Drug treatment

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"What should I inject next?" Challenging treatment decisions in the multiple anti-VEGF: a review of publications exploring anti-VEGF switching for nAMD.

Pikkel J, Attas S.

PURPOSE: The purpose of our work was to collate information from studies published to date focusing on switching in anti-VEGF therapy and describe the currently available data on anti-VEGF switching in nAMD.

METHODS: A PubMed search of published articles from January 2010 to January 2017 was conducted. Published studies were compared in parameters of sample size, reason for switch, duration of follow-up, and switch outcome (functional and anatomical).

RESULTS: Our search revealed 31 relevant publications. Switching from bevacizumab to ranibizumab mostly resulted in improvement in visual acuity (VA) and anatomical outcomes (CMT, CRT; 7/8 and 6/8 studies, respectively), whereas switching from ranibizumab to bevacizumab was less effective (no VA or anatomical improvement in 2/4 studies). Switching from either agent to aflibercept resulted mostly in improvement of anatomical outcomes (19/21 studies), but rarely in VA improvement (6/21 studies). Not all results were statistically significant, likely due to small sample sizes.

CONCLUSION: Switching anti-VEGF therapy from bevacizumab to ranibizumab might be of benefit (functionally and anatomically) for patients who failed to improve with intravitreal bevacizumab injections, whereas switching from either agent to aflibercept resulted mostly in reduced macular thickness only.

PMID: 28852904


The effect of intravitreal injections on dry eye, and proposed management strategies.

Laude A, Lim JW, Srinagesh V, Tong L.

Abstract: Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents has become a commonly used treatment method for a number of ophthalmic conditions, including age-related macular degeneration. Although anti-VEGF therapy has shown promising results for many patients, there are several aspects of its application that have not been thoroughly investigated. One of these is the development and/or escalation of concurrent dry eye syndrome. Many patients undergoing treatment are already predisposed to dry eye disease due to their age and overall ocular health. As dry eye can have a substantial impact on quality of life, it has become increasingly apparent that the clinical signs and symptoms should be closely monitored and aggressively managed. This will allow for the optimization of patient comfort and visual potential. Here, we discuss the reasons why dry eye may develop during the
course of repeated ocular anti-VEGF therapy, highlighting the key concerns about current practices and proposing possible solutions to improve the outcome for the patients.

PMID: 28860698 PMCID: PMC5566503


The effect of vitreomacular adhesion in exudative age-related macular degeneration on the results of ranibizumab intravitreal injection.


PURPOSE: To investigate whether vitreomacular adhesion (VMA) affects the outcome of anti-vascular endothelial growth factor (VEGF) therapy for the treatment of exudative age-related macular degeneration (AMD) in Japanese patients.

SUBJECTS AND METHODS: Of 88 Japanese AMD patients (28 men and 60 women, mean age: 72.7±7.5 years) who underwent intravitreal injection of ranibizumab for 3 years from 2010 to 2013, this study involved 12 eyes of 12 patients (10 men and two women) in whom VMA was observed based on optical coherence tomography (OCT) findings (VMA [+] group) and 17 eyes of 16 patients (seven men and nine women, control group) in whom no VMA was observed (VMA [-] group). In all enrolled patients, ranibizumab was administered monthly for 3 months, and then administered as needed (i.e., pro re nata) when deterioration was observed. The two groups were then compared in regard to changes in visual acuity (VA) and the frequency of ranibizumab administration over a 1-year period.

RESULTS: No significant difference was found between the two groups in regard to the transformation of the mean logarithm of the minimum angle of resolution VA change after the first visit. Over the 1-year treatment, the mean frequency of ranibizumab administration for the VMA (+) group was 5.6±2.5 times and for the VMA (-) group was 3.8±1.1 times, thus illustrating a significant difference between the two groups (Mann-Whitney’s U-test: P<0.05).

CONCLUSION: Our findings show that the mean frequency of ranibizumab administration for the VMA (+) group was higher than that in the VMA (-) group, thus indicating that VMA might possibly be involved in the progress of AMD pathology.

PMID: 28860695 PMCID: PMC5565387


Protocol for a randomised, double-masked, sham-controlled phase 4 study on the efficacy, safety and tolerability of intravitreal aflibercept monotherapy compared with aflibercept with adjunctive photodynamic therapy in polypoidal choroidal vasculopathy: the ATLANTIC study.

Marques JP, Farinha C, Costa MÂ, Ferrão Â, Nunes S, Silva R.

PURPOSE: The purpose of this study is to compare the efficacy and safety of intravitreal aflibercept (IVA) with sham photodynamic therapy (sPDT) versus IVA with verteporfin PDT (vPDT) in a Caucasian population with treatment-naive polypoidal choroidal vasculopathy (PCV), enrolling into a treat and extend (T&E) regimen.

METHODS AND ANALYSIS: Randomised, double-masked, sham-controlled, multicentre phase 4 investigator-driven clinical trial. The primary outcomes are (1) change in best-corrected visual acuity (BCVA) from baseline and (2) polyp regression at week 52, assessed by indocyanine green angiography (ICGA). Fifty patients with treatment-naive PCV will be recruited from Portuguese and Spanish clinical sites. Eligible patients will receive monthly IVA for 3 months (week 0, week 4 and week 8). At week 16, all patients will repeat ICGA and undergo central randomisation (1:1 ratio) into one of the following groups:
Group 1-IVA T&E + vPDT; Group 2-IVA T&E + sPDT. PDT will be performed at week 16, week 28 and week 40 in the presence of active polyps. After week 16, the presence of macular fluid on optical coherence tomography will determine the schedule of observations. When present, the interval between visits/injections will decrease 2 weeks (minimum 6 weeks). When not, the interval between visits/injections will increase 2 weeks (maximum 12 weeks). Efficacy will be evaluated based on BCVA, central retinal thickness and polyp regression. Safety parameters will include assessment of intraocular pressure, adverse events and serious adverse events.

ETHICS AND DISSEMINATION: This study was designed and shall be implemented and reported in accordance with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki. The study received approval from Comissão de Ética para a Investigação Clínica and Comité Ético de investigación Clínica del Hospital Universitari de Bellvitge.

TRIAL REGISTRATION NUMBER: This study is registered under the EudraCT number: 2015-001368-20 and the ClinicalTrials.gov Identifier: NCT02495181.

PMID: 28851779

MAbs. 2017 Aug 30:0. [Epub ahead of print]

Protein engineering to increase the potential of a therapeutic antibody Fab for long-acting delivery to the eye.


Abstract: To date, ocular antibody therapies for the treatment of retinal diseases rely on injection of the drug into the vitreous chamber of the eye. Given the burden for patients undergoing this procedure, less frequent dosing through the use of long-acting delivery (LAD) technologies is highly desirable. These technologies usually require a highly concentrated formulation and the antibody must be stable against extended exposure to physiological conditions. Here we have increased the potential of a therapeutic antibody antigen-binding fragment (Fab) for LAD by using protein engineering to enhance the chemical and physical stability of the molecule. Structure-guided amino acid substitutions in a negatively charged complementarity determining region (CDR-L1) of an anti-factor D (AFD) Fab resulted in increased chemical stability and solubility. A variant of AFD (AFD.v8), which combines light chain substitutions (VL-D28S:D30E:D31S) with a substitution (VH-D61E) to stabilize a heavy chain isomerization site, retained complement factor D binding and inhibition potency and has properties suitable for LAD. This variant was amenable to high protein concentration (>250 mg/mL), low ionic strength formulation suitable for intravitreal injection. AFD.v8 had acceptable pharmacokinetic (PK) properties upon intravitreal injection in rabbits, and improved stability under both formulation and physiological conditions. Simulations of expected human PK behavior indicated greater exposure with a 25-mg dose enabled by the increased solubility of AFD.v8.

PMID: 28854082


Widening use of dexamethasone implant for the treatment of macular edema.


Abstract: Sustained-release intravitreal 0.7 mg dexamethasone (DEX) implant is approved in Europe for the treatment of macular edema related to diabetic retinopathy, branch retinal vein occlusion, central retinal vein occlusion, and non-infectious uveitis. The implant is formulated in a biodegradable copolymer to release the active ingredient within the vitreous chamber for up to 6 months after an intravitreal injection,
allowing a prolonged interval of efficacy between injections with a good safety profile. Various other ocular pathologies with inflammatory etiopathogeneses associated with macular edema have been treated by DEX implant, including neovascular age-related macular degeneration, Irvine-Gass syndrome, vasoproliferative retinal tumors, retinal telangiectasia, Coats’ disease, radiation maculopathy, retinitis pigmentosa, and macular edema secondary to scleral buckling and pars plana vitrectomy. We undertook a review to provide a comprehensive collection of all of the diseases that benefit from the use of the sustained-release DEX implant, alone or in combination with concomitant therapies. A MEDLINE search revealed lack of randomized controlled trials related to these indications. Therefore we included and analyzed all available studies (retrospective and prospective, comparative and non-comparative, randomized and nonrandomized, single center and multicenter, and case report). There are reports in the literature of the use of DEX implant across a range of macular edema-related pathologies, with their clinical experience supporting the use of DEX implant on a case-by-case basis with the aim of improving patient outcomes in many macular pathologies. As many of the reported macular pathologies are difficult to treat, a new treatment option that has a beneficial influence on the clinical course of the disease may be useful in clinical practice.

PMID: 28860707 PMCID: PMC5566324

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Subretinal Injection: A Review on the Novel Route of Therapeutic Delivery for Vitreoretinal Diseases.

Peng Y, Tang L, Zhou Y.

Abstract: Compared to intravitreal injection, subretinal injection has more direct effects on the targeting cells in the subretinal space, which provides a new therapeutic method for vitreoretinal diseases, especially when gene therapy and/or cell therapy is involved. To date, subretinal delivery has been widely applied by scientists and clinicians as a more precise and efficient route of ocular drug delivery for gene therapies and cell therapies including stem cells in many degenerative vitreoretinal diseases, such as retinitis pigmentosa, age-related macular degeneration, and Leber's congenital amaurosis. However, clinicians should be aware of adverse events and possible complications when performing subretinal delivery. In the present review, the subretinal injection used in vitreoretinal diseases for basic research and clinical trials is summarized and described. Different methods of subretinal delivery, as well as its benefits and challenges, are also briefly introduced.

PMID: 28858866

Other treatment & diagnosis


Optical coherence tomography angiography reproducibility of lesion size measurements in neovascular age-related macular degeneration (AMD).

Amoroso F, Miere A, Semoun O, Jung C, Capuano V, Souied EH.

PURPOSE: To evaluate the reproducibility and interuser agreement of measurements of choroidal neovascularisation in optical coherence tomography angiography (OCTA).

DESIGN: Prospective non-interventional study.

METHODS: Consecutive patients, presenting with neovascular age-related macular degeneration (AMD), underwent two sequential OCTA examinations (AngioVue, Optovue, Fremont, California, USA), performed by the same trained examiner. Neovascular lesion area was then measured on both examinations in the choriocapillaris automatic segmentation by two masked readers, using the semiautomated measuring
software embedded in the instrument. Two measuring features were used: the first corresponding to the total manually contoured lesion area with the flow draw tool (select area) and the second to the total area of solely vessels with high flow within the lesion (vessel area). These measurements were then compared in order to assess both the reproducibility of OCTA examination and the interuser agreement with the embedded software.

RESULTS: Forty-eight eyes of 46 patients (77.4 mean age, +/- 8.2 SD, range from 62 to 95 years old, eight men, 38 women) were included in our study. Mean choroidal neovascularisation area was of 0.72 +/- 0.7 mm² for the first measurement and 0.75 +/- 0.76 mm² for the second measurement; difference between the first and the second measurement was 0.03 mm². Intrauser agreement was of 0.98 (CI 0.98 to 0.99) for both 'vessel area' and 'select area' features. Interuser agreement was of 0.98 (CI 0.97 to 0.99) for 'select area' and 'vessel area' features.

CONCLUSION: Our data suggest that OCTA provide reproducible imaging for evaluation of the neovascular size in the setting of AMD.

PMID: 28855197


Recent developments in age-related macular degeneration: a review.
Al-Zamil WM, Yassin SA.

BACKGROUND: Visual impairment in elderly people is a considerable health problem that significantly affects quality of life of millions worldwide. The magnitude of this issue is becoming more evident with an aging population and an increasing number of older individuals.

OBJECTIVE: The objective of this article was to review the clinical and pathological aspects of age-related macular degeneration (AMD), diagnostic tools, and therapeutic modalities presently available or underway for both atrophic and wet forms of the disease.

METHODS: An online review of the PubMed database was performed, searching for the key words. The search was limited to articles published since 1980 to date.

RESULTS: Several risk factors have been linked to AMD, such as age (>60 years), lifestyle (smoking and diet), and family history. Although the pathogenesis of AMD remains unclear, genetic factors have been implicated in the condition. Treatment for atrophic AMD is mainly close observation, coupled with nutritional supplements such as zinc and antioxidants, whereas treatment of wet AMD is based on targeting choroidal neovascular membranes.

CONCLUSION: Identification of modifiable risk factors would improve the possibilities of preventing the progression of AMD. The role of anti-vascular endothelial growth factor (anti-VEGF) agents has transformed the therapeutic approach of the potentially blinding disease "wet AMD" into a more favorable outcome.

PMID: 28860733 PMCID: PMC5573066

Pathogenesis


Ocular distribution of antioxidant enzyme paraoxonase & its alteration in cataractous lens & diabetic retina.
Bharathidevi SR, Babu KA, Jain N, Muthukumaran S, Umashankar V, Biswas J, Angayarkanni N.
BACKGROUND & OBJECTIVES: The enzyme paraoxonase (PON), an antioxidant enzyme that has both arylesterase and thiolactonase activity, is well studied in cardiovascular diseases. Although a few studies have shown altered PON activity in ocular diseases such as age-related macular degeneration and diabetic retinopathy, but the tissue-wise expression of PON in its three gene forms has not been studied. This study was conducted to see the ocular distribution of PON for any altered expression in ocular pathologies such as in cataract and diabetes mellitus.

METHODS: Immunohistochemistry (IHC) of the ocular tissues was done for localizing all three forms of the PON in the human donor eyeballs. The PON arylesterase (PON-AREase) and thiolactonase (PON-HCTLase) activities were determined by spectrophotometry in kinetic mode, and the mRNA expression of the PON genes (PON1-3) was determined by reverse transcription-polymerase chain reaction.

RESULTS: IHC showed the presence of both PON1 and 2 in all the ocular tissues and PON3 was seen only in retina. The mRNA expression analysis showed that PON2 and PON3 were present in all the tissues, whereas PON1 was seen only in ciliary and retina. Both the PON-AREase and PON-HCTLase activities were detected in all ocular tissues and was in the order of lens>retina>choroid>ciliary body>iris. The expression and activity were studied in cataractous lens and in diabetic retina of the donor eyes. A significant decrease in PON-AREase activity was seen in cataractous lens (P<0.05) but not in diabetic retina, and there was an increase in PON- HCTLase activity (P<0.05) only in diabetic retina. Bioinformatic studies and in vitro experiments indicated that advanced glycation end products (AGE) such as carboxymethyl -lysine might decrease the PON- AREase activity of the PON.

INTERPRETATION & CONCLUSIONS: Distribution of PON enzyme and its activity in ocular tissues is reported here. The study revealed maximal PON activity in lens and retina, which are prone to higher oxidative stress. Differential activities of PON were observed in the lens and retinal tissues from cataractous and diabetic patients, respectively.

PMID: 28862184


2016 Glenn A. Fry Award Lecture: Mechanisms and Potential Treatments of Early Age-Related Macular Degeneration.

Fletcher EL.

Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in those older than 80 years. Understanding the mechanisms that cause this condition or its progression is critical for developing novel treatments. Here we summarize our studies evaluating the role of purine, adenosine triphosphate (ATP), in early AMD as well as photoreceptor loss and have also provided some insights to our investigations of a new laser treatment for those with early AMD. One of the receptors that are activated by ATP, P2X7, is expressed by neurons and immune cells and has a different function in each cell type. In neurons, P2X7 receptors form a ligand-gated ion channel, whereas on immune cells P2X7 receptors act as a scavenger receptor. These distinct functions have provided new insights to the mechanisms of AMD. On the one hand, high concentrations of ATP can cause photoreceptor death, most likely via stimulation of P2X7 receptors localized on photoreceptor terminals. On the other hand, P2X7 receptors mediate removal of dead and dying cells by monocytes. By understanding the fundamental cell biological changes that occur in patients and animal models of disease, we have uncovered mechanisms that may help us manage and treat patients in the future.

PMID: 28858048


Reduction in ocular complement factor B protein in mice and monkeys by systemic administration of factor B antisense oligonucleotide.
Grossman TR, Carrer M, Shen L, Johnson RB, Hettrick LA, Henry SP, Monia BP, McCaleb ML.

PURPOSE: Age-related macular degeneration (AMD) is the leading cause of permanent vision loss among the elderly in many industrialized countries, and the complement system plays an important role in the pathogenesis of AMD. Inhibition of complement factor B, a key regulator of the alternative pathway, is implicated as a potential therapeutic intervention for AMD. Here we investigated the effect of liver factor B reduction on systemic and ocular factor B levels.

METHODS: Second-generation antisense oligonucleotides (ASOs) targeting mouse and monkey factor B mRNA were administered by subcutaneous injection to healthy mice or monkeys, and the level of factor B mRNA was assessed in the liver and the eye. In addition, the factor B protein level was determined in plasma and whole eyes from the treated animals.

RESULTS: Mice and monkeys treated with factor B ASOs demonstrated a robust reduction in liver factor B mRNA levels with no change in ocular factor B mRNA levels. Plasma factor B protein levels were significantly reduced in mice and monkeys treated with factor B ASOs, leading to a dramatic reduction in ocular factor B protein, below the assay detection levels.

CONCLUSIONS: The results add to the increasing evidence that the liver is the main source of plasma and ocular factor B protein, and demonstrate that reduction of liver factor B mRNA by an ASO results in a significant reduction in plasma and ocular factor B protein levels. The results suggest that inhibition of liver factor B mRNA by factor B ASOs would reduce systemic alternative complement pathway activation and has potential to be used as a novel therapy for AMD.

PMID: 28855795 PMCID: PMC5563462


Novel evidence for complement system activation in chick myopia and hyperopia models: a meta-analysis of transcriptome datasets.

Riddell N, Crewther SG.

Abstract: Myopia (short-sightedness) and hyperopia (long-sightedness) occur when the eye grows too long or short, respectively, for its refractive power. There are currently approximately 1.45 billion myopes worldwide and prevalence is rising dramatically. Although high myopia significantly increases the risk of developing a range of sight-threatening disorders, the molecular mechanisms underlying ocular growth regulation and its relationship to these secondary complications remain poorly understood. Thus, this study meta-analyzed transcriptome datasets collected in the commonly used chick model of optically-induced refractive error. Fifteen datasets (collected across five previous studies) were obtained from GEO, preprocessed in Bioconductor, and divided into 4 conditions representing early (≤1 day) and late (>1 day) myopia and hyperopia induction. Differentially expressed genes in each condition were then identified using Rank Product meta-analysis. The results provide novel evidence for transcriptional activation of the complement system during both myopia and hyperopia induction, and confirm existing literature implicating cell signaling, mitochondrial, and structural processes in refractive error. Further comparisons demonstrated that the meta-analysis results also significantly improve concordance with broader omics data types (i.e., human genetic association and animal proteomics studies) relative to previous transcriptome studies, and show extensive similarities with the genes linked to age-related macular degeneration, choroidal neovascularization, and cataract.

PMID: 28852117 PMCID: PMC5574905


TGF-β participates choroid neovascularization through Smad2/3-VEGF/TNF-α signaling in mice with Laser-induced wet age-related macular degeneration.
Wang X, Ma W, Han S, Meng Z, Zhao L, Yin Y, Wang Y, Li J.

Abstract: Choroidal neovascularization (CNV) is the most severe complication in Age-related macular degeneration (AMD) and the most common cause of irreversible blindness in the elderly in developed world. The aim of this study was to identify the effect of transforming growth factor-β (TGF-β) and Smad2/3-VEGF/TNF-α signaling on CNV angiopoiesis, and to explore TGF-β inhibitors on the development of CNV in a CNV mouse model. Fundus fluorescein angiography (FFA) was used to evaluate the laser-induced CNV formation. The histology of CNV lesions stained with hematoxylin-eosin (HE) was obtained. The immunofluorescent staining was performed to determine TGF-β protein expression. The expressions of TGF-β, phosphorylated Smad2/3, VEGF and TNF-α were determined by using Western blot analysis. The CNV areas were analyzed by using fluorescein stain on RPE/choroid-sclera flat mounts. We found the levels of TGF-β protein expression increasingly reached the peak till 3rd week during the CNV development. The protein levels of VEGF and TNF-α also increased significantly in CNV mice, which were inhibited by a synthetic TGF-β inhibitor LY2157299 or a natural TGF-β inhibitor Decorin. The phosphorylated Smad2/3 levels increased significantly in CNV mice, but this response was profoundly suppressed by the TGF-β inhibitors. Here we have demonstrated that TGF-β/Smad signaling plays an important role in Laser-induced CNV formation through down-regulation of VEGF and TNF-α expressions, suggesting TGF-β inhibitors may provide an alternative to traditional methods in wet AMD treatment.

PMID: 28852052 PMCID: PMC5575286


Metalloproteinases as mediators of inflammation and the eyes: molecular genetic underpinnings governing ocular pathophysiology.

Singh M, Tyagi SC.

Abstract: There are many vision threatening diseases of the eye affecting millions of people worldwide. In this article, we are summarizing potential role of various matrix metalloproteinases (MMPs); the Zn (2+) dependent endoproteases in eye health along with pathogenesis of prominent ocular diseases such as macular degeneration, diabetic retinopathy, and glaucoma via understanding MMPs regulation in affected patients, interactions of MMPs with their substrate molecules, and key regulatory functions of tissue inhibitor of metalloproteinases (TIMPs) towards maintaining overall homeostasis.

PMID: 28861360 PMCID: PMC5554853

Epidemiology


Risks of newly onset hemorrhagic stroke in patients with neovascular age-related macular degeneration.


PURPOSE: Age-related macular degeneration (AMD) is an eye disease causing blindness in the elderly. It shares many common possible pathogenic mechanisms with cardiovascular diseases. Many studies have discussed the association between AMD and stroke, but the results were inconsistent. Our aim was to determine the associations between neovascular AMD and the risk of stroke in the Taiwanese population.

METHODS: This is a retrospective cohort study. We used claims data from National Health Insurance Research Database. Patients aged more than 45 years without stroke, myocardial infarction, or any AMD were selected from 2001 to 2008 and followed until 2010. The index date was defined as the date of nAMD diagnosis (ICD-9 code, 362.52). The comparison group was patients without an nAMD diagnosis with age- and sex-matched to nAMD subjects at a ratio of up to 10 to 1. Kaplan-Meier survival analysis and Cox
regression analysis were used. The incidence of stroke events (ICD-9 codes, 430-434) and their subtypes (hemorrhagic and ischemic) were primary outcomes. Secondary outcomes included acute myocardial infarction (AMI), composite AMI/stroke, and all-cause mortality.

RESULTS: Patients with nAMD had a higher risk of developing stroke, with an adjusted HR of 1.30 (95% CI, 1.01-1.68). A higher risk for hemorrhagic stroke (HR, 1.70, 95% CI, 1.03-2.83) was also found. No significant differences were observed in ischemic stroke, the composite of AMI/stroke, and all-cause mortality.

CONCLUSIONS: Patients with nAMD had a significantly higher risk of developing stroke, which was driven mainly by the increased risk of developing the hemorrhagic subtype.

PMID: 28856767

Genetics & gene therapy


Phenotype Characteristics of Patients With Age-Related Macular Degeneration Carrying a Rare Variant in the Complement Factor H Gene.

Kersten E, Geerlings MJ, den Hollander AI, de Jong EK, Fauser S, Peto T, Hoyng CB.

IMPORTANCE: Rare variants in the complement factor H (CFH) gene and their association with age-related macular degeneration (AMD) have been described. However, there is limited literature on the phenotypes accompanying these rare variants. Phenotypical characteristics could help ophthalmologists select patients for additional genetic testing.

OBJECTIVE: To describe the phenotypical characteristics of patients with AMD carrying a rare variant in the CFH gene.

DESIGN, SETTING, AND PARTICIPANTS: In this cross-sectional study, we searched the genetic database of the department of ophthalmology at the Radboudumc (tertiary ophthalmologic referral center) and the European Genetic Database for patients with AMD with a rare genetic variant in the CFH gene. Patient recruitment took place from March 30, 2006, to February 18, 2013, and data were analyzed from November 30, 2015, to May 8, 2017. Phenotypical features on fundus photographs of both eyes of patients were graded by 2 independent reading center graders masked for carrier status.

MAIN OUTCOMES AND MEASURES: Differences in phenotypical characteristics between rare variant carriers and noncarriers were analyzed using univariable generalized estimated equations logistic regression models accounting for intereye correlation.

RESULTS: Analyses included 100 eyes of 51 patients with AMD carrying a CFH variant (mean [SD] age, 66.7 [12.1] years; 64.7% female) and 204 eyes of 102 age-matched noncarriers (mean [SD] age, 67.1 [11.8] years; 54.9% female). Carrying a rare pathogenic CFH variant was associated with larger drusen area (odds ratio range, 6.98 [95% CI, 2.04-23.89] to 18.50 [95% CI, 2.19-155.99]; P = .002), presence of drusen with crystalline appearance (odds ratio, 3.24; 95% CI, 1.24-8.50; P = .02), and drusen nasal to the optic disc (odds ratio range, 4.03 [95% CI, 1.70-9.56] to 7.42 [95% CI, 0.65-84.84]; P = .003).

CONCLUSIONS AND RELEVANCE: Identification of rare CFH variant carriers may be important for upcoming complement-inhibiting therapies. Patients with an extensive drusen area, drusen with crystalline appearance, and drusen nasal to the optic disc are more likely to have a rare variant in the CFH gene. However, it is not likely that carriers can be discriminated from noncarriers based solely on phenotypical characteristics from color fundus images. Therefore, ophthalmologists should consider genetic testing in patients with these phenotypic characteristics in combination with other patient characteristics, such as early onset, cuticular drusen on fluorescein angiography, and family history of AMD.

PMID: 28859202
RNA expression in human retina.

Li M, Zauhar RJ, Grazal C, Curcio CA, DeAngelis MM, Stambolian D.

Abstract: Recent Genome-wide Association Studies (GWASs) for eye diseases/traits have delivered a number of novel findings across a diverse range of diseases, including age-related macular degeneration (AMD), glaucoma and refractive error. However, despite this astonishing rate of success, the major challenge still remains to not only confirm that the genes implicated in these studies are truly the genes conferring protection from or risk of disease but also to define the functional roles these genes play in disease. Ongoing evidence is accumulating that the single nucleotide polymorphisms (SNPs) used in GWAS and fine mapping studies have causal effects through their influence on gene expression rather than affecting protein function. The biological interpretation of SNP regulatory effects for a tissue requires knowledge of the transcriptome for that tissue. We summarize the reasons to characterize the complete retinal transcriptome as well as the evidence to include an assessment of differences in regional retinal expression.

PMID: 28854577

Genetics of age-related macular degeneration (AMD).


Abstract: Age-related macular degeneration (AMD) is a progressive blinding disease and represents the leading cause of visual impairment in the aging population. AMD affects central vision which impairs one's ability to drive, read and recognize faces. There is no cure for this disease and current treatment modalities for the exudative form of the disease require repeated intravitreal injections which may be painful, are incompletely efficacious, and represent a significant treatment burden for both the patient and physician. As such, AMD represents a significant and important clinical problem. It is anticipated that in three years' time, 196 million individuals will be affected with AMD. Over 250 billion dollars per year are spent on care for AMD patients in the US. Over half of the heritability is explained by two major loci, thus AMD is considered the most well genetically defined of the complex disorders. A recent GWAS on 43,566 subjects identified novel loci and pathways associated with AMD risk, which has provided an excellent platform for additional functional studies. Genetic variants have been investigated, particularly with respect to anti-VEGF treatment, however to date, no pharmacogenomic associations have been consistently identified across these studies. It may be that if the goal of personalized medicine is to be realized and biomarkers are to have predictive value for determining the magnitude of risk for AMD at the genetic level, one will need to examine the relationships between these pathways across disease state and relative to modifiable risk factors such as hypertension, smoking, body mass index, and hypercholesterolemia. Further studies investigating protective alleles in populations with low AMD prevalence may lead to this goal.

PMID: 28854576

Rare Genetic Variants in Age-Related Macular Degeneration.

Seddon JM, Ferrara D.

PMID: 28859197
**Stem cells**


Subretinally Transplanted Embryonic Stem Cells Rescue Photoreceptor Cells from Degeneration in the RCS Rats.


Abstract: The Royal College of Surgeons (RCS) rat is an animal model for retinal degeneration such as the age-related macular degeneration. The RCS rat undergoes a progressive retinal degeneration during the early postnatal period. A potential treatment to prevent this retinal degeneration is the transplantation into the subretinal space of cells that would replace functions of the degenerating retinal pigment epithelium (RPE) cells or may form neurotrophic factors. In this study we have investigated the potential of subretinally transplanted embryonic stem cells to prevent the genetically determined photoreceptor cell degeneration in the RCS rat. Embryonic stem cells from the inner cell mass of the mouse blastocyst were allowed to differentiate to neural precursor cells in vitro and were then transplanted into the subretinal space of 20-day-old RCS rats. Transplanted and sham-operated rats were sacrificed 2 months following cell transplantation. The eyes were enucleated and photoreceptor degeneration was quantified by analyzing and determining the thickness of the outer nuclear layer by light and electron microscopy. In the eyes transplanted with embryonic cells up to 8 rows of photoreceptor cell nuclei were observed, whereas in nontreated control eyes the outer nuclear layer had degenerated completely. Transplantation of embryonic stem cells appears to delay photoreceptor cell degeneration in RCS rats.

PMID: 28858595


Stem cells in regenerative medicine - from laboratory to clinical application - the eye.

Dąbrowska AM, Skopiński P.

Abstract: Stem cells are currently one of the most researched and explored subject in science. They constitute a very promising part of regenerative medicine and have many potential clinical applications. Harnessing their ability to replicate and differentiate into many cell types can enable successful treatment of diseases that were incurable until now. There are numerous types of stem cells (e.g. ESCs, FSCs, ASCs, iPSCs) and many different methods of deriving and cultivating them in order to obtain viable material. The eye is one of the most interesting targets for stem cell therapies. In this article we summarise different aspects of stem cells, discussing their characteristics, sources and methods of culture. We also demonstrate the most recent clinical applications in ophthalmology based on an extensive current literature review. Tissue engineering techniques developed for corneal limbal stem cell deficiency, age-related macular degeneration (AMD) and glaucoma are among those presented. Both laboratory and clinical aspects of stem cells are discussed.

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**Diet, lifestyle & low vision**


Absolute and estimated values of macular pigment optical density in young and aged Asian participants with or without age-related macular degeneration.

Tsubota K.

BACKGROUND: Lutein and zeaxanthin are suggested micronutrient supplements to prevent the progression of age-related macular degeneration (AMD), a leading cause of blindness worldwide. To monitor the levels of lutein/zeaxanthin in the macula, macular pigment optical density (MPOD) is measured. A commercially available device (MPSII®, Elektron Technology, Switzerland), using technology based on heterochromatic flicker photometry, can measure both absolute and estimated values of MPOD. However, whether the estimated value is applicable to Asian individuals and/or AMD patients remains to be determined.

METHODS: The absolute and estimated values of MPOD were measured using the MPSII® device in 77 participants with a best-corrected visual acuity (BCVA) > 0.099 (logMAR score).

RESULTS: The studied eyes included 17 young (20-29 years) healthy, 26 aged (>50 years) healthy, 18 aged and AMD-fellow, and 16 aged AMD eyes. The mean BCVA among the groups were not significantly different. Both absolute and estimated values were measurable in all eyes of young healthy group. However, absolute values were measurable in only 57.7%, 66.7%, and 43.8%, of the aged healthy, AMD-fellow, and AMD groups, respectively, and 56.7% of the eyes included in the 3 aged groups. In contrast, the estimated value was measurable in 84.6%, 88.9% and 93.8% of the groups, respectively, and 88.3% of eyes in the pooled aged group. The estimated value was correlated with absolute value in individuals from all groups by Spearman's correlation coefficient analyses (young healthy: R² = 0.885, P = 0.0001; aged healthy: R² = 0.765, P = 0.001; AMD-fellow: R² = 0.851, P = 0.0001; and AMD: R² = 0.860, P = 0.013). Using the estimated value, significantly lower MPOD values were found in aged AMD-related eyes, which included both AMD-fellow and AMD eyes, compared with aged healthy eyes by Student's t-test (P = 0.02).

CONCLUSIONS: Absolute, in contrast to estimated, value was measurable in a limited number of aged participants; however, it was correlated with estimated value both in young and aged Asian populations with or without AMD. These results may inform future clinical studies investigating the measurement of MPOD in understanding the role of macular pigments in the pathogenesis of AMD.

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