Drug treatment


One-year outcome of intravitreal ziv-aflibercept therapy for non-responsive neovascular age-related macular degeneration.


AIM: To evaluate 12-month outcome of intravitreal ziv-aflibercept (IVZ) therapy in eyes with neovascular age-related macular degeneration (nAMD) that are non-responsive to bevacizumab and ranibizumab.

METHODS: This retrospective study included 16 eyes (14 patients) with nAMD who were on prior treatment with bevacizumab and ranibizumab and were treated with as-needed IVZ (1.25 mg/0.05 mL) for 12 months. The primary outcome measure was the mean change in best corrected visual acuity (BCVA) and secondary outcome measures included mean change in central macular thickness (CMT), retinal pigment epithelial detachment (RPED) heights, longest treatment free interval, presence of subretinal fluid (SRF) and intraretinal fluid (IRF) and adverse events.

RESULTS: There was no change in the mean logarithm of minimum angle of resolution (logMAR) BCVA at baseline and following treatment with IVZ therapy (p=0.978). The mean number of IVZ injections during 12 months was 5.9±3.3, and the mean number of antivascular endothelial growth factors (VEGFs) injections prior to switching to IVZ was 8.4±4.7. The mean treatment free interval was longer during IVZ therapy (114.4±67.1 days) compared with 76.3±54.6 days before IVZ therapy (p=0.03). Five (31.25%) eyes had visual gains of at least 0.1 logMAR, 3 (18.75%) eyes had stable BCVA (within 0.1 logMAR) and 8 (50%) eyes had BCVA decline of at least 0.1 logMAR. There was no significant difference in the mean CMT, RPED heights and presence of IRF and SRF at 12 months compared with baseline. No adverse events were noted.

CONCLUSION: IVZ increased the treatment free interval in non-responders but no significant change in visual and anatomic outcomes.

PMID: 28596286


HEMORRHAGIC VASCULITIS AND RETINOPATHY HERALDING AS AN EARLY SIGN OF BACTERIAL ENDOPHTHALMITIS AFTER INTRAVITREAL INJECTION.

Conrady CD, Feistmann JA, Roller AB, Boldt HC, Shakoor A.

PURPOSE: To describe a case series of postintravitreal injection, bacterial endophthalmitis heralded by hemorrhagic retinal vasculitis.
METHODS: Observational case series of three patients with a history of intravitreal injections for age-related macular degeneration at a tertiary referral center who presented with vision changes and eye pain that were eventually found to have bacterial endophthalmitis. Clinical course was then followed.

RESULTS: All patients developed bacterial endophthalmitis and hemorrhagic retinal vasculitis.

CONCLUSION: These three cases highlight the importance of hemorrhagic retinal vasculitis as the presenting fundus finding of bacterial endophthalmitis and that this finding in a postinjection patient should be treated as endophthalmitis until proven otherwise.

PMID: 28594738


Vitreomacular adhesion or vitreomacular traction may affect antivascular endothelium growth factor treatment for neovascular age-related macular degeneration.


OBJECTIVE: The aim of this review is to determine whether vitreomacular adhesion (VMA) or vitreomacular traction (VMT) has an influence on the outcomes of antivascular endothelium growth factor (anti-VEGF) treatment neovascular age-related macular degeneration (nAMD).

METHODS: A systematic literature search was performed in Pubmed.gov, Cochrane Library, Web of Science, China National Knowledge Infrastructure, Wanfang, SinoMed and ClinicalTrials.gov up to 30 June 2016 to identify eligible studies.

RESULTS: Nine studies and 2212 participants were finally identified. At month 6, the mean improvement in best-corrected visual acuity (BCVA) and mean decline in central retinal thickness (CRT) of the VMA/VMT(+) group was less than that of the VMA/VMT(-) group (95% CI -3.05 to -0.96 letters, p=0.0002; 15.53 to 32.98 μm, p<0.00001; respectively); at month 12, there was a small or only marginally significant difference (-0.01 to 2.00 letters, p=0.05; 0.17 to 23.7 μm, p=0.05; respectively) between the groups. During the 12 months, however, the VMA/VMT(+) group required more injections ((0.25 to 0.95), p=0.0008).

CONCLUSIONS: In using anti-VEGF drugs to treat nAMD, clinicians should take into account the fact that concurrent VMA or VMT might antagonise the efficacy of anti-VEGF drugs during the early stage of treatment.

PMID: 28596285


Evaluating the impact of vitreomacular adhesion on anti-VEGF therapy for retinal vein occlusion using machine learning.

Waldstein SM, Montuoro A, Podkowinski D, Philip AM, Gerendas BS, Bogunovic H, Schmidt-Erfurth U.

Abstract: Vitreomacular adhesion (VMA) represents a prognostic biomarker in the management of exudative macular disease using anti-vascular endothelial growth factor (VEGF) agents. However, manual evaluation of VMA in 3D optical coherence tomography (OCT) is laborious and data on its impact on therapy of retinal vein occlusion (RVO) are limited. The aim of this study was to (1) develop a fully automated segmentation algorithm for the posterior vitreous boundary and (2) to study the effect of VMA on anti-VEGF therapy for RVO. A combined machine learning/graph cut segmentation algorithm for the posterior vitreous boundary was designed and evaluated. 391 patients with central/branch RVO under standardized ranibizumab treatment for 6/12 months were included in a systematic post-hoc analysis. VMA
(70%) was automatically differentiated from non-VMA (30%) using the developed method combined with unsupervised clustering. In this proof-of-principle study, eyes with VMA showed larger BCVA gains than non-VMA eyes (BRVO: 15 ± 12 vs. 11 ± 11 letters, p = 0.02; CRVO: 18 ± 14 vs. 9 ± 13 letters, p < 0.01) and received a similar number of retreatments. However, this association diminished after adjustment for baseline BCVA, also when using more fine-grained VMA classes. Our study illustrates that machine learning represents a promising path to assess imaging biomarkers in OCT.

PMID: 28592811 PMCID: PMC5462785

Retina. 2017 Jan 11. [Epub ahead of print]

RECURRENT CHOROIDAL NEOVASCULARIZATION LESION ACTIVITY AFTER AFLIBERCEPT TREATMENT FOR AGE-RELATED MACULAR DEGENERATION.


PURPOSE: To examine the recurrence rate of choroidal neovascularization (CNV) lesion activity in age-related macular degeneration (AMD) and associated factors after 1-year aflibercept treatment.

METHODS: Age-related macular degeneration eyes with 1-year aflibercept fixed-regimen treatment and a follow-up period of at least 18 months from the initial aflibercept injection for treatment-naive exudative AMD were retrospectively evaluated. The recurrence rate was examined. Age, gender, visual acuity, AMD subtype, greatest linear dimension, and retinal and choroidal thicknesses at the 12th month examination were compared between eyes with and without recurrence. Presence of remnant polyps and pigment epithelial detachment (PED) morphology were also compared in polypoidal choroidal vasculopathy (PCV) eyes.

RESULTS: Of the 98 eyes studied, 69 displayed a dry macula at the 12th month examination; 43.7% exhibited recurrence during the subsequent 12-month period in Kaplan-Meier analysis. Although no factors associated with recurrence were detected in AMD, remnant polyps and pigment epithelial detachment morphology at the 12th month examination were significantly associated with recurrence in polypoidal choroidal vasculopathy (P = 0.018 and 0.048, respectively).

CONCLUSION: Continuous, proactive treatment would be considered overtreatment for more than half of the AMD eyes that achieved a dry macula. Angiography and optical coherence tomography analyses may be useful for predicting recurrence in polypoidal choroidal vasculopathy eyes.

PMID: 28590316

MAbs. 2017 Jun 6:0. [Epub ahead of print]

Tuning the specificity of a Two-in-One Fab against three angiogenic antigens by fully utilizing the information of deep mutational scanning.

Koenig P, Sanowar S, Lee CV, Fuh G.

Abstract: Monoclonal antibodies developed for therapeutic or diagnostic purposes need to demonstrate highly defined binding specificity profiles. Engineering of an antibody to enhance or reduce binding to related antigens is often needed to achieve the desired biological activity without safety concern. Here, we describe a deep sequencing-aided engineering strategy to fine-tune the specificity of an angiopoietin-2 (Ang2)/vascular endothelial growth factor (VEGF) dual action Fab, 5A12.1 for the treatment of age-related macular degeneration. This antibody utilizes overlapping complementarity-determining region (CDR) sites for dual Ang2/VEGF interaction with KD in the sub-nanomolar range. However, it also exhibits significant
(KD of 4 nM) binding to angiopoietin-1, which has high sequence identity with Ang2. We generated a large phage-displayed library of 5A12.1 Fab variants with all possible single mutations in the six CDRs. By tracking the change of prevalence of each mutation during various selection conditions, we identified 35 mutations predicted to decrease the affinity for Ang1 while maintaining the affinity for Ang2 and VEGF. We confirmed the specificity profiles for 25 of these single mutations as Fab protein. Structural analysis showed that some of the Fab mutations cluster near a potential Ang1/2 epitope residue that differs in the two proteins, while others are up to 15 Å away from the antigen-binding site and likely influence the binding interaction remotely. The approach presented here provides a robust and efficient method for specificity engineering that does not require prior knowledge of the antigen antibody interaction and can be broadly applied to antibody specificity engineering projects.

PMID: 28585908


Keratoacanthoma of the Nasal Septum Secondary to Ranibizumab Use.

Cohn JE, Caruso Sales HM, Nguyen GH, Spector H, Briskin K.

Abstract: Keratoacanthoma (KA) is a benign epithelial tumor that typically presents as a firm, cone-shaped, flesh-colored nodule with a central horn-filled crater. KA is considered to be a low-grade variant of squamous cell carcinoma (SCC). We report a rare case of a 72-year-old male who presented with a KA involving the nasal septum, possibly related to ranibizumab use. A flesh-colored lesion on the right anterior nasal septum lesion was visualized on examination. Histologic examination revealed a well-circumscribed, dome-shaped central crater filled with keratin, well-differentiated squamous epithelium with ground-glass cytoplasm with pushing margins, and intraepithelial microabscesses establishing the diagnosis of KA. KA of the nasal septum has only been reported once in the literature. This case is unusual because it normally presents on sun-exposed areas. Additionally, this patient was taking ranibizumab, a vascular endothelial growth factor (VEGF) inhibitor for macular degeneration. Despite ranibizumab not being directly linked to precancerous and cancerous skin lesions, agents in this medication class have been. Although it is difficult to prove associations in this isolated case, the role of ranibizumab causing cutaneous lesions should be further investigated.

PMID: 28584672 PMCID: PMC5443992

Other treatment & diagnosis


Evaluation of intraretinal migration of retinal pigment epithelial cells in age-related macular degeneration using polarimetric imaging.


Abstract: The purpose of the present study was to evaluate the intraretinal migration of the retinal pigment epithelium (RPE) cells in age-related macular degeneration (AMD) using polarimetry. We evaluated 155 eyes at various AMD stages. Depolarized light images were computed using a polarization-sensitive scanning laser ophthalmoscope (PS-SLO), and the degree of polarization uniformity was calculated using polarization-sensitive optical coherence tomography (OCT). Each polarimetry image was compared with the corresponding autofluorescence (AF) images at 488 nm (SW-AF) and at 787 nm (NIR-AF). Intraretinal RPE migration was defined by the presence of depolarization at intraretinal hyperreflective foci on PS-SLO and PS-OCT images, and by the presence of hyper-AF on both NIR-AF and SW-AF images. RPE migration was detected in 52 of 155 eyes (33.5%) and was observed in drusenoid pigment epithelial detachment (PED) and serous PED with significantly higher frequencies than in other groups (P = 0.015). The volume of
the migrated RPE cluster in serous PED was significantly correlated with the volume of the PED (R² = 0.26; P = 0.011). Overall, our results showed that intraretinal RPE migrations occurred in various AMD stages, and that they occurred more commonly in eyes with serous and drusenoid PED.

PMID: 28600515 PMCID: PMC5466639

[Characteristics and Clinical Significance of Outer Retinal Tubulation in Wet Age-macular Degeneration Treated by Anti-vascular Endothelial Growth Factor Through Optical Coherence Tomography.] [Article in Chinese]
Zuo C, Li X, Zhang ZR, Zhang MX.
OBJECTIVES: To determine the characteristics and clinical significance of outer retinal tabulation (ORT) in wet age-related macular degeneration (wAMD) treated by anti-vascular endothelial growth factor (anti-VEGF) through optical coherence tomography (OCT).
METHODS: The 35 wAMD patients with 39 ORT eyes treated by anti-VEGF were examined by OCT to determine the morphological features and evolution of the ORTs over time and their response to anti-VEGF.
RESULTS: ORTs were located in the places that exudation or edema had happened in the outer nuclear layer of retina. 38 ORTs remained stable on both quantity and morphology. One ORT became invisible temporarily and then reappeared.
CONCLUSIONS:
ORTs are reconstructed by photoreceptor cells that have survived after outer retina damages. There is no connection between anti-VEGF treatment and ORT formation.
PMID: 28598120

Natural History of Rod-Mediated Dark Adaptation over 2 Years in Intermediate Age-Related Macular Degeneration.
PURPOSE: To characterize the natural history of rod-mediated dark adaptation (RMDA) over 2 years in eyes with intermediate age-related macular degeneration (AMD). This information will be useful in understanding the potential of RMDA to serve as a functional endpoint in proof-of-concept studies and clinical trials on intermediate AMD.
METHODS: RMDA was measured in eyes with intermediate AMD at baseline and follow-up visits over 2 years at 6, 12, 18, and 24 months. A computerized dark adaptometer measured sensitivity for targets centered at 11° on the superior vertical meridian of the retina. Rod intercept time (RIT) characterized the speed of dark adaptation and was defined as the duration (in minutes) required for sensitivity to reach a criterion level of 3.0 log units of attenuation of the stimulus.
RESULTS: Mean change in RIT over 24 months for 30 eyes was 10.5 minutes (standard deviation 19.4), p < 0.0001; 73.3% of eyes had a RIT increase >1 minute, 56.7% had an increase >3 minutes, and 36.7% had an increase >6 minutes; for 26.7% RIT was unchanged (0- to 1-minute increase) or decreased. Greater increase in RIT over 24 months was associated with smoking.
CONCLUSIONS: RMDA slows in intermediate AMD over 2 years in most eyes. There was wide variability in RIT at both baseline and in the extent to which it increased over 24 months. A major risk factor for AMD, smoking, exacerbated RMDA slowing.

TRANSLATIONAL RELEVANCE:

RMDA as assessed by RIT may be useful as a functional endpoint in proof-of-concept studies and clinical trials on intermediate AMD with 2-year designs.

PMID: 28593103 PMCID: PMC5461063

Retina. 2017 May 2. [Epub ahead of print]

BIOMARKERS OF NEOVASCULAR ACTIVITY IN AGE-RELATED MACULAR DEGENERATION USING OCT ANGIOGRAPHY.

Al-Sheikh M, Iafe NA, Phasukkijwatana N, Sadda SR, Sarraf D.

PURPOSE: To study the qualitative and quantitative features of choroidal neovascular (NV) membranes in age-related macular degeneration using optical coherence tomography angiography in patients with active and quiescent NV lesions before and after treatment with anti-vascular endothelial growth factor.

METHODS: Macular optical coherence tomography angiography images were obtained using RTVue XR Avanti with AngioVue. Morphologic features and quantitative measurements of the NV lesion were analyzed using en face projection images. The NV lesion was subdivided into inner segment and outer fringe for further fractal dimension analysis.

RESULTS: In a series of 31 eyes, 11 eyes with active NV lesions at baseline and after consecutive follow-up after treatment with anti-vascular endothelial growth factor therapy and 20 eyes with quiescent NV lesions were included in this study. Morphologically, all the quiescent NV lesions versus 63.6% of the active NV lesions demonstrated a prominent central vessel and active lesions demonstrated a greater rate of small vessels branching (82%) and peripheral arcades (82%) than quiescent lesions (30% and 40% respectively) and this was statistically significant. The lesion area and vessel density was not statistically significantly different after treatment or versus quiescent lesions although the latter lesions were reduced in area. Lesion pattern complexity measured by the fractal dimension was statistically significantly lower in the inner part of the lesion after treatment and statistically significantly lower in the total lesion of the quiescent NV compared with the active NV.

CONCLUSION: Optical coherence tomography angiography is a new, noninvasive imaging modality that can be used to perform qualitative and quantitative analyses of NV lesions. In the future, OCT angiography may provide biomarkers of activity and guide the evaluation and treatment and monitoring of neovascularization in age-related macular degeneration.

PMID: 28582276


Interactome Mapping Guided by Tissue-Specific Phosphorylation in Age-Related Macular Degeneration.

Sripathi SR, He W, Prigge CL, Sylvester O, Um JY, Powell FL, Neksumi M, Bernstein PS, Choo DW, Bartoli M, Gutsaeva DR, Jahng WJ.

Abstract: The current study aims to determine the molecular mechanisms of age-related macular degeneration (AMD) using the phosphorylation network. Specifically, we examined novel biomarkers for
oxidative stress by protein interaction mapping using in vitro and in vivo models that mimic the complex and progressive characteristics of AMD. We hypothesized that the early apoptotic reactions could be initiated by protein phosphorylation in region-dependent (peripheral retina vs. macular) and tissue-dependent (retinal pigment epithelium vs. retina) manner under chronic oxidative stress. The analysis of protein interactome and oxidative biomarkers showed the presence of tissue- and region-specific post-translational mechanisms that contribute to AMD progression and suggested new therapeutic targets that include ubiquitin, erythropoietin, vitronectin, MMP2, crystalline, nitric oxide, and prohibitin. Phosphorylation of specific target proteins in RPE cells is a central regulatory mechanism as a survival tool under chronic oxidative imbalance. The current interactome map demonstrates a positive correlation between oxidative stress-mediated phosphorylation and AMD progression and provides a basis for understanding oxidative stress-induced cytoskeletal changes and the mechanism of aggregate formation induced by protein phosphorylation. This information could provide an effective therapeutic approach to treat age-related neurodegeneration.

PMID: 28580316 PMCID: PMC5450497


Optical Coherence Tomographic Angiography Imaging in Age-Related Macular Degeneration.

Ma J, Desai R, Nesper P, Gill M, Fawzi A, Skondra D.

Abstract: Optical coherence tomographic angiography (OCTA) is emerging as a rapid, noninvasive imaging modality that can provide detailed structural and flow information on retinal and choroidal vasculature. This review contains an introduction of OCTA and summarizes the studies to date on OCTA imaging in age-related macular degeneration.

PMID: 28579843 PMCID: PMC5422508

Surv Ophthalmol. 2017 Jun 1. [Epub ahead of print]

The use of microperimetry in assessing visual function in age-related macular degeneration.

Cassels NK, Wild JM, Margrain TH, Chong V, Acton JH.

Abstract: Microperimetry is a novel technique for assessing visual function and appears particularly suitable for age-related macular degeneration (AMD). Compared to standard automated perimetry (SAP), microperimetry offers several unique features. It simultaneously images the fundus, incorporates an eye tracking system to correct the stimulus location for fixation loss, and identifies any preferred retinal loci. A systematic review of microperimetry in the assessment of visual function in AMD identified 680 articles. Of these, 52 met the inclusion criteria. We discuss microperimetry and AMD in relation to disease severity, structural imaging outcomes, other measures of visual function, and evaluation of the efficacy of surgical and/ or medical therapies in clinical trials. The evidence for the use of microperimetry in the functional assessment of AMD is encouraging. Disruptions of the ellipsoid zone band and retinal pigment epithelium (RPE) are clearly associated with reduced differential light sensitivity (DLS) despite the maintenance of good visual acuity. Reduced DLS is also associated with outer segment thinning and RPE thickening in early AMD and with both a thickening and a thinning of the whole retina in choroidal neovascularization. Microperimetry, however, lacks the robust diffuse and focal loss age-corrected probability analyses associated with SAP, and the technique is currently limited by this omission.

PMID: 28579549

Choroidal Changes Associated with Subretinal Drusenoid Deposits in Age-related Macular Degeneration using Swept-source OCT.


PURPOSE: To compare choroidal vascular features of eyes with and without subretinal drusenoid deposits (SDD), using swept-source optical coherence tomography (SS-OCT).

DESIGN: Multicenter, cross-sectional study.

METHODS: We prospectively recruited patients with intermediate age-related macular degeneration (AMD), without other vitreoretinal pathology. All participants underwent complete ophthalmic exam, color fundus photography (used for AMD staging), and spectral-domain OCT (to evaluate the presence of SDD). SS-OCT was used to obtain automatic macular choroidal thickness (CT) maps, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) sectors. For data analysis, we considered mean choroidal thickness as the arithmetic mean value of the 9 ETDRS sectors. SS-OCT en face images of choroidal vasculature were also captured and converted to binary images. Choroidal vascular density (CVD) was calculated as a percent area occupied by choroidal vessels in a 6-mm diameter submacular circular. Choroidal vessel volume was calculated by multiplying the average CVD by macular area and CT. Multilevel mixed linear models (to account for the inclusion of two eyes of same subject) were performed for analysis.

RESULTS: We included 186 eyes (n=118 subjects), 94 (50.5%) presenting SDD. Multiple regression analysis revealed that, controlling for age, eyes with SDD presented a statistically thinner mean CT (β=-21.9, p=0.006) and CT in all the individual ETDRS fields (β≤-18.79, p≤ 0.026). Mean choroidal vessel volume was also significantly reduced in eyes with SDD (β=-0.003, p=0.007). No significant associations were observed with mean CVD.

CONCLUSION: In subjects with intermediate AMD, choroidal thickness and vessel volume are reduced in the presence of subretinal drusenoid deposits.

PMID: 28579063

Surv Ophthalmol. 2017 Jun 1. [Epub ahead of print]

The Application of Optical Coherence Tomography Angiography in Retinal Diseases.

Sambhav K, Grover S, Chalam KV.

Abstract: Optical coherence tomography angiography (OCTA) is a new, non-invasive imaging technique that generates real time volumetric data of chorioretinal vasculature and its flow pattern. With the advent of high-speed optical coherence tomography, established en-face chorioretinal segmentation, and efficient algorithms, OCTA generate images that resembles an angiogram. The principle of OCTA involves determining the change in backscattering between consecutive B-scans and then attributing the differences to the flow of erythrocytes through retinal blood vessels. OCTA has shown promise in the evaluation of common ophthalmologic diseases such as diabetic retinopathy, age-related macular degeneration (AMD) and retinal vascular occlusions. It quantifies vascular compromise reflecting the severity of diabetic retinopathy. OCTA detects the presence of choroidal neovascularization in exudative AMD and maps loss of choriocapillaries in non-exudative AMD. We describe principles of OCTA and findings in common and some uncommon retinal pathologies. Finally, we summarize its potential future applications. Its current limitations include a relatively small field of view, inability to show leakage, and a tendency for image artifacts. Further larger studies will define OCTAs utility in clinical settings and establish if the technology may offer its utility in decreasing morbidity through early detection and guide therapeutic interventions in
Pathogenesis


Altered bioenergetics and enhanced resistance to oxidative stress in human retinal pigment epithelial cells from donors with age-related macular degeneration.


Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among older adults. It has been suggested that mitochondrial defects in the retinal pigment epithelium (RPE) underlies AMD pathology. To test this idea, we developed primary cultures of RPE to ask whether RPE from donors with AMD differ in their metabolic profile compared with healthy age-matched donors. Analysis of gene expression, protein content, and RPE function showed that these cultured cells replicated many of the cardinal features of RPE in vivo. Using the Seahorse Extracellular Flux Analyzer to measure bioenergetics, we observed RPE from donors with AMD exhibited reduced mitochondrial and glycolytic function compared with healthy donors. RPE from AMD donors were also more resistant to oxidative inactivation of these two energy-producing pathways and were less susceptible to oxidation-induced cell death compared with cells from healthy donors. Investigation of the potential mechanism responsible for differences in bioenergetics and resistance to oxidative stress showed RPE from AMD donors had increased PGC1α protein as well as differential expression of multiple genes in response to an oxidative challenge. Based on our data, we propose that cultured RPE from donors phenotyped for the presence or absence of AMD provides an excellent model system for studying "AMD in a dish". Our results are consistent with the ideas that (i) a bioenergetics crisis in the RPE contributes to AMD pathology, and (ii) the diseased environment in vivo causes changes in the cellular profile that are retained in vitro.

PMID: 28600982


Disruption of retinal pigment epithelial cell properties under the exposure of cotinine.


Abstract: Cigarette smoking is a major risk factor for age-related macular degeneration (AMD), in which progressive retinal pigment epithelial (RPE) cell degeneration is a major pathological change. Nicotine is a major biologically active component in cigarette smoke. It is continuously catabolized into cotinine, which has longer half-life and higher concentration in tissue cells and fluids. Here we hypothesized that continuous exposure of cotinine has more potent effects on human RPE cell properties than nicotine. Human RPE cell line (ARPE-19) was treated continuously with 1-2 µM of nicotine and/or cotinine for 7 days. RPE cells treated with 2 µM cotinine and nicotine-cotinine mixture has lower MTT signals without significant changes in cell apoptosis or integrity. Moreover, RPE cell migration was retarded under cotinine treatments, but not nicotine. Both nicotine and cotinine treatments attenuated the phagocytotic activity of RPE cells. In addition, cotinine and nicotine-cotinine mixture suppressed VEGF and IL-8 expression and upregulated TIMP-2 expression. Expressions of autophagy genes were upregulated by the cotinine treatment, whereas expressions of epithelial-to-mesenchymal transition markers were downregulated. In conclusion, our study, for the first time, demonstrated that cotinine, rather than nicotine, affects the properties of RPE cells in vitro, which could explain the smoking-induced RPE pathology.

PMID: 28600524 PMCID: PMC5466671
Rho-Kinase/ROCK as a Potential Drug Target for Vitreoretinal Diseases.

Yamaguchi M, Nakao S, Arima M, Wada I, Kaizu Y, Hao F, Yoshida S, Sonoda KH.

Abstract: Rho-associated kinase (Rho-kinase/ROCK) was originally identified as an effector protein of the G protein Rho. Its involvement in various diseases, particularly cancer and cardiovascular disease, has been elucidated, and ROCK inhibitors have already been applied clinically for cerebral vasospasm and glaucoma. Vitreoretinal diseases including diabetic retinopathy, age-related macular degeneration, and proliferative vitreoretinopathy are still a major cause of blindness. While anti-VEGF therapy has recently been widely used for vitreoretinal disorders due to its efficacy, attention has been drawn to new unmet needs. The importance of ROCK in pathological vitreoretinal conditions has also been elucidated and is attracting attention as a potential therapeutic target. ROCK is involved in angiogenesis and hyperpermeability and also in the pathogenesis of various pathologies such as inflammation and fibrosis. It has been expected that ROCK inhibitors will become new molecular target drugs for vitreoretinal diseases. This review summarizes the recent progress on the mechanisms of action of ROCK and their applications in disease treatment.

PMID: 28596919 PMCID: PMC5449758

Let-7 contributes to diabetic retinopathy but represses pathological ocular angiogenesis.

Zhou Q, Frost RJA, Anderson C, Zhao F, Ma J, Yu B, Wang S.

Abstract: The in vivo function of microRNAs (miRNAs or miRs) in diabetic retinopathy (DR) and age-related macular degeneration (AMD) remains unclear. Here we report that let-7 family members are expressed in retinal and choroidal endothelial cells (EC). In ECs, overexpression of let-7 by adenovirus represses EC proliferation, migration, and networking in vitro, while inhibition of the let-7 family with a locked nucleic acid (LNA)-anti-miR has the opposite effect. Mechanistically, silencing of the let-7 target gene HMGA2 mimics the phenotype of let-7 overexpression in ECs. Let-7 transgenic (let-7-Tg) mice show features of non-proliferative DR, including tortuous retinal vessels and defective pericyte coverage. However, these mice develop significanly less choroidal neovascularization (CNV) compared to wildtype controls after laser injury. Consistently, silencing of let-7 in the eye increased laser-induced CNV in wild-type mice. Together, our data establish a causative role of let-7 in non-proliferative diabetic retinopathy and a repressive function of let-7 in pathological angiogenesis, suggesting distinct implications of let-7 in the pathogenesis of DR and AMD.

PMID: 28584193

Puerarin inhibits amyloid β-induced NLRP3 inflammasome activation in retinal pigment epithelial cells via suppressing ROS-dependent oxidative and endoplasmic reticulum stresses.


Abstract: Amyloid β (Aβ) is a critical stimulator that promotes the progression of age-related macular degeneration (AMD). NLRP3 inflammasome activation induced by Aβ is estimated to be responsible for retinal pigment epithelium (RPE) dysfunction in such disease. Puerarin, one of the major active constituents of Kudzu root, has been widely used in the clinical treatment of AMD in China for decades; however, the
detailed molecular mechanism remains far from clear. In this study, we investigated the protective effect and underlying mechanism of puerarin against Aβ1-40-induced NLRP3 inflammasome activation in LPS-primed ARPE-19 cells. The results showed that Aβ1-40 induced NLRP3 inflammasome activation mainly via triggering ROS-dependent oxidative stress, particularly lipid peroxidation, and endoplasmic reticulum stress in LPS-primed ARPE-19 cells; however, such effect could be significantly reversed by puerarin in a dose-dependent manner. Furthermore, the effect of puerarin was potentially mediated through activating Nrf2/HO-1 antioxidant signaling pathway and inhibiting Aβ1-40-induced phosphorylation of IRE1 and PERK as well as nuclear expression of ATF6α. Therefore, the significance of the current study is to reveal the novel mechanism of puerarin in the prevention of AMD.

**PMID:** 28583762

### Epidemiology

**Clin Ophthalmol. 2017 May 22;11:963-972. eCollection 2017.**

**Prevalence of and risk factors for age-related macular degeneration in Nepal: the Bhaktapur Retina Study.**


**AIM:** This study aimed to explore the prevalence of and risk factors for age-related macular degeneration (AMD) in an elderly population in Nepal.

**SUBJECTS AND METHODS:** This is a population-based, cross-sectional study. A sample size of 2,100 was calculated. A total of 1,860 (88.6%) subjects aged >60 years were enrolled for the study from 30 clusters in the district. Detailed history, visual acuity, and anterior segment and posterior segment examinations were performed. AMD was graded according to the International ARM Epidemiological Study Group.

**RESULTS:** Among the total study population, 659 subjects had any AMD (35.43%; 95% confidence interval [CI]: 33.25-37.65), 484 had mild dry AMD (26.02%; 95% CI: 24.04-28.08), 143 had intermediate dry AMD (7.69%; 95% CI: 6.52-8.99), 19 had geographic atrophy (1.02%; 95% CI: 0.61-1.59), and 13 had wet AMD (0.70%; 95% CI: 0.37-1.19). The overall prevalence of early and late AMD was 33.71% and 1.72%, respectively. Among subjects with dry and wet AMD, 36.53% and 46.1% had visual impairment, while 2.78% and 23.08% were blind, respectively. In multivariate analysis, AMD was significantly higher in subjects with an increased number of cigarettes smoked per day (odds ratio [OR] 1.02, 95% CI: 1.01-1.04; P=0.007) and in subjects with pseudophakia (OR 1.45, 95% CI: 1.12-1.87; P=0.005).

**CONCLUSION:** One-third of the population aged ≥60 years have some form of AMD. There was a significant association with the number of cigarettes consumed and with previous cataract surgery.

**PMID:** 28579747 **PMCID:** PMC5449112


**Serum APOE, leptin, CFH and HTRA1 levels in Pakistani age related macular degeneration patients.**

Qureshi IZ, Ambreen F.

**OBJECTIVE:** To determine the association between serum levels of apolipoprotein E, leptin, complimentary factor H and high temperature requirement A-1 in patients with age-related macular degeneration.

**METHODS:** This case-control study was conducted at the Quaid-i-Azam University, Islamabad, Pakistan, from May to October 2013, and comprised patients with age-related macular degeneration and matching
controls. The confirmation of age-related macular degeneration was carried out through slit lamp examination, fundoscopy and ocular coherence tomography. The selected subjects were not suffering with any other systemic or ophthalmic complication(s). Serum apolipoprotein E, leptin, complimentary factor H and high temperature requirement A-1 were estimated in serum samples of all subjects. SPSS 18 was used for data analysis.

RESULTS: Of the 190 participants, 90(47.4%) were patients with age-related macular degeneration and 100(52.6%) were controls. Significantly elevated serum apolipoprotein E (p<0.0024) and high temperature requirement A-1 (p<0.0001) levels were observed in the patients, while serum leptin (p<0.008) and complimentary factor H (p<0.0001) levels were significantly reduced. Logistic regression showed that lower leptin (p<0.026) and elevated high temperature requirement A-1 (p<0.0001) were the relevant risk factors.

CONCLUSIONS: Serum apolipoprotein E, leptin, complimentary factor H and high temperature requirement A-1 levels were altered in age-related macular degeneration patients.

PMID: 28585581

**Genetics**


Association of risk genotypes of ARMS2/LOC387715 A69S and CFH Y402H with age-related macular degeneration with and without reticular pseudodrusen: a meta-analysis.

Jabbarpoor Bonyadi MH, Yaseri M, Nikkhah H, Bonyadi M, Soheilian M.

Abstract: To pool the results of published data regarding association of ARMS2/LOC387715 A69S, CFH Y402H and CFH I62V genotypes with age-related macular degeneration (AMD) with and without reticular pseudodrusen (RPD). The results of this pooled data used to estimate the contribution of each of these genes in the pathogenesis of RPD. Heterogeneity of studies was evaluated using Cochran Q-test and I2 index. To modify the heterogeneity in the variables, we used the random effects model. Meta-analysis was performed using STATA. Odds ratio (OR) of genotypes in each study was calculated. Six studies of AMD with RPD and AMD without RPD cases included in this analysis. Analysis of pooled data showed that risk genotypes frequency of ARMS2 A69S was significantly different between AMD with RPD and AMD without RPD [OR = 1.82, 95% confidence interval (CI): 1.26-2.63 for GT versus GG ARMS2 A69S; OR = 2.40, 95% CI: 1.50-3.84 for TT versus GG ARMS2 A69S]. Further analysis also showed that the risk genotype frequency of CFH Y402H was not significantly different between these two groups (OR = 1.02, 95% CI: 0.69-1.50 for CT versus TT CFH Y402H; OR = 1.09, 95% CI: 0.74-1.60 for CC versus TT CFH Y402H). Comparison of above-mentioned ORs revealed statistically higher values for GT and TT genotypes of ARMS2 A69S compared with CFH Y402H genotypes (p = 0.011, p = 0.014, respectively). Our analysis showed stronger contribution of ARMS2 in AMD with RPD group versus AMD without RPD group, in comparison with CFH genotypes.

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**Stem cells**


Bringing the age-related macular degeneration high-risk allele age-related maculopathy susceptibility 2 into focus with stem cell technology.

Sun S, Li Z, Glencer P, Cai B, Zhang X, Yang J, Li X.
Abstract: Age-related macular degeneration (AMD) is a major cause of blindness in older adults in developed countries. It is a multifactorial disease triggered by both environmental and genetic factors. High-temperature requirement A serine peptidase 1 (HTRA1) and age-related maculopathy susceptibility 2 (ARMS2) are two genes that are strongly associated with AMD. Because ARMS2 is an evolutionarily recent primate-specific gene and because the ARMS2/HTRA1 genes are positioned at a locus on chromosome 10q26 in a region with strong linkage disequilibrium, it is difficult to distinguish the functions of the individual genes. Therefore, it is necessary to bring these genes into focus. Patient-specific induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) provides direct access to a patient's genetics and allows for the possibility of identifying the initiating events of RPE-associated degenerative diseases. In this paper, a review of recent epidemiological studies of AMD is offered. An argument for a definite correlation between the ARMS2 gene and AMD is presented. A summary of the use of ARMS2 genotyping for medical treatment is provided. Several ARMS2-related genetic models based on such stem cells as iPSCs are introduced. The possibility of applying gene-editing techniques and stem-cell techniques to better explore the mechanisms of the ARMS2 high-risk allele, which will lead to important guidance for treatment, is also discussed.

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Intravitreal use of bone marrow mononuclear fraction containing CD34+ stem cells in patients with atrophic age-related macular degeneration.

Cotrim CC, Toscano L, Messias A, Jorge R, Siqueira RC.

PURPOSE: To evaluate the therapeutic potential and safety of intravitreal injections of bone marrow mononuclear fraction (BMMF) containing CD34+ cells in patients with atrophic age-related macular degeneration (AMD).

METHODS: Ten patients with atrophic AMD and best-corrected visual acuity (BCVA) in the worse-seeing eye of ≤20/100 were enrolled in this study. The bone marrow from all patients was aspirated and processed for mononuclear cell separation. A 0.1 mL suspension of BMMF CD34+ cells was injected into the vitreous cavity of the worse-seeing eye. Patients were evaluated at Baseline and 1,3,6,9 and 12 months after injection. Ophthalmic evaluation included BCVA measurement, microperimetry, infrared imaging, fundus autofluorescence and SD-optical coherence tomography at all study visits. Fluorescein angiography was performed at Baseline and at 6 and 12 months after intravitreal therapy.

RESULTS: All patients completed the 6-month follow-up, and six completed the 12-month follow-up. Prior to the injection, mean BCVA was 1.18 logMAR (20/320-1), ranging from 20/125 to 20/640-2, and improved significantly at every follow-up visit, including the 12-month one, when BCVA was 1.0 logMAR (20/200) (P<0.05). Mean sensitivity threshold also improved significantly at 6, 9 and 12 months after treatment (P<0.05). Considering the area of atrophy identified by fundus autofluorescence, significant mean BCVA and mean sensitivity threshold improvement were observed in patients with the smallest areas of atrophy. Fluorescein angiography did not identify choroidal new vessels or tumor growth.

CONCLUSION: The use of intravitreal BMMF injections in patients with AMD is safe and is associated with significant improvement in BCVA and macular sensitivity threshold. Patients with small areas of atrophy have a better response. The paracrine effect of CD34+ cells may explain the functional improvement observed; however, larger series of patients are necessary to confirm these preliminary findings.

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Diet, lifestyle & low vision

Food components and ocular pathophysiology: a critical appraisal of the role of oxidative mechanisms.
Raman R, Vaghefi E, Braakhuis AJ.

BACKGROUND AND OBJECTIVES: Three of the major ocular diseases, namely cataracts, age-related macular degeneration and glaucoma are associated with oxidative damage. Disease risk and progression may be reduced through consumption of dietary components. To critically examine the literature on dietary and supplemental intakes of fruit and vegetables, meat, antioxidants (vitamins C, E and A), calcium, folic acid, iron, and their association with ocular disease.

METHODS AND STUDY DESIGN: Google Scholar and key references from texts and publications were searched using search terms (eye disease, antioxidants), (vision, nutrition), no date restriction, only articles in English were included.

RESULTS: We found probable evidence that dietary intake of fruits and vegetables, and vitamin C lowered incidence of cataracts and age-related macular degeneration. In high supplemental doses, vitamin C increases macular degeneration risk. Vitamin A from food was protective for cataracts and glaucoma, but not in supplemental form. Vitamin A was associated with lower incidence of macular degeneration. We also found probable evidence that higher intakes of meat increased the risk of cataracts and macular degeneration. Dietary calcium and iron appeared protective against glaucoma, but not in supplemental form.

CONCLUSIONS: While a nutrient rich diet high in fruit and vegetables, and associated antioxidants appeared to be protective, we would caution intake of supplementary antioxidants for those with ocular disease.

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Compromised Integrity of Central Visual Pathways in Patients With Macular Degeneration.
Malania M, Konrad J, Jägle H, Werner JS, Greenlee MW.

PURPOSE: Macular degeneration (MD) affects the central retina and leads to gradual loss of foveal vision. Although, photoreceptors are primarily affected in MD, the retinal nerve fiber layer (RNFL) and central visual pathways may also be altered subsequent to photoreceptor degeneration. Here we investigate whether retinal damage caused by MD alters microstructural properties of visual pathways using diffusion-weighted magnetic resonance imaging.

METHODS: Six MD patients and six healthy control subjects participated in the study. Retinal images were obtained by spectral-domain optical coherence tomography (SD-OCT). Diffusion tensor images (DTI) and high-resolution T1-weighted structural images were collected for each subject. We used diffusion-based tensor modeling and probabilistic fiber tractography to identify the optic tract (OT) and optic radiations (OR), as well as nonvisual pathways (corticospinal tract and anterior fibers of corpus callosum). Fractional anisotropy (FA) and axial and radial diffusivity values (AD, RD) were calculated along the nonvisual and visual pathways.

RESULTS: Measurement of RNFL thickness reveals that the temporal circumpapillary retinal nerve fiber layer was significantly thinner in eyes with macular degeneration than normal. While we did not find significant differences in diffusion properties in nonvisual pathways, patients showed significant changes in
diffusion scalars (FA, RD, and AD) both in OT and OR.

CONCLUSIONS: The results indicate that the RNFL and the white matter of the visual pathways are significantly altered in MD patients. Damage to the photoreceptors in MD leads to atrophy of the ganglion cell axons and to corresponding changes in microstructural properties of central visual pathways.

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