Drug treatment


[Recommendations for the use of ranibizumab in diabetic macular edema at IMSS],[Article in Spanish]


Abstract: Diabetic macular edema can occur at any stage of diabetic retinopathy. It represents the main cause of vision loss in diabetes type I and II with a prevalence of 3-10% in diabetic patients of the Instituto Mexicano del Seguro Social (IMSS). Our aim is to elaborate treatment guidelines and provide recommendations for the use of intravitreal ranibizumab for diabetic medical edema at IMSS. Nine retina specialists and 10 ophthalmologists from IMSS high specialty medical units gathered to discuss the bibliographic evidence for the safety and efficacy of ranibizumab for this disease, in order to create consensus on its use in the institution. Intravitreal ranibizumab injection should be used on patients presenting diffuse or cystic diabetic macular edema who have strict metabolic control and visual acuity between 20/30 and 20/200 ETDRS, as well as structural features, such as inferior foveal limit of 280 μm and ischemic areas no larger than 50% of the central foveal area. Treatment regime should consist of a loading charge of three monthly injections of ranibizumab 0.5 mg, followed by monthly follow-ups and treatment as needed according to anatomic and functional criteria. This consensus decision-making process on the criteria to treat and re-treat patients with this drug will result in better health outcomes than those currently observed among patients with diabetic macular edema at IMSS.

PMID: 29190870

Retina. 2017 Nov 22. [Epub ahead of print]

AFLIBERCEPT AFTER RANIBIZUMAB INTRAVITREAL INJECTIONS IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION: The ARI2 Study.


PURPOSE: To analyze the efficacy of aflibercept switch treatment for regression of pigment epithelial detachment (PED) in patients previously treated with ranibizumab.

METHODS: Multicenter, prospective, nonrandomized clinical trial. One eye of patients presenting neovascular age-related macular degeneration with PED of more than 250 μm in height, with persistent
fluid, was included. Patients had to have received at least six ranibizumab intravitreal injections during the 12 months before enrollment. Patients were switched from ranibizumab pro re nata to aflibercept (fixed regimen, 3 monthly intravitreal injections, and then Q6). Main outcome measure was change in PED height from baseline to Week 12 after switch. Secondary outcomes were best-corrected visual acuity and PED volume changes.

RESULTS: Eighty four patients were included. Mean delay between last ranibizumab intravitreal injection and switch was 44.7 days. Mean maximal PED height at baseline visit was 347 μm (±109) and reduced to a mean of 266 μm (±114) at Week 12 (P < 0.001) and 288.2 μm at Week 32 (P < 0.001). Mean PED volume was reduced from 1.3 mm to 0.98 mm at Week 12 (P < 0.001). Best-corrected visual acuity improved by 3.3 Early Treatment Diabetic Retinopathy Study letters at Week 32 (P = 0.003).

CONCLUSION: Aflibercept switch therapy seems to be effective on large PED in patients previously treated with pro re nata ranibizumab.

PMID: 29190241


Real-life clinical data for dexamethasone and ranibizumab in the treatment of branch or central retinal vein occlusion over a period of six months.


PURPOSE: To evaluate the therapeutic outcome for dexamethasone implant (DEX) or intravitreal ranibizumab (IVR) injections over 6 months in patients with macular edema due to branch or central retinal vein occlusion (BRVO, CRVO), in a real-life setting.

METHODS: A total of 107 patients with BRVO or CRVO were included into this retrospective single-center observational study. Patients were treated with monotherapy consisting of DEX or three monthly IVR injections following a pro re nata regimen (PRN). Best-corrected visual acuity (BCVA), central retinal thickness (CRT) and intraocular pressure (IOP) were compared between the two therapy groups after 1, 3 and 6 months.

RESULTS: BRVO patients treated with DEX achieved a statistically significant gain in BCVA measured in logMAR after 1 month (mean gain, 95% CI: 0.21, 0.08-0.34, p = 0.001), 3 months (0.16, 0.03-0.28, p = 0.012) and 6 months (0.19, 0.07-0.32, p = 0.002), whereas patients treated with IVR showed a statistically significant BCVA gain in month 3 (mean improvement, 95% CI: 0.13, 0.01-0.26, p = 0.039) and month 6 (0.16, 0.03-0.29, p = 0.018). BCVA in CRVO patients with DEX worsened slightly at month 6 (mean worsening, 95% CI: -0.08, -0.24 to 0.08, p = 0.305), while IVR treated-patients achieved a statistically significant BCVA gain at 3 months (mean improvement, 95% CI: 0.14, 0.02-0.25, p = 0.021). Both therapies were accompanied by statistically significant CRT reductions of 150 to 200 μm (median). Adverse events reported were predictable and limited.

CONCLUSIONS: In a clinical setting, comparable improvement in BCVA and CRT were observed after DEX and IVR injections for treatment of BRVO. CRVO patients showed greater benefit with IVR.

PMID: 29185099


AREDS simplified severity scale as a predictive factor for response to aflibercept therapy for typical neovascular age-related macular degeneration.

PURPOSE: To investigate whether the severity of the condition in the untreated fellow eye is a predictive factor for the response to intravitreal aflibercept injection (IAI) for exudative age-related macular degeneration (AMD).

METHODS: A retrospective medical chart review was conducted for 88 patients with treatment-naïve neovascular AMD, who were initially treated with three monthly IAIs, followed by monthly monitoring and re-injection as needed for at least 12 months. Subjects were classified into three groups according to the severity of the condition in their untreated eye, based on the severity scale in the Age-Related Eye Disease Study (AREDS): group 0, AREDS severity level 1 (no drusen); group 1, AREDS severity level 2 or 3 (any drusen); group 2, AREDS severity level 4 (advanced AMD). Genotyping was performed in all cases for ARMS2 A69S and CFH I62V.

RESULTS: Fellow-eye severity was associated with age and the risk variant of ARMS2 A69S (P = 0.005 and 0.001, respectively). Although best-corrected visual acuity (BCVA) had improved significantly after 12 months in all groups, this improvement was significantly greater in group 0 than in the other groups (P = 0.008). The retreatment-free period was also significantly longer for group 0 than for the other groups (P = 0.016), and the number of additional injections was significantly associated with fellow-eye severity (P = 0.007).

CONCLUSIONS: Fellow-eye severity was associated with treatment response in terms of visual improvement and retreatment and may be a predictive factor for response to IAI for neovascular AMD.

PMID: 29177890


Effects of Intravitreal Aflibercept on Galectin-1 and Vascular Endothelial Growth Factor-A Plasma Levels in Patients with Diabetic Retinopathy.

Waltl I, Zehetner C, Seifarth C, Handle F, Kieselbach GF, Angermann R, Kralinger MT.

PURPOSE: To analyze the interaction between aflibercept and galectin-1 and evaluate the plasma levels of galectin-1 and vascular endothelial growth factor (VEGF)-A after intravitreal injection of aflibercept in patients with diabetic retinopathy (DR).

METHODS: Interaction of galectin-1 with aflibercept was determined via immunoprecipitation. Seventeen patients with type 2 diabetes and diabetic macular edema (DME) were each treated with a single intravitreal injection of aflibercept (2.0 mg, 50 µL) monthly for three consecutive months. Plasma galectin-1 and VEGF-A levels were measured just before an injection was administered, 1 week after the first injection, and 2 months after the last injection. Nineteen age- and sex-matched healthy participants served as controls.

RESULTS: Irrespective of the tested galectin-1 concentration, 24% of added galectin-1 was precipitated by aflibercept. Baseline plasma concentrations of galectin-1 were 22.0 and 23.0 ng/mL in the control and aflibercept-treated groups, respectively. Systemic galectin-1 levels increased to 27.0 and 24.0 ng/mL at 7 days and 4 weeks, respectively, after treatment. At week 8, plasma galectin-1 levels significantly increased to 36.0 ng/mL. This level persisted for 20 weeks. Systemic VEGF-A levels significantly reduced to below the minimum detectable dose in 16 DME patients at 7 days after treatment. This level persisted for 4 weeks. Plasma VEGF-A levels were reduced at weeks 8 (p = 0.099) and 20 (p = 0.023). Decreased plasma VEGF-A levels were observed in all patients after treatment.

CONCLUSION: We confirmed that physiological aflibercept levels precipitate galectin-1 in in vitro assays. Additionally, systemic upregulation of galectin-1 might be induced by intravitreal aflibercept, which may be relevant in the clinical outcomes of DR treatment.

PMID: 29172741

Aflibercept treatment for neovascular AMD beyond the first year: consensus recommendations by a UK expert roundtable panel, 2017 update.


Abstract: National recommendations on continued administration of aflibercept solution for injection after the first year of treatment for neovascular age-related macular degeneration (nAMD) have been developed by an expert panel of UK retina specialists, based on clinician experience and treatment outcomes seen in year 2. The 2017 update reiterates that the treatment goal is to maintain or improve the macular structural and functional gains achieved in year 1 while attempting to reduce or minimize the treatment burden, recognizing the need for ongoing treatment. At the end of year 1 (ie, the decision visit at month 11), two treatment options should be considered: do not extend the treatment interval and maintain fixed 8-weekly dosing, or extend the treatment interval using a treat-and-extend regimen up to a maximum 12 weeks. Criteria for considering not extending the treatment interval are persistent macular fluid with stable vision, recurrent fluid, decrease in vision in the presence of fluid, macular hemorrhage, new choroidal neovascularization or any other sign(s) of exudative disease activity considered vision threatening in the opinion of the treating clinician. Treatment extension is recommended for eyes with a dry macula (ie, without macular fluid) and stable vision. Under both options, the treatment interval may be shortened if visual and/or anatomic outcomes deteriorate. Monitoring without treatment may be considered for eyes with a fluid-free macula for a minimum duration of 48 weeks. A patient completing one full year of monitoring without requiring injections may be considered for discharge from clinic. The treatment algorithm incorporates return to fixed 8-weekly dosing for disease reactivation during treatment extension and reinstatement of treatment for disease recurrence following discontinuation or discharge. For bilateral nAMD, either the eye requiring the more intensive treatment or the eye with the better vision, guided by local clinical practice, should determine the retreatment schedule overall.

PMID: 29184385 PMCID: PMC5685136

Klin Monbl Augenheilkd. 2017 Nov 27. [Epub ahead of print]

[Vitreomacular Traction Following Anti-VEGF Therapy - Two Cases]. [Article in German]

Wallraf SH, Markova K, Haritoglou C.

Abstract: Vitreomacular traction syndrome (VMTS) is defined as an incomplete or anomalous posterior vitreous detachment resulting in tractional forces at the macular region. In the context of anti-VEGF therapy, the formation of vitreoretinal traction has mainly been reported as a potential complication of VEGF inhibition in ischemic proliferative retinal disease, such as proliferative diabetic retinopathy. In this report, we present two patients who developed VMTS during anti-VEGF therapy for exudative age-related macular degeneration and diabetic macular edema. VMTS following anti-VEGF therapy of exudative macular diseases is rare. The exact pathomechanism remains unclear. However, there is a hypothesis that in eyes with adherent vitreous cortex, the induction of fibrosis as a result of the VEGF inhibition may lead to vitreomacular traction.

PMID: 29179221


Time to ask patients about drugs for macular degeneration.

Mackenzie JW.

PMID: 29184013
Other treatment & diagnosis


Both Autocrine Signaling and Paracrine Signaling of HB-EGF Enhance Ocular Neovascularization.


OBJECTIVE: The incidence of blindness is increasing because of the increase in abnormal ocular neovascularization. Anti-VEGF (vascular endothelial growth factor) therapies have led to good results, although they are not a cure for the blindness. The purpose of this study was to determine what role HB-EGF (heparin-binding epidermal growth factor-like growth factor) plays in ocular angiogenesis.

APPROACH AND RESULTS: We examined the role played by HB-EGF in ocular neovascularization in 2 animal models of neovascularization: laser-induced choroidal neovascularization (CNV) and oxygen-induced retinopathy. We also studied human retinal microvascular endothelial cells in culture. Our results showed that the neovascularization was decreased in both the CNV and oxygen-induced retinopathy models in HB-EGF conditional knockout mice compared with that in wild-type mice. Moreover, the expressions of HB-EGF and VEGF were increased after laser-induced CNV and oxygen-induced retinopathy, and their expression sites were located around the neovascular areas. Exposure of human retinal microvascular endothelial cells to HB-EGF and VEGF increased their proliferation and migration, and CRM-197, an HB-EGF inhibitor, decreased the HB-EGF-induced and VEGF-induced cell proliferation and migration. VEGF increased the expression of HB-EGF mRNA. VEGF-dependent activation of EGFR (epidermal growth factor receptor)/ERK1/2 (extracellular signal-regulated kinase 1/2) signaling and cell proliferation of endothelial cells required stimulation of the ADAM17 and ADAM12. CRM-197 decreased the grades of the fluorescein angiograms and size of the CNV areas in marmoset monkeys.

CONCLUSIONS: These findings suggest that HB-EGF plays an important role in the development of CNV. Therefore, further investigations of HB-EGF are needed as a potential therapeutic target in the treatment of exudative age-related macular degeneration.

PMID: 29191924

Retina. 2017 Nov 28. [Epub ahead of print]

MACULAR ATROPHY FINDINGS BY OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY COMPARED WITH FUNDUS AUTOFLUORESCENCE IN TREATED EXUDATIVE AGE-RELATED MACULAR DEGENERATION.


PURPOSE: To compare the areas of choriocapillaris (CC) nonperfusion and macular atrophy (MA) in treated exudative age-related macular degeneration.

METHODS: This was a prospective, observational, cross-sectional study. Forty-four eyes exhibiting MA (42 patients with age-related macular degeneration), with a dry macula, underwent fundus autofluorescence and optical coherence tomography angiography. The area of MA detected by fundus autofluorescence and CC nonperfusion detected by optical coherence tomography angiography was measured using image analysis software. The rates of concordance between the MA and CC nonperfusion areas were calculated. We qualitatively and quantitatively compared the areas of MA and CC nonperfusion in age-related macular degeneration eyes.

RESULTS: The mean areas of MA and CC nonperfusion were 5.95 ± 4.50 mm and 10.66 ± 7.05 mm, respectively (paired t-test, P < 0.001). In 39 eyes (88.6%), the CC nonperfusion area was larger than the MA area, and the mean CC nonperfusion area was significantly larger than the mean MA area. Fundus
autofluorescence matching optical coherence tomography angiography showed that the CC nonperfusion area was almost included in the MA area. The mean concordance rate for the MA area inside the CC nonperfusion area was 87.7 ± 13.9%.

CONCLUSION: The MA and CC nonperfusion areas markedly overlapped. The area of CC nonperfusion correlated with the MA area. Choroidal ischemia might be involved in the pathogenesis of MA in treated age-related macular degeneration. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

PMID: 29190232


Quantification of retinal changes after resolution of submacular hemorrhage secondary to polypoidal choroidal vasculopathy.

Kim JH, Chang YS, Lee DW, Kim CG, Kim JW.

PURPOSE: To evaluate changes in the thickness of retinal layers after resolution of submacular hemorrhage secondary to polypoidal choroidal vasculopathy (PCV).

STUDY DESIGN: Retrospective, observational study.

METHODS: This study included 21 patients (21 eyes) who had been diagnosed with submacular hemorrhage secondary to PCV and treated using anti-vascular endothelial growth factor monotherapy. After the hemorrhage had resolved, the thicknesses of the retinal layers were measured on horizontal- and vertical-crosshair optical coherence tomography scan images. The thickness of each layer in the region affected by the hemorrhage was compared with the thickness of the layer in the corresponding region in the fellow eye, as well as between an unaffected region in the eye with the hemorrhage and the corresponding region in the fellow eye.

RESULTS: Optical coherence tomography (OCT) was performed 5.5±2.8 months after diagnosis. In the horizontal OCT images, the outer plexiform layer (OPL) and outer nuclear layer (ONL) + photoreceptor layer (PRL) were significantly thinner in the affected region than in the corresponding region (P = 0.019 and P <0.001, respectively). In the vertical OCT image, the ONL+PRL was significantly thinner in the affected region than in the corresponding region (P <0.001). The thickness of the retinal layer in the unaffected region did not differ from that in the corresponding region of the fellow eye.

CONCLUSIONS: The significant thinning of the outer retinal layers in the regions affected by submacular hemorrhage suggests that the hemorrhage induces marked damage in the outer retinal layers, explaining the poor visual prognosis of submacular hemorrhage.

PMID: 29188462


Querques G, Cicinelli MV, Rabiolo A, de Vitis L, Sacconi R, Querques L, Bandello F.

PURPOSE: To give an updated review of laser approaches to non-exudative age-related macular degeneration (AMD).
METHODS: PubMed and Medline database searches were carried out using the terms "laser" and "photocoagulation" associated with "age-related macular degeneration", and latest publications up to May 2017 have been reviewed. Moreover, the design of an ongoing single-center, non-randomized, phase I-II, pilot study, the PASCAL-GA trial, coordinated by F. Bandello, MD and G. Querques, MD from the IRCCS Ospedale San Raffaele, is described.

RESULTS: Either standard or subthreshold laser strategies have been tried to induce regression of distinct phenotypes of AMD, as reticular pseudodrusen (RPD), nascent geographic atrophy (nGA), and drusen-associated geographic atrophy (DAGA), with heterogeneous results. The aim of the PASCAL-GA protocol is to assess if subthreshold laser can restore the retinal pigment epithelium function in eyes with RPD and nGA offering a protective effect against extensive GA.

CONCLUSIONS: New-generation medical and surgical approaches, including subthreshold laser photocoagulation, may have some success in downstaging AMD.

PMID: 29177712


Automatic detection of the foveal center in optical coherence tomography.


Abstract: We propose a method for automatic detection of the foveal center in optical coherence tomography (OCT). The method is based on a pixel-wise classification of all pixels in an OCT volume using a fully convolutional neural network (CNN) with dilated convolution filters. The CNN-architecture contains anisotropic dilated filters and a shortcut connection and has been trained using a dynamic training procedure where the network identifies its own relevant training samples. The performance of the proposed method is evaluated on a data set of 400 OCT scans of patients affected by age-related macular degeneration (AMD) at different severity levels. For 391 scans (97.75%) the method identified the foveal center with a distance to a human reference less than 750 μm, with a mean (± SD) distance of 71 μm ± 107 μm. Two independent observers also annotated the foveal center, with a mean distance to the reference of 57 μm ± 84 μm and 56 μm ± 80 μm, respectively. Furthermore, we evaluate variations to the proposed network architecture and training procedure, providing insight in the characteristics that led to the demonstrated performance of the proposed method.

PMID: 29188111 PMCID: PMC5695961


Novel grid combined with peripheral distortion correction for ultra-widefield image grading of age-related macular degeneration.


PURPOSE: Eyes with age-related macular degeneration (AMD) often harbor pathological changes in the retinal periphery and perimacular region. These extramacular changes have not been well classified, but may be phenotypically and functionally relevant. The purpose of this study was to demonstrate a novel grid to systematically study peripheral retinal abnormalities in AMD using geometric distortion-corrected ultra-widefield (UWF) imaging.

METHODS: This is a cross-sectional observational case series. Consecutive patients with AMD without any other coexisting vitreoretinal disease and control patients over age 50 without AMD or any other vitreoretinal disease were imaged using Optos 200 Tx. Captured 200° UWF images were corrected for
Peripheral geometric distortion using Optos transformation software. A newly developed grid to study perimacular and peripheral abnormalities in AMD was then projected onto the images.

RESULTS: Peripheral and perimacular changes such as drusen, retinal pigment epithelium changes and atrophy were found in patients with AMD. The presented grid in conjunction with geometric distortion-corrected UWF images allowed for systematic study of these peripheral changes in AMD.

CONCLUSION: We present a novel grid to study peripheral and posterior pole changes in AMD. The grid is unique in that it adds a perimacular zone, which may be important in characterizing certain phenotypes in AMD. Our UWF images were corrected for geometric peripheral distortion to accurately reflect the anatomical dimensions of the retina. This grid offers a reliable and reproducible foundation for the exploration of peripheral retinal pathology associated with AMD.

PMID: 29184386 PMCID: PMC5687493


Automated drusen detection in dry age-related macular degeneration by multiple-depth, en face optical coherence tomography.


Abstract: We introduce a method to automatically detect drusen in dry age-related macular degeneration (AMD) from optical coherence tomography with minimum need for layer segmentation. The method is based on the en face detection of drusen areas in C-scans at certain distances above the Bruch's membrane, circumventing the difficult task of pathologic retinal pigment epithelium segmentation. All types of drusen can be detected, including the challenging subretinal drusenoid deposits (pseudodrusen). The high sensitivity and accuracy demonstrated here shows its potential for detection of drusen onset in early AMD.

PMID: 29188102 PMCID: PMC5695952


Understanding aneurysmal type 1 neovascularisation (polypoidal choroidal vasculopathy): a lesson in the taxonomy of "expanded spectra".

Dansingani KK, Gal-Or O, Sadda SR, Yannuzzi LA, Freund KB.

Abstract: The term aneurysmal type 1 neovascularization is derived from terminology which is established in the literature but which has fallen out of use. We believe that aneurysmal type 1 neovascularization accurately describes the lesions which define the entity known as polypoidal choroidal vasculopathy. Over the last 3 decades the clinical spectrum of PCV has expanded to recognize the occurrence of the aneurysmal (polypoidal) lesions in different contexts, resulting in a complex and unwieldy taxonomy based sometimes on circumstantial findings rather than mechanistic considerations. Advanced in multimodal imaging provide increasingly convincing evidence that the lesions which define various forms of PCV are indeed vascular and arise from type 1 neovascular networks. The understanding of PCV as type 1 neovascularization with aneurysms renews focus on the question as to why some patients with type 1 neovascularization develop aneurysms while others do not. Conceptual themes and potential for further study are discussed.

PMID: 29178419
Automatic classification of retinal three-dimensional optical coherence tomography images using principal component analysis network with composite kernels.

Fang L, Wang C, Li S, Yan J, Chen X, Rabbani H.

Abstract: We present an automatic method, termed as the principal component analysis network with composite kernel (PCANet-CK), for the classification of three-dimensional (3-D) retinal optical coherence tomography (OCT) images. Specifically, the proposed PCANet-CK method first utilizes the PCANet to automatically learn features from each B-scan of the 3-D retinal OCT images. Then, multiple kernels are separately applied to a set of very important features of the B-scans and these kernels are fused together, which can jointly exploit the correlations among features of the 3-D OCT images. Finally, the fused (composite) kernel is incorporated into an extreme learning machine for the OCT image classification. We tested our proposed algorithm on two real 3-D spectral domain OCT (SD-OCT) datasets (of normal subjects and subjects with the macular edema and age-related macular degeneration), which demonstrated its effectiveness.

PMID: 29188661

Review of the association between retinal microvascular characteristics and eye disease.

Newman A, Andrew N, Casson R.

Abstract: Computerized retinal imaging technologies enable the static and dynamic measurement of a range of retinal microvascular parameters. Large population-based studies have reported associations between these microvascular indices and various ophthalmic diseases including diabetes, age-related macular degeneration, retinal artery embolism, retinal vein occlusion, glaucoma, and non-glaucomatous optic neuropathies. Increasingly sophisticated imaging and analysis techniques have the potential to provide relevant clinical information regarding disease risk and progression; however, further studies are required to verify associations and strengthen the predictive power of these techniques. We summarise the current state of knowledge regarding retinal microvascular characteristics and eye disease.

PMID: 29193621

cGAS drives noncanonical-inflammasome activation in age-related macular degeneration.

Kerur N, Fukuda S, Banerjee D, et al

Abstract: Geographic atrophy is a blinding form of age-related macular degeneration characterized by retinal pigmented epithelium (RPE) death; the RPE also exhibits DICER1 deficiency, resultant accumulation of endogenous Alu-retroelement RNA, and NLRP3-inflammasome activation. How the inflammasome is activated in this untreatable disease is largely unknown. Here we demonstrate that RPE degeneration in human-cell culture and mouse models is driven by a noncanonical-inflammasome pathway that activates caspase-4 (caspase-11 in mice) and caspase-1, and requires cyclic GMP-AMP synthase (cGAS)-dependent interferon-β production and gasdermin D-dependent interleukin-18 secretion. Decreased DICER1 levels or Alu-RNA accumulation triggers cytosolic escape of mitochondrial DNA, which engages cGAS. Moreover, caspase-4, gasdermin D, interferon-β, and cGAS levels were elevated in the RPE in...
human eyes with geographic atrophy. Collectively, these data highlight an unexpected role of cGAS in responding to mobile-element transcripts, reveal cGAS-driven interferon signaling as a conduit for mitochondrial-damage-induced inflammasome activation, expand the immune-sensing repertoire of cGAS and caspase-4 to noninfectious human disease, and identify new potential targets for treatment of a major cause of blindness.

PMID: 29176737


Chemical Proteomics Reveals Soluble Epoxide Hydrolase as a Therapeutic Target for Ocular Neovascularization.


Abstract: The standard-of-care therapeutics for the treatment of ocular neovascular diseases like wet age-related macular degeneration (AMD) are biologics targeting vascular endothelial growth factor signaling. There are currently no FDA approved small molecules for treating these blinding eye diseases. Therefore, therapeutic agents with novel mechanisms are critical to complement or combine with existing approaches. Here, we identified soluble epoxide hydrolase (sEH), a key enzyme for epoxy fatty acid metabolism, as a target of an antiangiogenic homoisoflavonoid, SH-11037. SH-11037 inhibits sEH in vitro and in vivo and docks to the substrate binding cleft in the sEH hydrolase domain. sEH levels and activity are up-regulated in the eyes of a choroidal neovascularization (CNV) mouse model. sEH is overexpressed in human wet AMD eyes, suggesting that sEH is relevant to neovascularization. Known sEH inhibitors delivered intraocularly suppressed CNV. Thus, by dissecting a bioactive compound's mechanism, we identified a new chemotype for sEH inhibition and characterized sEH as a target for blocking the CNV that underlies wet AMD.

PMID: 29193961

Antioxid Redox Signal. 2017 Nov 29. [Epub ahead of print]

Oxidative stress induces an interactive decline in Wnt and Nrf2 signaling in degenerating retinal pigment epithelium.


AIMS: Cells have evolved a highly sophisticated web of cytoprotective systems to neutralize unwanted oxidative stress, but are challenged by unique modern day stresses such as cigarette smoking and ingestion of a high fat diet. Age-related disease, such as age-related macular degeneration (AMD), the most common cause of blindness among the elderly in western societies, develops in part, when oxidative stress overwhelms cytoprotective systems to injure tissue. Since most studies focus on the protection by a single protective system, the aim of this study was to investigate the impact of more than one cytoprotective system against oxidative stress.

RESULTS: Wnt and Nrf2, two fundamental signaling systems that are vital to cell survival, decline after mice are exposed to chronic cigarette smoke and high fat diet, two established AMD risk factors, in a bidirectional feedback loop through phosphorylated GSK3β. Decreased Wnt and Nrf2 signaling leads to RPE dysfunction and apoptosis, and a phenotype that is strikingly similar to geographic atrophy, an advanced form of AMD with no effective treatment.

INNOVATION: This study is the first to show that chronic oxidative stress from common modern day environmental exposures reduces two fundamental and vital cytoprotective networks in a bidirectional
feedback loop, and their decline leads to advanced disease phenotype.

CONCLUSION: Our data offer new insights into how the combined modern oxidative stresses of cigarette smoking and high fat diet contribute to geographic atrophy through an interactive decline in Wnt and Nrf2 signaling.

PMID: 29186981


Plasma levels of hypoxia-regulated factors in patients with age-related macular degeneration.


PURPOSE: Various hypoxia-related proteins are differentially expressed in the retina and secreted to the vitreous and/or aqueous humor of patients affected by dry or neovascular age-related macular degeneration (nAMD). To determine whether these conditions alter concentrations of cytokines also in the systemic circulation, we measured plasma levels of six hypoxia-related proteins.

METHODS: Plasma was prepared from EDTA blood that was collected from patients affected by dry AMD (n = 5), nAMD (n = 11), proliferative diabetic retinopathy (PDR; n = 9), and patients with an epiretinal membrane (ERM; n = 11). ERM samples served as negative controls, PDR samples as positive controls. Protein concentrations of vascular endothelial growth factor (VEGF), erythropoietin (EPO), angiopoietin-like 4 (ANGPTL4), placental growth factor (PlGF), tumor necrosis factor alpha (TNF-α), and pigment epithelium-derived factor (PEDF) were determined by enzyme-linked immunosorbent assay (ELISA).

RESULTS: The concentration of PlGF was significantly increased in plasma of patients affected by nAMD. Although no statistically significant differences were found for EPO, ANGPTL4, PlGF, TNF-α, and PEDF, the mean concentration of VEGF was lowest in the nAMD group. Plasma concentrations of the six factors did not correlate with gender or age of patients.

CONCLUSIONS: nAMD may increase plasma concentrations of PlGF, making it a candidate as a biomarker for the neovascular form of AMD. Other factors, however, were not differentially regulated, suggesting that their systemic concentrations are not generally increased in hypoxia-related retinal diseases.

PMID: 29177891


PPARα is essential for retinal lipid metabolism and neuronal survival.


BACKGROUND: Peroxisome proliferator activated receptor-alpha (PPARα) is a ubiquitously expressed nuclear receptor. The role of endogenous PPARs in retinal neuronal homeostasis is unknown. Retinal photoreceptors are the highest energy-consuming cells in the body, requiring abundant energy substrates. PPARα is a known regulator of lipid metabolism, and we hypothesized that it may regulate lipid use for oxidative phosphorylation in energetically demanding retinal neurons.

RESULTS: We found that endogenous PPARα is essential for the maintenance and survival of retinal neurons, with Pparα -/- mice developing retinal degeneration first detected at 8 weeks of age. Using extracellular flux analysis, we identified that PPARα mediates retinal utilization of lipids as an energy substrate, and that ablation of PPARα ultimately results in retinal bioenergetic deficiency and
neurodegeneration. This may be due to PPARα regulation of lipid transporters, which facilitate the internalization of fatty acids into cell membranes and mitochondria for oxidation and ATP production.

CONCLUSION: We identify an endogenous role for PPARα in retinal neuronal survival and lipid metabolism, and furthermore underscore the importance of fatty acid oxidation in photoreceptor survival. We also suggest PPARα as a putative therapeutic target for age-related macular degeneration, which may be due in part to decreased mitochondrial efficiency and subsequent energetic deficits.

PMID: 29183319 PMCID: PMC5706156

**Epidemiology**


**Presenting characteristics and prevalence of polypoidal choroidal vasculopathy in Scandinavian patients with treatment-naïve exudative age-related macular degeneration.**

Lorentzen TD, Subhi Y, Sørensen TL.

PURPOSE: To study presenting characteristics and prevalence of polypoidal choroidal vasculopathy (PCV) in Scandinavian Caucasians with treatment-naïve exudative age-related macular degeneration (AMD).

METHODS: We reviewed all patients referred in year 2014 and diagnosed using fundus examination, optical coherence tomography, and fluorescein and indocyanine green angiography (ICGA). Details of found PCVs and its subtypes (clinical and angiographical) were correlated to the baseline best-corrected visual acuity (BCVA).

RESULTS: Of 299 Caucasian patients with a tentative diagnosis of exudative AMD, 18 eyes of 17 patients (5.7%, CI 95%: 3.5-9.1%) had PCV. Patients with PCV were 75.8 (SD: 7.5) years old and 11 (65%) were females. Lesions were predominantly extramacular. Most eyes (56%) had subretinal haemorrhage, 39% had the exudative type and one (6%) eye had the quiescent type. Larger lesion area and disruption of the foveal inner-segment/outer-segment layer correlated with worse baseline BCVA. Polypoidal choroidal vasculopathy (PCV) type 1 was present in 50% and PCV type 2 in the other 50%. Polypoidal choroidal vasculopathy (PCV) type 1 was associated with a worse baseline BCVA and greater lesion size.

CONCLUSION: Polypoidal choroidal vasculopathy (PCV) is not a rare condition in Danes with exudative AMD and presents often extramacular and with haemorrhage. This study underscores the importance of ICGA as a part of the diagnostic repertoire in AMD and suggests its routine use in Scandinavian populations.

PMID: 29193780


**Causes and Three-year Incidence of Irreversible Visual Impairment in Jing-An District, Shanghai, China from 2010-2015.**

Xia F, Wu L, Weng C, Zhou X.

BACKGROUND: The registry system can be used to observe the distribution trend of diseases and analyze the related data to provide useful information in a way that enables the government to take appropriate interventional measures. The purpose of this study was to determine the causes and three-year incidence of newly registered disabled patients who were blind or had low vision in Jing-An District, Shanghai, China from 2010 to 2015.
METHODS: Data from the registration system of visual disability in Jing-An District, Shanghai from 2010 to 2015 were collected and analyzed. In this registry, the only person with permanent visual impairment (VI) was identified as being a certified visually impaired person. The main causes of visual disability were obtained, the three-year incidence of visual disability was calculated, and the relationships between blindness or low vision and age, as well as those between blindness or low vision and gender, were analyzed.

RESULTS: Six-hundred and forty-six newly certified people with VI were registered, including 206 blind patients and 440 low vision patients. The major causes of blindness were myopia macular degeneration (MMD, 23.30%), glaucoma (20.39%), and age-related macular degeneration (AMD, 17.96%). The three leading causes of low vision were MMD (58.86%), AMD (16.36%), and diabetic retinopathy (DR, 7.27%). DR (16.0%) was the first leading cause of blindness and the second leading cause of VI in patients aged 30-59 yrs. from 2010 to 2015. The three-year incidences of blindness in 2010-2012 and 2013-2015 (P = 0.43), which remained stable throughout this time period, were 32.74/100000 and 36.51/100000, respectively. However, the three-year incidence of low vision was 64.51/100000 in 2010-2012 and 83.58/100000 in 2013-2015 (P = 0.007), which shows that the incidence increased significantly due to the increase of patients with low vision caused by MMD and DR (P = 0.003 and P = 0.01, respectively).

CONCLUSIONS: MMD, glaucoma, and AMD were the main causes of blindness, while DR was becoming a major cause of VI, especially in working-age people of Jing-An District, Shanghai, China.

PMID: 29179756 PMCID: PMC5704622

**Genetics & gene therapy**

*Gene Ther. 2017 Nov 30. [Epub ahead of print]*

**In situ regeneration of retinal pigment epithelium by gene transfer of E2F2: a potential strategy for treatment of macular degenerations.**


Abstract: The retinal pigment epithelium (RPE) interacts closely with photoreceptors to maintain visual function. In degenerative diseases such as Stargardt disease and age-related macular degeneration, the leading cause of blindness in the developed world, RPE cell loss is followed by photoreceptor cell death. RPE cells can proliferate under certain conditions, suggesting an intrinsic regenerative potential, but so far this has not been utilised therapeutically. Here, we used E2F2 to induce RPE cell replication and thereby regeneration. In both young and old (2 and 18 month) wildtype mice, subretinal injection of non-integrating lentiviral vector expressing E2F2 resulted in 47% of examined RPE cells becoming BrdU positive. E2F2 induced an increase in RPE cell density of 17% compared with control vector-treated and 14% compared with untreated eyes. We also tested this approach in an inducible transgenic mouse model of RPE loss, generated through activation of diphtheria toxin-A gene. E2F2 expression resulted in a 10-fold increase in BrdU uptake and a 34% increase in central RPE cell density. Although in mice this localised rescue is insufficiently large to be demonstrable by electroretinography, a measure of massed retinal function, these results provide proof-of-concept for a strategy to induce in situ regeneration of RPE for the treatment of RPE degeneration. Gene Therapy advance online publication, 30 November 2017; doi:10.1038/gt.2017.89.

PMID: 29188796
Stem cells


Dual AAV Vectors for Stargardt Disease.

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Abstract: Stargardt disease (STGD1), due to mutations in the large ABCA4 gene, is the most common inherited macular degeneration in humans. Attempts at developing gene therapy approaches for treatment of STGD1 are currently ongoing. Among all the vectors available for gene therapy of inherited retinal diseases, those based on adeno-associated viruses (AAV) are the most promising given the efficacy shown in various animal models and their excellent safety profile in humans, as confirmed in many ongoing clinical trials. However, one of the main obstacles for the use of AAV is their limited effective packaging capacity of about 5 kb. Taking advantage of the AAV genome’s ability to concatemerize, others and we have recently developed dual AAV vectors to overcome this limit. We tested dual AAV vectors for ABCA4 delivery, and found that they transduce efficiently both mouse and pig photoreceptors, and rescue the Abca4−/− mouse retinal phenotype, indicating their potential for gene therapy of STGD1. This chapter details how we designed dual AAV vectors for the delivery of the ABCA4 gene and describes the techniques that can be explored to evaluate dual AAV transduction efficiency in vitro and in the retina, and their efficacy in the mouse model of STGD1.

PMID: 29188512


Development of Multigenic Lentiviral Vectors for Cell-Specific Expression of Antiangiogenic miRNAs and Protein Factors.

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Abstract: Generation of lentivirus (LV)-based vectors holding multiple gene cassettes for coexpression of several therapeutic factors provides potent tools in both gene delivery studies as well as in gene therapy. Here we describe the development of such multigenic LV gene delivery vectors enabling cell-specific coexpression of antiangiogenic microRNA (miRNA) and protein factors and, if preferred, a fluorescent reporter, from RNApol(II)-driven expression cassettes orientated in a back-to-back fashion. This configuration may contribute to the development of new combination therapies for amelioration of diseases involving intraocular neovascularization including exudative age-related macular degeneration (AMD).

PMID: 29188505

Diet, lifestyle & low vision


The Relationship Between Plasma Concentrations of Lutein and Zeaxanthin with Self-Reported and Actual Prevalence of AMD in an Irish Population-Based Sample.


PURPOSE: To investigate plasma lutein (L) and zeaxanthin (Z) concentrations with grading-confirmed and self-reported prevalence of age-related macular degeneration (AMD).

MATERIAL AND METHODS: Data collected from a nationally representative prospective cohort study of community-dwelling adults aged 50 years and over in the Republic of Ireland. Participants underwent a
computer-assisted personal interview and a center-based health assessment. Plasma concentrations of L and total Z (Z and meso-zeaxanthin [MZ]) were measured by high performance liquid chromatography, and retinal photographs were graded using a version of the AMD International Classification and Grading System. Consumption of supplements containing L and/or Z and/or MZ was recorded as supplement use. Four groups were identified: Group 1 (n = 24): AMD-afflicted and correctly aware; Group 2 (n = 264): AMD-afflicted but unaware; Group 3 (n = 41): AMD-free and incorrectly believed that they were afflicted with the condition; Group 4 (n = 4094): AMD-free and correctly self-reported absence of AMD.

RESULTS: Of 4,423 participants with plasma concentrations of L and Z and gradable retinal photographs, 288 (6.5%) were afflicted with AMD, and 65 (1.5%) self-reported AMD. Controlling for family history and age, the relationship between grading-confirmed AMD and plasma L was positive and significant (p < 0.001). Mean plasma concentrations of L in Group 2 (mean = 0.2162 ± 0.132 µmol) and Group 4 (mean = 0.2040 ± 0.121 µmol/L) were significantly lower than Group 1 (mean = 0.4691 ± 0.0.372 µmol/L) and Group 3 (mean = 0.3176 ± 0.0.235 µmol/L). Supplement use was reported by 41.7% and 17.1% of participants in Groups 1 and 3, respectively, but only 2.7% and 1.9% of participants in Groups 2 and 4, respectively.

CONCLUSION: A belief that one suffers from AMD, whether justified or not, is associated with supplement use and with higher plasma concentrations of L.

PMID: 29172786