1.68]), but was not statistically significant.

CONCLUSIONS: New MA was detected in 29% of study eyes after 24 months of treatment. Clinically significant BCVA gains were achieved with MA present over 24 months. Baseline subretinal fluid absence, intraretinal cyst presence, and fellow eye atrophy presence were associated with month 24 MA presence. With existing data, the benefits of ranibizumab for neovascular AMD outweighed the risk of MA development over 24 months in HARBOR, although outcomes >2 years were not evaluated.

PMID: 29477692
Association of Changes in Macular Perfusion With Ranibizumab Treatment for Diabetic Macular Edema: A Subanalysis of the RESTORE (Extension) Study.

Karst SG, Deak GG, Gerendas BS, Waldstein SM, Lammer J, Simader C, Guerin T, Schmidt-Erfurth UM.

IMPORTANCE: Anti-vascular endothelial growth factor treatment is the first-line therapy in the treatment of center-involving diabetic macular edema. Data on capillary perfusion changes under repeated treatment in a possibly compromised vascular network are limited.

OBJECTIVE: To evaluate the association of repeated ranibizumab injections on macular perfusion in patients with diabetic macular edema.

DESIGN, SETTING, AND PARTICIPANTS: This study analyzed prospectively collected data from the 12-month RESTORE core study and the 24-month open label RESTORE extension study, which assessed the efficacy and safety of ranibizumab in patients with visual impairment due to diabetic macular edema. Of 345 patients with center-involving diabetic macular edema who had enrolled in the 12-month RESTORE core study, 240 entered the 24-month RESTORE extension study. Of these, 83 (34.6%) received ranibizumab, 83 (34.6%) received ranibizumab and laser combination therapy, and 74 (30.8%) received laser monotherapy in the first year of the study; 208 completed the 24-month extension study. Fluorescence angiography images were taken from each participant twice each year graded by Vienna Reading Center on severity of capillary loss in the parafoveal area, regularity of the foveal avascular zone outline, and measurement of the size of the foveal avascular zone, following a standardized protocol. Data analysis took place from July 2014 through December 2017.

MAIN OUTCOMES AND MEASURES: Change in 3 fluorescence angiography perfusion parameters over the course of treatment.

RESULTS: Mean (SD) patient age was 62.6 (8.8) years; 124 of 208 (59.2%) were male and 197 of 208 (94.6%) were white. The number of patients with definite altered foveal avascular zone regularity at baseline was 103 of 240 patients (42.9%); another 118 patients (49.2%) had questionably altered regularity at baseline. Definitive capillary loss was found in 65 of 240 patients (27.1%) at baseline. Mean (SD) foveal avascular zone size at baseline was 0.261 (0.232) mm² in ranibizumab monotherapy, 0.231 (0.219) mm² in ranibizumab and macular laser combination therapy, and 0.201 (0.13) mm² in laser monotherapy. No treatment arm experienced significant increase in foveal avascular zone size at any time in the study period. At month 36, ranibizumab monotherapy resulted in a mean increase of 0.073 mm² (95% CI, 0.005-0.142 mm²) and combination therapy resulted in a mean increase of 0.117 mm² (95% CI, 0.045-0.188 mm²), but no changes were statistically significant. No changes occurred in foveal avascular zone regularity in any treatment group, and no differences were found in capillary loss around the fovea in the 3 treatment groups; neither element could be correlated with visual acuity or central retinal thickness.

CONCLUSIONS AND RELEVANCE: Repeated ranibizumab treatment was not associated with impaired macular perfusion in our study cohort. Because our data do not suggest a harmful effect of anti-vascular endothelial growth factor therapy on capillary integrity, patients with severe microangiopathy and advanced capillary dropout should not be denied these treatments.

PMID: 29494727

Effects of intravitreal injection of ranibizumab on choroidal structure and blood flow in eyes with diabetic macular edema.

Okamoto M, Yamashita M, Ogata N.

PURPOSE: To determine the effects of an intravitreal injection of ranibizumab (IVR) on the choroidal structure and blood flow in eyes with diabetic macular edema (DME).
METHODS: Twenty-eight consecutive patients with DME who received an IVR and 20 non-diabetic, age-matched controls were followed for 1 month. The eyes with DME were divided into those with prior panretinal photocoagulation (PRP, n = 16) and those without prior PRP (no-PRP, n = 12). The enhanced depth imaging optical coherence tomography (EDI-OCT) scans and Niblack’s image binarization were performed to determine the choroidal structure. The choroidal blood flow was determined by laser speckle flowgraphy.

RESULTS: The subfoveal choroidal thickness at the baseline was significantly thicker in the no-PRP group than in the PRP-treated group. After IVR, the best-corrected visual acuity (BCVA) and central retinal thickness in eyes with DME were significantly improved compared to the baseline values. There were significant differences in the choroidal thickness, total choroidal area, and choroidal vascularity index between the groups after IVR. Choroidal vascular index and choroidal blood flow were significantly reduced only in the no-PRP group and not in the PRP-treated group. In addition, the correlation between the central retinal thickness and the choroidal blood flow was significant in the no-PRP group (r = 0.47, P < 0.05).

CONCLUSIONS: A single IVR will reduce the central retinal thickness and improve the BCVA in eyes with DME in both the no-PRP and PRP-treated group. IVR affected the choroidal vasculature and blood flow significantly, and a significant correlation was found between the central retinal thickness and the choroidal blood flow in eyes without PRP.

PMID: 29492689


Real-life experience of ranibizumab therapy for neovascular age-related macular degeneration from Turkey.

Cebeci Z, Yilmaz YC, Kir N.

AIM: To report the real-life experience and clinical results of intravitreal ranibizumab injections to neovascular age-related macular degeneration (nAMD) in a single institution in Turkey.

METHODS: A total of 101 eyes of 89 patients with nAMD treated with intravitreal ranibizumab injection, followed up for at least 24mo between 2009 and June 2014, which were evaluated retrospectively. A pro re nata (PRN) treatment protocol was performed after the patients had received three, monthly loading injections. Best corrected visual acuity (BCVA) and central macular thickness measurements were evaluated at baseline and 3, 6, 12, 18, and 24mo. Number of injections and visits were also recorded.

RESULTS: Of the 89 patients, 34 (38.2%) were male and 55 (61.8%) were female and the mean age was 74.0±9.5 (52-91)y. The mean follow-up period was 24.82±4.4 (24-29)mo. Mean number of visits was 8.4±1.2 (7-12) in the first year and 6.6±1.33 (4-12) in the second year. The mean number of injections was 5.8±1.6 (3-10) and 4.2±2.2 (0-9) in the first and second year, respectively. The mean BCVA was 59±15.8 letters at baseline by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart. The mean BCVA at 3, 12, and 24mo was 70.3±15.9, 67.9±14.3 and 67.3±16.9 letters, respectively. Improvement in visual acuity for each of the visits from baseline was found to be statistically significant (P<0.01). Visual acuity in 9 eyes at month 3, 7 eyes at month 12, and 13 eyes at month 24 did not change. The mean central macular thickness (CMT) was 437.99±164.78 µm at baseline. The mean CMT was 348.05±138.47 µm, 349.27±139.79 µm, and 344.13±146.30 µm at months 3, 12, and 24, respectively. The decrease in CMT for each of the visits from baseline was found to be statistically significant (P<0.01).

CONCLUSION: Anatomical and functional achievement are obtained in our study, but the mean number of injections and visits are found to be lower than the findings reported in randomized controlled clinical trials in the literature. However, the mean number of injections and visits in our study are compatible with the findings reported in real-life experience studies in the literature.

PMID: 29487818 PMCID: PMC5824083
Outcomes and costs of Ranibizumab and Aflibercept treatment in a health-service research context.

Schmid MK, Reich O, Blozik E, Faes L, Bodmer NS, Locher S, Thiel MA, Rapold R, Kuhn M, Bachmann LM.

BACKGROUND: To compare anti-VEGF treatments for macular disease in terms of costs and clinical outcomes.

METHODS: We identified patients suffering from macular disease and treated either with aflibercept, ranibizumab or both at the largest public eye clinic in Switzerland between January 1st and December 31st 2016 who were insured in one of the two participating health insurance companies. Clinical data were extracted from the electronic health record system. The health insurers provided the health claim costs for the ophthalmologic care and the total health care costs of each patient in the observation period. Using multivariate regression models, we assessed the monthly ophthalmologic and the monthly total costs of patients with no history of switching (ranibizumab vs. aflibercept), patients with a history of switching from ranibizumab to aflibercept, patients switching during the observation period and a miscellaneous group. We examined baseline differences in age, proportion of males, visual acuity (letters), central retinal thickness (CRT) and treatment history before entering the study. We investigated treatment intensity and compared the changes in letters and CRT.

RESULTS: The analysis involved 488 eyes (361 patients), 182 on ranibizumab treatment, and 63 on aflibercept treatment, 160 eyes with a history of switching from ranibizumab to aflibercept, and 45 switchers during follow-up and 38 eyes of the miscellaneous group. Compared to ranibizumab, monthly costs of ophthalmologic treatment were slightly higher for aflibercept treatment +175.0 CHF (95%CI: 1.5 CHF to 348.3 CHF; p = 0.048) as were the total monthly costs +581.0 CHF (95%CI: 159.5 CHF to 1002.4 CHF; p = 0.007). Compared to ranibizumab, the monthly treatment intensity with aflibercept was similar (+0.057 injections/month (95%CI -0.023 to 0.137; p = 0.162), corresponding to a projected annual number of 5.4 injections for ranibizumab vs. 6.1 injections for aflibercept. During follow-up, visus dropped by 0.7 letters with ranibizumab and increased by 0.6 letters with aflibercept (p = 0.243). CRT dropped by -14.9 μm with ranibizumab and by -19.5 μm with aflibercept (p = 0.708). The monthly costs of all other groups examined were higher.

CONCLUSION: These real-life data show that aflibercept treatment is equally expensive, and clinical outcomes between the two drugs are similar.

PMID: 29486762
vascular endothelial growth factor, oxidative stress, failure of the clearance of proteins and organelles, and glial cell dysfunction in AMD.

PMID: 29484106 PMCID: PMC5816845


Intravitreal Ziv-Aflibercept in Treatment of Naïve Chronic Central Serous Chorioretinopathy Related Choroidal Neovascular Membrane.

Radke N, Kalamkar C, Mukherjee A, Radke S.

Purpose: To study the effect and outcome of intravitreal Ziv-Aflibercept (IVZ) in treatment of Chronic Central Serous Chorioretinopathy (CSCR) related Choroidal Neovascular Membrane (CNVM).

Methods: A case report of 48-year-old male patient treated with 1.25 mg/0.05 ml IVZ (total 3 doses at monthly intervals) in CSCR related CNVM. Pre- and posttreatment fundus fluorescein angiography (FFA) and Optical Coherence Tomography (OCT) were done to document response along with improvement in visual acuity.

Patients: Single eye of a 48-year-old male patient.

Results: Regression of CNVM was noted with improvement of macular contour and thickness on OCT and cessation of leakage on FFA. Visual acuity improved from 3/60, <N36 to 6/12, N12.

Discussion: Anti-VEGF injections have shown benefit in treatment of CNVM. There is very little information about benefit of IVZ in CSCR related CNVM.

Conclusion: IVZ is effective in regression of CSCR related CNVM and is associated with better macular anatomy and improved visual function.

PMID: 29479487 PMCID: PMC5733174

Other treatment & diagnosis


Shortest Distance from Fovea to Subfoveal Hemorrhage Border is Important in Patients with Neovascular Age-Related Macular Degeneration.


PURPOSE: To identify factors influencing visual outcome in patients with neovascular age-related macular degeneration (NVAMD) and subfoveal hemorrhage (SFH) treated with anti-vascular endothelial growth factor (VEGF) agents DESIGN: Retrospective case series METHODS: Anti-VEGF-treated eyes with SFH >1 disc area (DA) were identified (n=16) and changes in visual acuity (VA) and central subfield thickness (CST) from baseline to last follow up along with SFH area, thickness, minimum distance from fovea to SFH border, and time to resolution were determined.

RESULTS: At baseline, mean (± SEM) size and thickness of SFH were 14.9 ± 2.8 DA and 386.6 ± 46.9 μm, and mean Snellen VA and CST were 20/250 and 591.7 ± 57.0 μm. Median follow up was 47.6 months. While more than 50% of patients had VA ≤ 20/200 at baseline and all time points through week 48, the percentage of patients with VA ≥ 20/50 increased to 30-40% at months 6 and 12 and remained stable through month 48. Spearman rank correlation demonstrated two independent variables that correlated with good visual outcome, smaller area of SFH at baseline (r=-0.630; p=0.009) and high frequency of anti-VEGF injections (r=0.646; p=0.007). In exceptional patients with good visual outcome despite large baseline SFH,
shortest distance between the fovea and hemorrhage border significantly correlated with baseline VA (r=-0.503, p=0.047) and final VA (r=-0.575, p=0.02).

CONCLUSIONS: Patients with NVAMD and thick SFH, but short distance between fovea and uninvolved retina can have good visual outcomes when given frequent anti-VEGF injections.

PMID: 29499174

Klin Monbl Augenheilkd. 2018 Feb 28. [Epub ahead of print]

[Correlation of Quantitative Metamorphopsia Measurement and Central Retinal Thickness in Diabetic Macular Edema and Age-Related Exudative Macular Degeneration]. [Article in German]

Claessens D, Schuster AK.

BACKGROUND: Amsler Test is the standard used to detect metamorphopsia. To develop a tool to quantitatively measure and monitor metamorphopsia, the computer-based test "AMD - A Metamorphopsia Detector®" was developed. This study was performed to examine the correlation of metamorphopsia index (MI) and central retinal thickness (CRT) in exudative age-related macular degeneration (AMD) and diabetic macular edema (DME).

MATERIAL AND METHODS: Sixty-six eyes of 66 patients, DME: 19 (11 males, 8 females; age 42-76); AMD: 47 (13 male, 34 female; age 56-93) were included in this convenient sample study and classified as having or not having macular edema (central 500 µm, Cirrus HD-OCT). Best corrected monocular distance visual acuity (BCVA), Amsler Test, Metamorphopsia Index of AMD - A Metamorphopsia Detector, binocular ophthalmoscopy, central retinal thickness (SD-OCT) and fluorescein angiography, if necessary, were performed. Correlation of central retinal thickness and metamorphopsia index was evaluated by Spearman correlation.

RESULTS: Mean BCVA (logMAR) was 0.27 (SD 0.3) in DME and 0.29 (SD 0.2) in AMD. Spearman's rho as a measure for correlation between CRT and MI was 0.88 (p < 0.001) in DME and 0.56 (p < 0.001) in AMD.

CONCLUSIONS: Correlation of CRT und MI was high in DME and moderate in AMD. Future studies will examine if metamorphopsia measurement is a feasible tool for detection of conversion into neovascular AMD and for (self-)monitoring.

PMID: 29490395

Curr Drug Deliv. 2018 Feb 26. [Epub ahead of print]

Biodegradable Microspheres as Intravitreal Delivery Systems for Prolonged Drug Release. What is their Eminence in the Nanoparticle Era?

Gavini E, Bonferoni MC, Rassu G, Obinu A, Ferrari F, Giunchedi P.

Abstract: Drug administration to the posterior segment of the eye has many challenges due to the natural barriers and consequent problems of low and unpredictable bioavailability. There is an increasing need for managing severe posterior eye diseases, such as age related macular degeneration, diabetic retinopathy, etc.: most of these diseases, if untreated, lead to blindness. Traditional ocular formulations and topical administrations are almost inefficient and the drug delivery to the back of the eye requires direct administrations through intravitreal injections of innovative drug delivery systems. These systems must be easily injectable, able to release the drug for a prolonged period of time (to overcome the problem of repeated administrations) and made of biodegradable/biocompatible polymers. Among these delivery systems microspheres still have an important role. This overview wants to highlight the use of microspheres as intravitreal systems to overcome the challenges of back of the eye diseases. Studies have shown that
microspheres are able to enhance the intravitreal half-life and thus bioavailability of many drugs, protecting them from degradation. Furthermore personalized therapies can be made by changing the amount of administered microspheres. The focus of this review has been done on the materials (polymers) used for the preparation of the microparticulate systems and comparative remarks are made with respect to the use of nanoparticles.

**Pathogenesis**

*Ophthalmologica. 2018 Feb 27. [Epub ahead of print]*

**Activation of the ERK1/2-MAPK Signaling Pathway by Complement Serum in UV-POS-Pretreated ARPE-19 Cells.**

Busch M, Wasmuth S, Spital G, Lommatzsch A, Pauleikhoff D.

BACKGROUND: Retinal pigment epithelial (RPE) cells undergo functional changes upon complement stimulation, which play a role in the pathogenesis of age-related macular degeneration (AMD). These effects are in part enhanced by pretreating ARPE-19 cells with UV-irradiated photoreceptor outer segments (UV-POS) in vitro. The aim of this study was to investigate the effects of human complement serum (HCS) treatment on p44/42 mitogen-activated protein kinase (extracellular signal-regulated kinase 1/2 [ERK1/2]) activation in ARPE-19 cells pretreated with UV-POS.

METHODS: UV-POS-pretreated ARPE-19 cells were stimulated with 5% HCS or heat-inactivated HCS (HI-HCS) as a control. Protein expression of phosphorylated (activated) ERK1/2, total ERK1/2, Bax, and Bcl-2 was analyzed by Western blotting. Cell culture supernatants were analyzed for IL-6, IL-8, MCP-1, and VEGF by enzyme-linked immunosorbent assay (ELISA). Furthermore, extra- and intracellular reactive oxygen species (ROS) were determined.

RESULTS: The amount of phosphorylated ERK1/2 was increased in UV-POS-pretreated ARPE-19 cells, especially in combination with HCS stimulation, compared to non-pretreated ARPE-19 cells incubated with HCS alone or HI-HCS. The same observation was made for Bax and Bcl-2 expression. Furthermore, an increase in extra- and intracellular ROS was detected in UV-POS-pretreated ARPE-19 cells. The ELISA data showed that the production of IL-6, IL-8, and MCP-1 tended to increase in response to HCS in both UV-POS-pretreated and non-pretreated ARPE-19 cells.

CONCLUSIONS: Our data imply that ERK1/2 activation in ARPE-19 cells may represent a response mechanism to cellular and oxidative stress, associated with apoptosis-regulating factors such as Bax and Bcl-2, which might play a role in AMD, while ERK1/2 seems not to represent the crucial signaling pathway mediating the functional changes in RPE cells in response to complement stimulation.

**Biogerontology. 2018 Feb 28. [Epub ahead of print]**

**Involvement of the autophagic pathway in the progression of AMD-like retinopathy in senescence-accelerated OXYS rats.**

Kozhevnikova OS, Telegina DV, Devyatkin VA, Kolosova NG.

Abstract: Age-related macular degeneration (AMD) is a complex neurodegenerative disease resulting in a loss of central vision in the elderly. It is currently assumed that impairment of autophagy may be one of the key mechanisms leading to AMD. Here we estimated the influence of age-related autophagy alterations in the retina on the development of AMD-like retinopathy in senescence-accelerated OXYS rats. Significant changes in the expression of the autophagy proteins were absent at the age preceding the development of
Human aging and disease: Lessons from age-related macular degeneration.

Luu J, Palczewski K.

Abstract: Aging is the most significant risk factor associated with chronic disease in humans. The accumulation of genetic damage throughout life leads to a variety of biological aberrations, including disrupted protein homeostasis, metabolic dysfunction, and altered cellular signaling. Such changes ultimately result in cellular senescence, death, or transformation to uncontrolled proliferation, thereby compromising human health. Events contributing to age-dependent physiological decline also occur in the context of hormonal and metabolic changes, affecting interconnected cellular networks. This complexity often confounds the development of effective treatments for aging and age-related diseases. In contrast to monotherapy and polypharmacology, an innovative systems pharmacology approach can identify synergistic combinations of drugs that modulate distinct mechanistic nodes within a network, minimizing off-target side effects and enabling better therapeutic outcomes. G protein-coupled receptors (GPCRs) are particularly good targets for the application of systems pharmacology, because they activate different signal transduction pathways that can culminate in a common response. Here, we describe a systems pharmacology strategy for the treatment of age-related macular degeneration (AMD), a multifactorial chronic disease of the eye. By considering the retina as part of a large, interconnected network, systems pharmacology will enable the identification of combination therapies targeting GPCRs to help restore genomic, proteomic, and endocrine homeostasis. Such an approach can be advantageous in providing drug regimens for the treatment of AMD, while also having broader ramifications for ameliorating adverse effects of chronic, age-related disease in humans.

PMID: 29483257
regulated splicing and, relative to the first-generation SRPK inhibitor SRPIN340 or small interfering RNA-mediated SRPK knockdown, SRPKIN-1 is more potent in converting the pro-angiogenic VEGF-A165a to the anti-angiogenic VEGF-A165b isoform and in blocking laser-induced neovascularization in a murine retinal model. These findings encourage further development of SRPK inhibitors for treatment of age-related macular degeneration.

PMID: 29478907

Biomed Pharmacother. 2018 Feb 22;101:87-93. [Epub ahead of print]

Nepetin inhibits IL-1β induced inflammation via NF-κB and MAPKs signaling pathways in ARPE-19 cells.


BACKGROUND: Chronic inflammation in retinal pigment epithelial (RPE) cells is related to the pathogenesis of retinal inflammatory blind causing diseases such as age-related macular degeneration (AMD) and diabetic retinopathy (DR). Nepetin, a natural flavonoid compound, has shown potent anti-inflammatory activities but has not been studied on ocular resident cells yet. Here, we assess the ability of Nepetin to alleviate the inflammatory responses of ARPE-19 cells induced by interleukin (IL)-1β.

METHODS: The secretion and mRNA expression of inflammatory cytokines IL-6, IL-8 and monocyte chemoattractant protein-1 (MCP-1) induced by IL-1β are measured by enzyme-linked immunosorbent assay (ELISA) and real-time polymerase chain reaction (RT-PCR) respectively. To clarify the underlying action mechanism, we examine the effect of Nepetin on activation of nuclear factor of kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways using Western blot.

RESULTS: Nepetin can significantly decrease the three inflammatory mediators at both protein and mRNA level in a dose-dependent manner. Western blot results show that Nepetin can decrease the nuclear translocation of p65 through suppressing phosphorylation of inhibitor of nuclear factor kappa B (IκB) and IκB kinase (IKK). Also, Nepetin can decrease the phosphorylation of extracellular signal-regulated kinases (ERK) 1/2, c-Jun N-terminal kinase (JNK) and p38 MAPK.

CONCLUSIONS: Taken together, Nepetin abolishes IL-1β-induced IL-6, IL-8 and MCP-1 secretion and mRNA expression by repressing the activation of NF-κB and MAPKs. These results indicate that Nepetin shows potential to be used for prevention and treatment of inflammatory retinal diseases or as a lead compound.

PMID: 29477475

Biochim Biophys Acta. 2018 Feb 23;1864(5 Pt A):1583-1595. [Epub ahead of print]

Suppression of aberrant choroidal neovascularization through activation of the aryl hydrocarbon receptor.

Choudhary M, Safe S, Malek G.

Abstract: the aryl hydrocarbon receptor (AhR) is a ligand activated transcription factor, initially discovered for its role in regulating xenobiotic metabolism. There is extensive evidence supporting a multi-faceted role for AhR, modulating physiological pathways important in cell health and disease. Recently we demonstrated that the AhR plays a role in the pathogenesis of age-related macular degeneration (AMD), the leading cause of vision loss in the elderly. We found that loss of AhR exacerbates choroidal neovascular (CNV) lesion formation in a murine model. Herein we tested the therapeutic impact of AhR activation on CNV lesion formation and factors associated with aberrant neovascularization. We screened a panel of synthetic drugs and endogenous AhR ligands, assessed their ability to activate AhR in choroidal endothelial cells, and inhibit angiogenesis in vitro. Drugs with an anti-angiogenic profile were then administered to a murine
Two compounds, leflunomide and flutamide, significantly inhibited CNV formation concurrent with positive modifying effects on angiogenesis, inflammation, extracellular matrix remodeling, and fibrosis. These results validate the role of the AhR pathway in regulating CNV pathogenesis, identify mechanisms of AhR-based therapies in the eye, and argue in favor of developing AhR as a drug target for the treatment of neovascular AMD.

PMID: 29481912

Retinal Degeneration, Remodeling and Plasticity.

Jones BW, Marc RE, Pfeiffer RL.

Editors In: Kolb H, Fernandez E, Nelson R, editors. SourceWebvision: The Organization of the Retina and Visual System [Internet]. Salt Lake City (UT): University of Utah Health Sciences Center; 1995-.


Excerpt: Retinal degeneration and remodeling encompasses a group of pathologies at the molecular, cellular and tissue levels that are initiated by inherited retinal diseases like retinitis pigmentosa (RP), genetic and environmental diseases like age-related macular degeneration (AMD) and other insults to the eye/retina including trauma and retinal detachment. These retinal changes and apparent plasticity result in neuronal rewiring and reprogramming events that include alterations in gene expression, de novo neuritogenesis as well as formation of novel synapses, creating corruptive circuitry in bipolar cells through alterations in the dendritic tree and supernumerary axonal growth. In addition, neuronal migration occurs throughout the vertical axis of the retina along Müller cell columns showing altered metabolic signals, and retinal pigment epithelium (RPE) invades the retina forming the pigmented bone spicules that have been classic clinical observations of RP diseases. Retinal photoreceptors drive signal processing networks in the neural retina comprising bipolar, horizontal, amacrine and ganglion cells. It has been historically thought that retinal degenerative diseases such as RP affect the sensory retina, leaving the neural retina relatively unscathed. This is incorrect as the resulting loss of rod and cone input to the neural retina constitutes deafferentation and remodeling at the cellular and molecular level becomes unavoidable (1-22) . Retinal degenerative diseases have a number of potential initiating events that result from naturally occurring disease processes (23), trauma like retinal detachment (24, 25) or any of the forms of retinitis pigmentosa (5, 23, 26, 27), but regardless of cause, if photoreceptors are lost, particularly cones, a sequence of progressive events is initiated that induces negative plastic remodeling of the neural retina (9-11, 14, 15, 21, 22, 28, 29). Essentially every disease process that results in photoreceptor loss triggers retinal remodeling as the final common pathway culminating with cell death and topological restructuring of the retina. The progression of retinal remodeling is like the negative plasticity that occurs in CNS pathologies like trauma and epilepsy and constitutes substantial impediments to rescue strategies of all types.

Sections:

1. Introduction
2. Phases of retinal remodeling.
3. Age-related macular degeneration (AMD).
4. Retinitis pigmentosa (RP)
5. Historical histological methods.
6. Plasticity in the retina.
7. The plasticity and remodeling that occurs in retinitis pigmentosa like diseases in mammalian retinas.
8. The TgP347L rabbit and P23H porcine models of retinitis pigmentosa
9. The earliest changes in the retina occur before obvious histological changes occur.

10. Conclusion

PMID: 29493934

**Epidemiology**


Projection of Eye Disease Burden in Singapore.

Ansah JP, Koh V, de Korne DF, Bayer S, Pan C, Thiyagarajan J, Matchar DB, Lamoureux E, Quek D.

INTRODUCTION: Singapore's ageing population is likely to see an increase in chronic eye conditions in the future. This study aimed to estimate the burden of eye diseases among resident Singaporeans stratified for age and ethnicity by 2040.

MATERIALS AND METHODS: Prevalence data on myopia, epiretinal membrane (ERM), retinal vein occlusion (RVO), age macular degeneration (AMD), diabetic retinopathy (DR), cataract, glaucoma and refractive error (RE) by age cohorts and educational attainment from the Singapore Epidemiology of Eye Diseases (SEED) study were applied to population estimates from the Singapore population model.

RESULTS: All eye conditions are projected to increase by 2040. Myopia and RE will remain the most prevalent condition, at 2.393 million (2.32 to 2.41 million) cases, representing a 58% increase from 2015. It is followed by cataract and ERM, with 1.33 million (1.31 to 1.35 million), representing an 81% increase, and 0.54 million (0.53 to 0.549 million) cases representing a 97% increase, respectively. Eye conditions that will see the greatest increase from 2015 to 2040 in the Chinese are: DR (112%), glaucoma (100%) and ERM (91.4%). For Malays, DR (154%), ERM (136%), and cataract (122%) cases are expected to increase the most while for Indians, ERM (112%), AMD (101%), and cataract (87%) are estimated to increase the most in the same period.

CONCLUSION: Results indicate that the burden for all eye diseases is expected to increase significantly into the future, but at different rates. These projections can facilitate the planning efforts of both policymakers and healthcare providers in the development and provision of infrastructure and resources to adequately meet the eye care needs of the population. By stratifying for age and ethnicity, high risk groups may be identified and targeted interventions may be implemented.

PMID: 29493707

**Genetics & gene therapy**


Uncovering genetic and non-genetic biomarkers specific for exudative age-related macular degeneration: significant association of twelve variants.


Abstract: Age-related Macular Degeneration (AMD) represents one of the most sight-threatening diseases in developed countries that substantially impacts the patients' lifestyle by compromising everyday activities, such as reading and driving. In this context, understanding the prevalence, burden, and population-specific risk/protective factors of AMD is essential for adequate health care planning and provision. Our work aimed to characterize exudative AMD in Italian population and to identify the susceptibility/protective factors
(genetic variants, age, sex, smoking and dietary habits) which are specific for the onset of disease. Our study involved a cohort of 1976 subjects, including 976 patients affected with exudative AMD and 1000 control subjects. In particular, the sample cohort has been subjected to a large genotyping analysis of 20 genetic variants which are known to be associated with AMD among European and Asiatic populations. This analysis revealed that 8 genetic variants (CFH, ARMS2, IL-8, TIMP3, SLC16A8, RAD51B, VEGFA and COL8A1) were significantly associated with AMD susceptibility. Successively, we performed a multivariate analysis, considering both genetic and non-genetic data available for our sample cohort. The multivariate analysis showed that age, smoking, dietary habits and sex, together with the genetic variants, were significantly associated with AMD in our population. Altogether, these data represent a starting point for the set-up of adequate preventive and personalized strategies aimed to decrease the burden of disease and improve the patients’ quality of life.

PMID: 29487693 PMCID: PMC5814260

**Diet, lifestyle & low vision**


**The effect of non-neovascular age-related macular degeneration on face recognition performance.**

Taylor DJ, Smith ND, Binns AM, Crabb DP.

PURPOSE: There is a well-established research base surrounding face recognition in patients with age-related macular degeneration (AMD). However, much of this existing research does not differentiate between results obtained for ‘wet' AMD and ‘dry' AMD. Here, we test the hypothesis that face recognition performance is worse in patients with dry AMD compared with visually healthy peers.

METHODS: Patients (>60 years of age, logMAR binocular visual acuity 0.7 or better) with dry AMD of varying severity and visually healthy age-related peers (controls) completed a modified version of the Cambridge Face Memory Test (CFMT). Percentage of correctly identified faces was used as an outcome measure for performance for each participant. A 90% normative reference limit was generated from the distribution of CFMT scores recorded in the visually healthy controls. Scores for AMD participants were then specifically compared to this limit, and comparisons between average scores in the AMD severity groups were investigated.

RESULTS: Thirty patients (median [interquartile range] age of 76 [70, 79] years) and 34 controls (median age of 70 [64, 75] years) were examined. Four, seventeen and nine patients were classified as having early, intermediate and late AMD (geographic atrophy) respectively. Five (17%) patients recorded a face recognition performance worse than the 90% limit (Fisher’s exact test, p = 0.46) set by controls; four of these had geographic atrophy. Patients with geographic atrophy identified fewer faces on average (±SD) (61% ± 22%) than those with early and intermediate AMD (75 ± 11%) and controls (74% ± 11%).

CONCLUSIONS: People with dry AMD may not suffer from problems with face recognition until the disease is in its later stages; those with late AMD (geographic atrophy) are likely to have difficulty recognising faces. The results from this study should influence the management and expectations of patients with dry AMD in both community practice and hospital clinics.

PMID: 29484559


**Visual function metrics in early and intermediate dry age-related macular degeneration for use as clinical trial endpoints.**

PURPOSE: To evaluate and quantify visual function metrics to be used as endpoints of AMD stages and visual acuity (VA) loss in patients with early and intermediate AMD.

DESIGN: Cross-sectional analysis of baseline data from a prospective study.

METHODS: 101 patients were enrolled at Duke Eye Center: 80 patients with early AMD age-related eye disease study (AREDS) stage 2 (N=33) and intermediate stage 3 (N=47) and 21 age-matched, normal controls. A dilated retinal examination, macular pigment optical density measurements, and several functional assessments: best-corrected VA, MAIA mesopic microperimetry, dark adaptometry, low luminance VA (LLVA) (standard using a log 2.0 neutral density filter and computerized method) and cone contrast test (CCT) were performed. Low luminance deficit (LLD) was defined as the difference in numbers of letters read at standard vs. low luminance. Group comparisons were performed to evaluate differences between the control and the early and intermediate AMD groups using two-sided significance tests.

RESULTS: Functional measures that significantly distinguished between normal and intermediate AMD were standard and computerized (0.5 cd/m²) LLVA, percent reduced threshold and average threshold on microperimetry, CCTs, and rod intercept on dark adaptation (p < 0.05). The intermediate group demonstrated deficits in microperimetry reduced threshold, computerized LLD2 and dark adaptation (p < 0.05) relative to early AMD.

CONCLUSIONS and Relevance: Our study suggests that LLVA, microperimetry, CCT and dark adaptation may serves as functional measures differentiating early-intermediate stages of dry AMD.

PMID: 29477964

Lab Anim (NY). 2018 Feb 26. [Epub ahead of print]

New technologies for developing second generation retinal prostheses.

Benfenati F, Lanzani G.

Abstract: Inherited or age-dependent retinal dystrophies such as Retinitis pigmentosa (RP) and macular degeneration (MD) are among the most prevalent causes of blindness. Despite enormous efforts, no established pharmacological treatment to prevent or cure photoreceptor degeneration has been identified. Given the relative survival of the inner retina, attempts have been made to restore vision with optogenetics or with retinal neuroprostheses to allow light-dependent stimulation of the inner retinal network. While microelectrode and photovoltaic devices based on inorganic technologies have been proposed and in many cases implanted in RP patients, a new generation of prosthetics based on organic molecules, such as organic photoswitches and conjugated polymers, is demonstrating an unexpected potential for visual rescue and intimate interactions with functioning tissue. Organic devices are starting a new era of tissue electronics, in which light-sensitive molecules and live tissues integrate and tightly interact, producing a new ecosystem of organic prosthetics and intelligent biotic/abiotic interfaces. In addition to the retina, the applications of these interfaces might be extended in the future to other biomedical fields.

PMID: 29483694