Drug treatment


The Finnish national guideline for diagnosis, treatment and follow-up of patients with wet age related macular degeneration.


Abstract: Age-related macular degeneration (AMD) is the main cause of visual impairment in developed countries. Several improvements in the visualization of posterior segment of the eye together with the introduction of intravitreal anti-VEGF treatment have revolutionized the prognosis of the wet form of AMD (wAMD). Increasing incidence of wAMD together with the limited resources of society and of the healthcare system poses challenges for the provision and development of care. In context of these current aspects, we aimed to set evidence-based medical guidelines for diagnosis, treatment and follow-up of patients with wAMD.

PMID: 28686003


Association of Vascular vs. Avascular Subretinal Hyperreflective Material with Aflibercept Response in Age-related Macular Degeneration.


PURPOSE: To investigate flow signal within subretinal hyperreflective material (SHRM) using optical coherence tomography angiography (OCTA) and its association with aflibercept treatment responses in treatment-naïve neovascular age-related macular degeneration (nAMD).

DESIGN: Prospective consecutive interventional case series

METHODS: Forty-four eyes of 44 patients with treatment-naive nAMD manifesting SHRM on OCT were studied. All patients underwent OCTA and received three monthly aflibercept injections. The intrinsic flow signals within SHRM were quantitatively analyzed using OCTA, and eyes were classified into the vascular and avascular SHRM groups.

RESULTS: Of 44 eyes, 21 (47.7%) and 23 (52.3%) showed vascular SHRM and avascular SHRM, respectively. Compared with eyes with avascular SHRM, eyes with vascular SHRM showed higher rates of external limiting membrane (ELM) disruption due to SHRM (P=.015), classic choroidal neovascularization (CNV) (85.7% vs. 26.1%, P=.87 x 10-4), and intraretinal fluid (P=.008) at baseline. After three aflibercept injections, 38 eyes (86.4%) showed dry macula despite persistent SHRM in 24 eyes (54.5%). Compared
with the eyes with resolved SHRM, those with persistent SHRM showed higher rate of vascular SHRM (75.0% vs. 15.0%, P=.86 × 10^{-4}), classic CNV (P=.032), absence of polypoidal lesion (P=.020), ELM disruption due to SHRM (P=.042), and intraretinal fluid (P=.008). Dry macula after loading injections was significantly associated with SHRM resolution (P=.025).

CONCLUSIONS: In nAMD, SHRM can be categorized as vascular and avascular by quantitative OCTA analysis. Vascular SHRM persisted after treatment and was associated with failure to achieve dry macula, suggesting vascular SHRM is predictive of lower response to anti-VEGF therapy.

PMID: 28669776


Two-year results of a treat-and-extend regimen with aflibercept for polypoidal choroidal vasculopathy.

Morimoto M, Matsumoto H, Mimura K, Akiyama H.

PURPOSE: To evaluate the effects of aflibercept therapy using a treat-and-extend regimen on treatment-naïve polypoidal choroidal vasculopathy (PCV).

METHODS: In a retrospective interventional case series of 58 eyes of 58 patients with PCV, we assessed best-corrected visual acuity (BCVA), central macular thickness (CMT), central choroidal thickness (CCT), and number of injections for 2 years. Polypoidal lesions were also evaluated before treatment and after the loading phase by indocyanine green angiography.

RESULTS: BCVA significantly improved after the loading phase and was maintained in the maintenance phase. CMT and CCT significantly reduced after the loading phase and were maintained throughout the follow-up period. The number of injections averaged 7.72 in the first year and 4.67 in the second year. The average number of polypoidal lesions per patient was 2.43 before treatment. In 32 patients (55.2%), polypoidal lesions regressed completely after the loading phase; these patients also needed significantly fewer injections compared to other patients. CCT at baseline was positively correlated with the decreased amount of CCT after 2 years and negatively correlated with the number of injections for 2 years.

CONCLUSIONS: Treat-and-extend intravitreal therapy with aflibercept may be effective for improving BCVA and exudative change in eyes with PCV. The regression of polypoidal lesions after the loading phase and thicker choroid at baseline might lead to fewer total number of intravitreal injections of aflibercept.

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OUTCOMES OF PATIENTS WITH EXUDATIVE AGE-RELATED MACULAR DEGENERATION TREATED WITH ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR THREE OR MORE YEARS: A Review of Current Outcomes.

Qin VL, Young J, Silva FQ, Conti FF, Singh RP.

PURPOSE: To summarize the findings of long-term outcomes of anti-vascular endothelial growth factor (VEGF) therapy (≥36 months) in patients with exudative age-related macular degeneration.

METHODS: Studies reporting long-term outcomes (≥36 months) of anti-VEGF therapy (n = 11) were identified and analyzed for changes in visual acuity (VA), optical coherence tomography, and safety findings.

RESULTS: Six prospective extension studies of Phase 3 clinical trials and five retrospective evaluation studies were identified. The largest improvements in VA with anti-VEGF treatment were found in Years 1 to
2 after treatment initiation. In five studies, VA ultimately declined below patients' pretreatment initial baseline; in three studies, VA ultimately returned to patients' baseline; in three studies, VA decreased but ultimately remained improved over patients' baseline. There was a trend demonstrating that a higher frequency of intravitreal injections showed a better maintenance in VA. Rates of adverse events were similar to previous registration studies of anti-VEGF drugs.

CONCLUSION: The body of evidence to date regarding long-term anti-VEGF treatment indicates a variable course at greater than 36 months follow-up and seems to be dependent on the treatment protocol. Consistent dosing with fluid-free interval is suggested to maintain VA gains in patients with exudative age-related macular degeneration. There is no evidence suggesting that there are additional adverse events from long-term anti-VEGF use.

PMID: 28671895

High-frequency aflibercept injections in persistent neovascular age-related macular degeneration.
Călugăru D, Călugăru M.
PMID: 28687872

Other treatment & diagnosis

Klin Monbl Augenheilkd. 2017 Jul 6. [Epub ahead of print]
[Autofluorescence of the Human Retinal Pigment Epithelium in Normal Aging and in Age-Related Macular Degeneration: Histology and Clinical Correlation]. [Article in German]
Ach T, Bermond K.
Abstract: Autofluorescence images of the fundus have been part of the routine diagnostics of the human eye for almost two decades. Further development of imaging techniques makes fundus autofluorescence (FAF) imaging a safe, non-invasive, easy-to-perform and reproducible diagnostic tool. FAF uses the autofluorescent properties of tissues, in particular the retinal pigment epithelium (RPE) and its fluorophores. FAF images display phenomena of normal aging as well as disease-related changes of the fundus, but also can be used for monitoring retinal diseases and therapy. After a short introduction into the basics of FAF, the results of the latest histology studies regarding age-related and pathological changes of the human RPE will be summarized for a better understanding and interpretation of FAF images. The normal age-related changes of the RPE are contrasted with the pathological changes in age-related macular degeneration, both clinically and histologically.
PMID: 28683482

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Fluorescence lifetime imaging ophthalmoscopy.
Abstract: Imaging techniques based on retinal autofluorescence have found broad applications in ophthalmology because they are extremely sensitive and noninvasive. Conventional fundus autofluorescence measures fluorescence intensity of retinal fluorophores. It mainly derives its signal from lipofuscin at the level of the retinal pigment epithelium. Fundus autofluorescence, however, can not only be characterized by the spatial distribution of the fluorescence intensity or emission spectrum, but also by a
within characteristic fluorescence lifetime function. The fluorescence lifetime is the average amount of time a fluorophore remains in the excited state following excitation. Fluorescence lifetime imaging ophthalmoscopy (FLIO) is an emerging imaging modality for in vivo measurement of lifetimes of endogenous retinal fluorophores. Recent reports in this field have contributed to our understanding of the pathophysiology of various macular and retinal diseases. Within this review, the basic concept of fluorescence lifetime imaging is provided. It includes technical background information and correlation with in vitro measurements of individual retinal metabolites. In a second part, clinical applications of fluorescence lifetime imaging and fluorescence lifetime features of selected retinal diseases such as Stargardt disease, age-related macular degeneration, choroideremia and retinal artery occlusion are discussed. Potential areas of use for fluorescence lifetime imaging ophthalmoscopy will be outlined at the end of this review.

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EVALUATION OF MACULAR ISCHEMIA IN EYES WITH CENTRAL RETINAL VEIN OCCLUSION: An Optical Coherence Tomography Angiography Study.

PURPOSE: To quantitatively assess macular perfusion status using optical coherence tomography angiography in eyes with aflibercept-treated central retinal vein occlusion and resolved macular edema and to investigate the impact of macular morphology and perfusion status on visual function.

METHODS: This prospective consecutive case series included 23 patients with central retinal vein occlusion. All patients received intravitreal aflibercept injections before analysis. Visual acuity, macular sensitivity, and the macular nonperfusion area (NPA) were evaluated in eyes without macular edema. The macular NPA was evaluated by optical coherence tomography angiography using 3 mm × 3 mm images of the macula. Foveal ellipsoid zone disruption was also analyzed.

RESULTS: The superficial macular NPA measured 4.15 mm ± 0.71 mm (95% confidence interval 3.85-4.46), and the deep macular NPA measured 4.23 mm ± 0.97 mm (95% confidence interval 3.82-4.56). The logarithm of the minimum angle of resolution visual acuity was significantly associated with foveal ellipsoid zone disruption (P = 0.001), the superficial macular NPA (P = 0.015), and the deep macular NPA (P = 0.018). Macular sensitivity correlated negatively with logarithm of the minimum angle of resolution visual acuity (P = 0.007), the superficial macular NPA (P = 0.029), and the deep macular NPA (P = 0.040), but not with the foveal ellipsoid zone disruption (P = 0.435).

CONCLUSION: Optical coherence tomography angiography is a novel technique that enables segmented evaluation of the macular perfusion status in eyes with central retinal vein occlusion and provides visual prognostic information. Enlargement of the macular NPA in the superficial and deep layers was significantly correlated with impaired visual acuity and with decreased macular sensitivity in patients with aflibercept-treated central retinal vein occlusion and resolved macular edema.

PMID: 28671896


Ocriplasmin treatment for vitreomacular traction in real life: can the indication spectrum be expanded?
Manousaridis K, Peter-Reichart S, Mennel S.

PURPOSE: To evaluate the efficacy of intravitreal ocriplasmin for the resolution of vitreomacular traction (VMT) with or without a full thickness macular hole (FTMH) in the clinical setting and to assess whether the
indication spectrum of this treatment modality can be expanded beyond that of the MIVI-TRUST trials.

METHODS: The records of patients with VMT with or without FTMH, who were treated with intravitreal ocriplasmin were reviewed. Patients were divided in two groups. In the first group, VMT with or without FTMH was present without any other macular pathology. In the second group, VMT with or without FTMH occurred alongside of other macular disease including age-related macular degeneration, diabetic maculopathy and post-operative pseudophakic cystoid macular edema.

RESULTS: Release of the VMT was achieved in 12/20 patients (12/20 eyes) of the first group. 16 eyes in this group met 3 or more criteria known to be associated with favorable prognosis after intravitreal ocriplasmin treatment. No cases of release of the VMT were observed in the second group, which included 15 patients (15 eyes). Significant improvement of visual acuity and reduction of the central macular thickness was observed only in the subgroup of eyes which responded to treatment.

CONCLUSIONS: Concomitant macular pathology was a significant factor for treatment failure and we suggest that ocriplasmin should be regarded with caution in these cases. Careful patient selection for treatment with ocriplasmin using specific criteria in the clinical setting can provide superior results to those reported in the MIVI-TRUST trials.

PMID: 28681138

Pathogenesis


Effects of epoxyeicosatrienoic acids (EETs) on retinal macular degeneration in rat models.

Mei F, Wang JG, Chen ZJ, Yuan ZL.

OBJECTIVE: Here we use a rat model to investigate the effects of epoxyeicosatrienoic acids (EETs) on retinal macular degeneration along with pathological and physiological mechanisms of the disease.

MATERIALS AND METHODS: Six choroidal neovascularization (CNV) rats were created with a 532 nm laser and received intravitreal injections of EETs in both eyes. On day 1, 3, 7 and 14 after photocoagulation, the thickness and area of CNV were measured with HE staining and choroidal flat mounts. COX-2 and VEGF levels in CNV were detected by immunohistochemistry method. Protein and mRNA expression were studied by Western blotting and RT-PCR.

RESULTS: 14 days after photocoagulation, CNV thickness and area were significantly reduced (p<0.01) in the treatment group compared with the control group. COX-2 and VEGF had high expression in vascular endothelial cells and stromal cells of CNV. Peak expression of COX-2 and VEGF was significantly higher (p<0.01) in the treatment group than in the control group. 7 days after photocoagulation, VEGF protein and mRNA expression were significantly lower (p<0.05) in the treatment group than in the control group, whereas COX-2 mRNA showed no significant difference (p>0.05). FFA found that CNV fluorescein leakage area was significantly reduced (p<0.05) in the treatment group than in the control group. 14 days after photocoagulation, neovascularization area was significantly smaller (p<0.05) in the treatment group than in the control group. Vitreous EETs levels in the treatment group were significantly higher than in the control group. Compared with the control group, the celecoxib treatment group had significantly increased vitreous EETs (p<0.05).

CONCLUSIONS: Intravitreal injection of celecoxib could suppress the thickness and area of laser-induced macular degeneration CNV. It also improved the vitreous EETs levels in CNV model rats. COX-2 expression was upregulated in the early generation of laser-induced CNV, which may play an important role in regulating expression of VEGF.

PMID: 28682418
Distribution and Function of the Bestrophin-1 (Best1) Channel in the Brain.

Oh SJ, Lee CJ.

Abstract: Bestrophin-1 (Best1) is a calcium-activated anion channel identified from retinal pigment epithelium where human mutations are associated with Best's macular degeneration. Best1 is known to be expressed in a variety of tissues including the brain, and is thought to be involved in many physiological processes. This review focuses on the current state of knowledge on aspects of expression and function of Best1 in the brain. Best1 protein is observed in cortical and hippocampal astrocytes, in cerebellar Bergmann glia and lamellar astrocytes, in thalamic reticular neurons, in meninges and in the epithelial cells of the choroid plexus. The most prominent feature of Best1 is its significant permeability to glutamate and GABA in addition to chloride ions because glutamate and GABA are important transmitters in the brain. Under physiological conditions, both Best1-mediated glutamate release and tonic GABA release from astrocytes modulate neuronal excitability, synaptic transmission and synaptic plasticity. Under pathological conditions such as neuroinflammation and neurodegeneration, reactive astrocytes phenotypically switch from GABA-negative to GABA-producing and redistribute Best1 from the perisynaptic microdomains to the soma and processes to tonically release GABA via Best1. This implicates that tonic GABA release from reactive astrocyte via redistributed Best1 is a common phenomenon that occur in various pathological conditions with astrogliosis such as traumatic brain injury, neuroinflammation, neurodegeneration, and hypoxic and ischemic insults. These properties of Best1, including the permeation and release of glutamate and GABA and its redistribution in reactive astrocytes, promise us exciting discoveries of novel brain functions to be uncovered in the future.

PMID: 28680296 PMCID: PMC5491579

Negative regulators of angiogenesis: important targets for treatment of exudative AMD.

Farnoodian M, Wang S, Dietz J, Nickells RW, Sorenson CM, Sheibani N.

Abstract: Angiogenesis contributes to the pathogenesis of many diseases including exudative age-related macular degeneration (AMD). It is normally kept in check by a tightly balanced production of pro- and anti-angiogenic factors. The up-regulation of the pro-angiogenic factor, vascular endothelial growth factor (VEGF), is intimately linked to the pathogenesis of exudative AMD, and its antagonism has been effectively targeted for treatment. However, very little is known about potential changes in expression of anti-angiogenic factors and the role they play in choroidal vascular homeostasis and neovascularization associated with AMD. Here, we will discuss the important role of thrombospondins and pigment epithellium-derived factor, two major endogenous inhibitors of angiogenesis, in retinal and choroidal vascular homeostasis and their potential alterations during AMD and choroidal neovascularization (CNV). We will review the cell autonomous function of these proteins in retinal and choroidal vascular cells. We will also discuss the potential targeting of these molecules and use of their mimetic peptides for therapeutic development for exudative AMD.

PMID: 28679845

Neovascular age-related macular degeneration is associated with cataract surgery.

Ho JD, Xirasagar S, Kao LT, Lin HC.
PURPOSE: This retrospective cohort study examines the association between cataract surgery and neovascular age-related macular degeneration (AMD) during 5-year follow-up using population-based claims data.

METHODS: We analysed data sourced from the Taiwan Longitudinal Health Insurance Database 2005. The study included 3465 patients who had undergone cataract operations and did not have a diagnosis of AMD before or on the surgery date (study group), and 10 395 age- and sex-matched comparison patients selected randomly from the remaining patients without an AMD diagnosis before the index date. We tracked the claims of each patient for a 5-year period to identify patients with a subsequent diagnosis of neovascular AMD.

RESULTS: The incidence rate of neovascular AMD was 0.88 (95% confidence interval (CI): 0.66-1.14) per 1000 person-years among all sampled patients, 1.60 (95% CI: 1.04-2.36) among the cataract surgery patients and 0.64 (95% CI: 0.43-0.91) among comparison patients (p < 0.001). Stratified Cox proportional analysis showed that relative to the comparison cohort, the adjusted hazard ratio for neovascular AMD during 5-year follow-up was 2.68 (95% CI: 1.55-4.66) for patients who had undergone cataract operation. We censored those who died during follow-up period and adjusted for patients’ monthly income, geographical location, urbanization level, diabetes, hypertension, cardiovascular disease and hyperlipidaemia.

CONCLUSION: This study demonstrated epidemiological evidence of a link between cataract surgery and neovascular AMD during a 5-year follow-up period.

PMID: 28671319


An epidemiological investigation of age-related macular degeneration in aged population in China: the Hainan study.


PURPOSE: The aim of this study was to investigate the prevalence of age-related macular degeneration (AMD) and the risk factors in the residents aged ≥50 years in Hainan Province.

METHODS: Random sampling was carried out in four separated cities in Hainan Province in 2015. All the subjects accomplished the standard questionnaire and ocular examinations. The diagnosis of AMD was performed based on the criteria proposed by Beckman Initiative for Macular Research Classification Committee.

RESULTS: Three hundred and fifty-seven subjects (15.6%) were diagnosed with AMD, including 267 (11.7%) of early AMD, 64 (2.80%) of intermediate AMD and 24 (1.1%) of late AMD, respectively. The factors associated with the prevalence of AMD included age, educational level, smoking, outdoor activities and diet. The prevalence of AMD increased with age, lower educational level, smoking or less outdoor activities. The prevalence of AMD in those with a diet of meat or eggs was higher compared with a diet of vegetables or fish. The prevalence of early, intermediate and late AMD in the aged population in Hainan Province was 11.7, 2.8 and 1.1%, respectively.

CONCLUSIONS: Age and smoking were the risk factors for AMD, while the educational level and outdoor activities were the protective factors. Early AMD mostly occurred in those aged 50-59 years and 60-69 years, while intermediate and late AMD occurred in 70-79 years and older than 80 years.

PMID: 28688024
Systemic complement activation in central serous chorioretinopathy.


PURPOSE: A clear link between several variants in genes involved in the complement system and chronic central serous chorioretinopathy (CSC) has been described. In age-related macular degeneration, a disease that shows clinical features that overlap with CSC, both genetic risk factors and systemic activation of the complement system have previously been found. In this case-control study, we assessed whether there is evidence of either systemic activation or inhibition of the complement system in patients with chronic CSC.

METHODS: A prospective case-control study of 76 typical chronic CSC patients and 29 controls without ophthalmological history was conducted. Complement activity assays (classical, alternative, and mannose-binding lectin pathway), complement factors 3, 4, 4A, 4B, B, D, H, I, and P, activation products C3d, C5a, and sC5b-C9, and the C3d/C3 ratio were analysed in either serum or plasma. A correction for possible effects of gender, age, body mass index, and smoking status was performed.

RESULTS: In this study, none of the tested variables, including regulation and activation products, proved to be significantly different between the groups. Moreover, no associations with either CSC disease activity or possible CSC related steroid use were observed.

CONCLUSION: Despite the available literature regarding a possible relationship between chronic CSC and variants in genes involved in the complement system, we did not find evidence of an association of chronic CSC with either systemic complement activation or inhibition.

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