Drug treatment


Clinical and social characteristics associated with reduced visual acuity at presentation in Australian patients with neovascular age-related macular degeneration: a prospective study from a long term observational dataset. The Fight Retinal Blindness Project.

Nguyen V, Dainen V, Guymner RH, McAllister IL, Morlet N, Barthelmes D, Gillies MC.

IMPORTANCE: Identifying variables that influence presenting visual acuity (VA) in patients with neovascular age-related macular degeneration (nAMD) is important because it is a strong predictor of long-term outcomes.

BACKGROUND: To assess the clinical and social characteristics associated with low presenting VA in nAMD patients.

DESIGN: Cross-sectional analysis from a prospective, observational database.

PARTICIPANTS: We identified 3242 treatment-naïve patients from 54 Australian practices in the Fight Retinal Blindness! registry.

METHODS: Age, gender, ethnicity and VA were recorded at the baseline visit. Socio-economic status was determined using the Australian Bureau of Statistics socio-economic indexes for areas.

MAIN OUTCOME MEASURES: Association between clinical and socio-economic characteristics with presenting VA.

RESULTS: Poor VA (≤35 letters) in the presenting eye was associated with older age (adjusted odds ratio [AOR] 1.33 for patients ≥80 years vs. <80 years [95%CI 1.04-1.71]), treatment at a public practice (AOR 1.91 for public vs. private practices [95%CI 1.46-2.50]) and intermediate (36-69 letters) VA in the fellow eye (AOR 0.67 [95%CI 0.47-0.95] and 0.64 [95%CI 0.48-0.85] for poor [≤35 letters] and good [≥70 letters] VA vs. intermediate VA in fellow eye). Gender, ethnicity and socio-economic status were not independently associated with VA at presentation.

CONCLUSIONS AND RELEVANCE: Poor presenting vision is detrimental to the long-term outcomes of nAMD. Poor presentation of nAMD in Australia may not be related to socio-economic circumstances, but due to systems of care. Further research is warranted to determine why patients at public practices present with worse vision compared with private practices in Australia.

PMID: 28842956
Comparison of 12-month therapeutic effect of conbercept and ranibizumab for diabetic macular edema: a real-life clinical practice study.


BACKGROUND: To compare the efficacy of intravitreal conbercept and ranibizumab in the treatment of diabetic macular edema (DME) in a real-life clinical practice.

METHODS: This was a retrospective study. Among 62 Chinese patients with DME, 32 patients (36 eyes) received intravitreal conbercept (IVC) injections and 30 patients (32 eyes) received intravitreal ranibizumab (IVR) injections, once a month for 3 months followed by as needed therapy. All participants had at least 12 months of follow-up. We compared the changes in best-corrected visual acuity (BCVA) letter score and central retinal thickness (CRT) between groups, as well as the number of intravitreal injections delivered. Safety was assessed with the incidence of adverse events (AEs).

RESULTS: At month 12, the mean BCVA letter score improved by 9.3 ± 5.2 with conbercept, and by 8.9 ± 4.4 with ranibizumab, the mean CRT reduction was 138.4 ± 97.7 μm and 145.2 ± 72.5 μm, respectively. There was no statistically significant difference of improvement in BCVA (P = 0.756) and decrease in CRT (P = 0.748) between the two groups. The number of intravitreal injections delivered was significantly higher (P = 0.027) in the IVR group (7.2 ± 1.0 per eye) than in the IVC group (6.6 ± 0.9 per eye). There were no severe ocular adverse reactions or systemic adverse events.

CONCLUSIONS: Both conbercept and ranibizumab are effective in the treatment of DME, achieving the similar clinical efficacy. In comparison to ranibizumab, conbercept shows a longer treatment interval and fewer intravitreal conbercept injections are needed.

PMID: 28841827

Variations in Treatment Delivery for Patients with Neovascular AMD in the UK: Results from an Ophthalmology Trainee Clinical Research Network Study.


Collaborators (29)

INTRODUCTION: The aim of this study was to determine treatment delivery patterns for patients with neovascular age-related macular degeneration (nAMD) across the UK through an ophthalmology trainee research network delivered observational study.

METHODS: Data were collected via an online tool by potential research collaborators identified by the Ophthalmology Trainee Clinical Trial Network (OCTN). Collaborators were asked to comment on periprocedural practices of treatment of nAMD in their eye unit including treatment location and injectors, clinical assessment and routine observation in patients undergoing intravitreal treatment.

RESULTS: Data were available from 26 units around the United Kingdom. Survey methodology refinement was approximately 3 months, and the average response time was 4.9 ± 2.4 days. The majority of responders confirmed that treatment was undertaken as a "one-stop" service (n = 15, 58%), delivered in a clean room (n = 23, 88%). In the majority of units, doctors administered injections (n = 24, 92%), but significant treatment was also given by nurse injectors (n = 21, 81%). All collaborators reported that patients underwent visual acuity testing and optical coherence tomography imaging at all visits, but other imaging
CONCLUSIONS: These results demonstrate the feasibility of conducting ophthalmology trainee led and delivered observational studies. Our results show that FFA is not routinely used in the diagnosis of nAMD in the units sampled; most injections are carried out in a clean room, and ophthalmic nurses delivering injections is a highly prevalent model of care in the UK.

PMID: 28849579


Factors Affecting Compliance to Intravitreal Anti-Vascular Endothelial Growth Factor Therapy in Patients with Age-Related Macular Degeneration.

Polat O, İnan S, Özcan S, Doğan M, Küsbeci T, Yavaş GF, İnan ÜÜ.

OBJECTIVES: To determine factors influencing compliance in patients with neovascular age-related macular degeneration (n-AMD) undergoing intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

MATERIALS AND METHODS: The files of n-AMD patients recommended treatment with ranibizumab were reviewed retrospectively. The treatment regimen was 3 consecutive monthly injections followed by monthly follow-up with intravitreal injections as needed (pro re nata, PRN). Demographic and ocular characteristics were recorded. The patients were categorized into 2 groups: full compliance to treatment, or incomplete loading schedule and/or irregular maintenance treatment. All patients were interviewed by phone about factors affecting continuation of treatment.

RESULTS: Mean age of the 314 patients (160 female, 154 male) included in the study was 71.6±9.1 years. A total of 246 patients (78.3%) could complete 3 consecutive injections at 1-month intervals after the start of treatment; 57 patients (18.2%) did not attend monthly follow-up during the 1-year follow-up period following the 3 consecutive monthly injections. Overall, 39.8% of the patients were not able to fully comply with the ranibizumab treatment by PRN regimen for 1 year. Better visual acuity at baseline, smaller lesion size, living closer to the hospital, higher education and sociocultural level, and better financial status were determined as factors affecting patient compliance. The most frequent reasons to discontinue treatment were fear of injection, disbelief in the benefit of the treatment, financial limitations, continuation of treatment at another center, and comorbid systemic diseases.

CONCLUSION: Patient compliance and success rates of anti-VEGF therapy may be increased by determining the factors affecting patient compliance and raising awareness about n-AMD among patients and their relatives.

PMID: 28845324 PMCID: PMC5563548


Pharmacologic Treatment of Wet Type Age-related Macular Degeneration; Current and Evolving Therapies.

Shams Najafabadi H, Daftarian N, Ahmadieh H, Soheili ZS.

Abstract: Age-related macular degeneration as the major cause of blindness in the elderly population has remained at the epicenter of clinical research in ophthalmology. This retinal disorder is characterized by the photoreceptor and retinal pigment epithelial cells loss, occurring within the macula. The disease represents a spectrum of clinical manifestations. It is a multifactorial disease resulting from a combination of genetic
predispositions and environmental risk factors. AMD is classified into two different types, dry and wet. Wet AMD is in close relation with angiogenesis and inflammatory processes. A variety of anti-angiogenesis and anti-inflammatory drugs have been proposed for the treatment of the disease. The purpose of this paper is to briefly review the pharmacological therapies of the wet form of AMD and focus on new drugs that are currently in different stages of research and development.

PMID: 28846017


A prospective multicenter study on genome wide associations to ranibizumab treatment outcome for age-related macular degeneration.

Yamashiro K, Mori K, Honda S, Kano M, et al

Abstract: We conducted a genome-wide association study (GWAS) on the outcome of anti-VEGF treatment for exudative age-related macular degeneration (AMD) in a prospective cohort. Four hundred and sixty-one treatment-naïve AMD patients were recruited at 13 clinical centers and all patients were treated with 3 monthly injections of ranibizumab followed by pro re nata regimen treatment for one year. Genomic DNA was collected from all patients for a 2-stage GWAS on achieving dry macula after the initial treatment, the requirement for an additional treatment, and visual acuity changes during the 12-month observation period. In addition, we evaluated 9 single-nucleotide polymorphisms (SNPs) in 8 previously reported AMD-related genes for their associations with treatment outcome. The discovery stage with 256 patients evaluated 8,480,849 SNPs, but no SNPs showed genome-wide level significance in association with treatment outcomes. Although SNPs with P-values of <5 × 10^-6 were evaluated in replication samples of 205 patients, no SNP was significantly associated with treatment outcomes. Among AMD-susceptibility genes, rs10490924 in ARMS2/HTRA1 was significantly associated with additional treatment requirement in the discovery stage (P = 0.0023), and pooled analysis with the replication stage further confirmed this association (P = 0.0013). ARMS2/HTRA1 polymorphism might be able to predict the frequency of injection after initial ranibizumab treatment.

PMID: 28835685


Treatment for neovascular age-related macular degeneration in Sweden: outcomes at seven years in the Swedish Macula Register.

Westborg I, Granstam E, Rosso A, Albrecht S, Karlsson N, Lövestam-Adrian M.

PURPOSE: To present Swedish Macula Register (SMR) data regarding treatment of neovascular age-related macular degeneration (AMD) in clinical practice since 2008.

METHODOLOGICAL: A retrospective register-based study was conducted. Evaluation of baseline demographics, visual outcome and number of injections during this period is presented.

RESULTS: Mean age at diagnosis was 79 ± (SD) 8 years; 65% were female. The proportion of patients with <2 months’ duration of symptoms increased from 26% in 2008 to 41% in 2014 (p = 0.001). Mean visual acuity (VA) at baseline increased from 54.3 ± 15.0 early treatment diabetic retinopathy study (ETDRS) letters in 2008 to 57.8 ± 15.6 letters in 2014 (CI95 2.6; 4.3; p < 0.001). Mean VA after 1 year of treatment increased from 57.8 ± 17.7 ETDRS letters for patients who started the treatment in 2008 to 62.8 ± 16.4 ETDRS letters for patients starting treatment in 2014 (CI95 2.67; 4.64; p < 0.001). During all study years, the proportion of patients with an improvement in VA of between 5 and 15 letters was around 30%, while 14% had VA improvement of more than 15 letters. The mean number of injections during the first treatment year
increased from 4.3 ± 1.9 in 2008 to 5.9 ± 2.9 in 2014 (CI95 1.40; 1.67; p < 0.001). Seven-year follow-up of 322 eyes showed a mean change of -1 letters from baseline, with a mean of 21 injections for the entire period.

CONCLUSION: The duration of symptoms before treatment decreased, while VA at baseline and after 1 year of treatment increased over the years and so did the number of injections. Long-term follow-up demonstrated stable VA.

PMID: 28834299
AMD disease quiescence (determined by retinal examination) not requiring treatment for at least 180 days. All patients were seen at Colorado Retina Associates between October 31, 2005 and December 31, 2015. VA was measured at the time of first treatment, last treatment, and final clinic visit showing changes in VA during the treatment and quiescent periods. The sample was stratified to compare those with VA gain throughout the study to those with VA loss.

RESULTS: The aggregate group showed VA stability during the treatment period (20/117 to 20/116) with a significant decline during the quiescent period (to 20/235; P < 0.001). The VA gainers had a significant increase in VA during the treatment period (20/187 to 20/88; P < 0.001) and VA stability during the quiescent period (to 20/93). VA losers had a significant decline in VA during both the treatment and quiescent periods (P < 0.001).

CONCLUSION: Overall, PRN treatment resulted in a decline in VA during a period of apparent disease quiescence. There is a group of patients that does not lose VA during this period, and if patients like these can be identified, their treatment could be optimized to include a period of clinically justified nontreatment.

PMID: 28829220


Sustained intraocular pressure elevation in eyes treated with intravitreal injections of anti-vascular endothelial growth factor for diabetic macular edema in a real-life setting.

Vo Kim S, Fajnkuchen F, Sarda V, Qu-Knafo L, Bodaghi B, Giocanti-Aurégan A.

PURPOSE: The aim of this study was to investigate the sustained intraocular pressure (IOP) elevation after repeated anti-VEGF intravitreal injections (IVI) in patients with diabetic macular edema (DME).

METHODS: A retrospective study included 140 eyes without prior glaucoma, treated with at least three anti-VEGF injections for DME between 2012 and 2016. IOP elevation was defined by an increase above baseline IOP by ≥6 mmHg. Baseline IOP was defined as the mean of IOP values before treatment initiation. Three groups were differentiated: group 1 without IOP elevation, groups 2 and 3 with IOP elevation and IOP <21 mmHg (group 2) and ≥21 mmHg (group 3). Rate and several risk factors of IOP elevation were assessed and compared between the three groups.

RESULTS: IOP elevation occurred in ten eyes (7.1%). IOP was <21 mmHg in six eyes and ≥21 mmHg in four eyes. Statistically significant associations were found between IOP elevation and the number of injections, and HbA1c level. Two patients required local hypotonic treatment.

CONCLUSIONS: In a real-life setting, we confirmed in eyes with center-involved DME without prior glaucoma or IOP elevation that repeated anti-VEGF IVI may increase the risk of sustained IOP elevation in about 7% of eyes.

PMID: 28831613

Anti-Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions: A Review of the Safety [Internet].

Deonandan R, Jones S.

Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2017 Feb.

CADTH Rapid Response Reports.

Excerpt: Retinal conditions, such as age related macular degeneration (AMD), diabetic macular edema
(DME), retinal vein occlusion (RVO), and choroidal neovascularization due to pathologic myopia (CNV due to PM) are an important public health concern that threatens the vision of millions of patients in Canada.1 The mechanism of these conditions involve the new formation of blood vessels in the retina that eventually leads to loss of vision.2 Anti-vascular endothelial growth factor (Anti-VEGF) inhibits this growth and allows the restoration of vision.1 Currently in Canada, two licensed anti-VEGF agents are available in the market; ranibizumab and aflibercept. Bevacizumab, on the other hand, has been developed as an anti-cancer drug.3 However, its close molecular resemblance to ranibizumab and identical mechanism of action has made it a widely used option, especially in environments that are strained on health resources.4, 5 However, despite the wide use of bevacizumab for retinal conditions, and the availability of several high-quality randomized controlled trials for its efficacy,2 Bevacizumab still lacks a Health Canada review for retinal indications.1 The bevacizumab product monograph carries a warning regarding the intravitreal use of bevacizumab, citing increased risk of ophthalmic complications.3 In addition, the intravenous use of bevacizumab in cancer patients is often associated with increased risk of thromboembolic events (e.g. stroke).3 The CADTH therapeutic review titled “Anti-Vascular Endothelial Growth Factor Drugs for the Treatment of Retinal Conditions” established that the efficacy of bevacizumab is not different than ranibizumab or aflibercept, and did not observe any signals indicating issues regarding bevacizumab comparative safety.2 However, the CADTH recommendation report for the therapeutic review identifies the lack of large randomized trials powered to detect differences in harms outcomes as a research gap.1 The statistical power required to detect a difference in harms outcome can make a randomized clinical trial prohibitive.6 A review of available evidence regarding safety of bevacizumab from real-world evidence is of high clinical value, as it represents a useful tool for identifying any potential issues regarding the safety of bevacizumab for use in treating retinal conditions. A summary and critical appraisal of studies regarding bevacizumab safety, contrasted with those of ranibizumab and aflibercept, for the treatment of retinal conditions would allow for a more informed and evidence-based policy and clinical decision process. 

PMID: 28825785

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Aflibercept, bevacizumab or ranibizumab for diabetic macular oedema: recent clinically relevant findings from DRCR.net Protocol T.

Cai S, Bressler NM.

PURPOSE OF REVIEW: The aim of this study was to provide clinically relevant findings from the DRCR.net Protocol T, a multicentre randomized clinical trial comparing intravitreous aflibercept, repackaged (compounded) bevacizumab and ranibizumab for vision-impairing centre-involved diabetic macular oedema (DME).

RECENT FINDINGS: At 1 year, all three antivascular endothelial growth factor (anti-VEGF) drugs, on average, improved visual acuity. There was no difference among drugs in mean change in visual acuity from baseline among eyes with baseline Snellen equivalent visual acuity of 20/32 to 20/40, whereas aflibercept yielded superior vision outcomes among eyes with baseline visual acuity of 20/50 to 20/320. At 2 years, aflibercept remained superior, on average, to bevacizumab, but not ranibizumab, among eyes with baseline visual acuity of 20/50 to 20/320. Over 2 years, in post-hoc area-under-the-curve analysis, aflibercept vision outcomes were superior to bevacizumab or ranibizumab among these eyes. All three drugs had comparable ocular and systemic safety profiles. The substantial cost differential between aflibercept and bevacizumab raises challenges when safety and efficacy are at odds with cost-effectiveness results.

SUMMARY: When initial visual acuity loss is mild, there are no apparent differences, on average, among aflibercept, bevacizumab and ranibizumab for treating DME. When visual acuity loss is moderate or worse, aflibercept is more likely to improve visual acuity.

PMID: 28837425

Chen YY, Lin LY, Chang PY, Chen FT, Mai ELC, Wang JK.

PURPOSE: To describe the efficacy of laser and intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents for patients with symptomatic retinal arterial macroaneurysm (RAM).

DESIGN: From 2009 to 2016, we collected patients with exudative or hemorrhagic RAM all treated by focal laser photocoagulation.

METHODS: Nd:YAG laser was performed in patients with subinternal limiting membrane (sub-ILM) hemorrhage. Intravitreal anti-VEGF agents were given in eyes with macular exudation as adjuncts. Changes of visual acuity and central foveal thickness before and after treatment were recorded and compared with Wilcoxon signed-rank test.

RESULTS: Thirty-five eyes that underwent a single session of laser photocoagulation for RAM resulted in macroaneurysm regression. The hemorrhagic group included 24 eyes having ruptured macroaneurysms without macular exudation. Five eyes with simultaneous sub-ILM hemorrhage receiving Nd:YAG laser membranotomy had resolution of preretinal hemorrhage. Exudative RAM having cystoid macular edema or submacular fluid with or without ruptured macroaneurysms was treated by focal laser photocoagulation alone in 3, or combined with single intravitreal anti-VEGF agent in 8 eyes. All patients had significantly improved vision when comparing visual acuity at baseline and final follow-up (P = 0.00016). Significant reduction of macular thickness was also observed after laser monotherapy or combined treatment in exudative RAM (P = 0.018).

CONCLUSIONS: Focal laser photocoagulation was helpful for the management of ruptured or leaky RAM. Combined focal laser and intravitreal anti-VEGF agents could better reduce macular exudation caused by RAM. Additionally, Nd:YAG laser was a safe and effective method to remove the sub-ILM hemorrhage caused by RAM.

PMID: 28828763


Visual outcomes in patients with neovascular age-related macular degeneration.

Tan CS, Ngo WK, Lim LW.

PMID: 28834272


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

Călugăru D, Călugăru M.

PMID: 28828522
Other treatment & diagnosis


Sorsby fundus dystrophy - A review of pathology and disease mechanisms.

Christensen DRG, Brown FE, Cree AJ, Ratnayaka JA, Lotery AJ.

Abstract: Sorsby fundus dystrophy (SFD) is an autosomal dominant macular dystrophy with an estimated prevalence of 1 in 220,000 and an onset of disease around the 4th to 6th decade of life. Similar to age-related macular degeneration (AMD), ophthalmoscopy reveals accumulation of protein/lipid deposits under the retinal pigment epithelium (RPE), referred to as drusen, in the eyes of patients with SFD. SFD is caused by variants in the gene for tissue inhibitor of metalloproteinases-3 (TIMP3), which has been found in drusen-like deposits of SFD patients. TIMP3 is constitutively expressed by RPE cells and, in healthy eyes, resides in Bruch's membrane. Most SFD-associated TIMP3 variants involve the gain or loss of a cysteine residue. This suggests the protein aberrantly forms intermolecular disulphide bonds, resulting in the formation of TIMP3 dimers. It has been demonstrated that SFD-associated TIMP3 variants are more resistant to turnover, which is thought to be a result of dimerisation and thought to explain the accumulation of TIMP3 in drusen-like deposits at the level of Bruch's membrane. An important function of TIMP3 within the outer retina is to regulate the thickness of Bruch's membrane. TIMP3 performs this function by inhibiting the activity of matrix metalloproteinases (MMPs), which have the function of catalysing breakdown of the extracellular matrix. TIMP3 has an additional function to inhibit vascular endothelial growth factor (VEGF) signalling and thereby to inhibit angiogenesis. However, it is unclear whether SFD-associated TIMP3 variant proteins retain these functions. In this review, we discuss the current understanding of the potential mechanisms underlying development of SFD and summarise all known SFD-associated TIMP3 variants. Cell culture models provide an invaluable way to study disease and identify potential treatments. These allow a greater understanding of RPE physiology and pathophysiology, including the ability to study the blood-retinal barrier as well as other RPE functions such as phagocytosis of photoreceptor outer segments. This review describes some examples of such recent in vitro studies and how they might provide new insights into degenerative diseases like SFD. Thus far, most studies on SFD have been performed using ARPE-19 cells or other, less suitable, cell-types. Now, induced pluripotent stem cell (iPSC) technologies allow the possibility to non-invasively collect somatic cells, such as dermal fibroblast cells and reprogram those to produce iPSCs. Subsequent differentiation of iPSCs can generate patient-derived RPE cells that carry the same disease-associated variant as RPE cells in the eyes of the patient. Use of these patient-derived RPE cells in novel cell culture systems should increase our understanding of how SFD and similar macular dystrophies develop.

PMID: 28847738


Optical Coherence Tomography Predictors of Risk for Progression to Non-Neovascular Atrophic Age-Related Macular Degeneration.

Sleiman K, Veerappan M, Winter KP, McCall MN, Yiu G, Farsiu S, Chew EY, Clemons T, Toth CA; Age-Related Eye Disease Study 2 Ancillary Spectral Domain Optical Coherence Tomography Study Group.

Collaborators (17)

PURPOSE: Appearance of geographic atrophy (GA) on color photography (CP) is preceded by specific features on spectral-domain optical coherence tomography (SD OCT). We aimed to build SD OCT-based risk assessment models for 5-year new onset of GA and central GA on CP.

DESIGN: Prospective, longitudinal study.
PARTICIPANTS: Age-Related Eye Disease Study 2 Ancillary SD OCT study participants with age-related macular degeneration (AMD) with bilateral large drusen or noncentral GA and at least 1 eye without advanced disease (n = 317).

METHODS: For 1 eye per participant, qualitative and quantitative SD OCT variables were derived from standardized grading and semiautomated segmentation, respectively, at baseline. Up to 7 years later, annual outcomes were extracted and analyzed to fit multivariate logistic regression models and build a risk calculator.

MAIN OUTCOME MEASURES: New onset of CP-visible GA and central GA.

RESULTS: Over a follow-up median of 4.0 years and among 292 AMD eyes (without advanced disease at baseline) with complete outcome data, 46 (15.8%) developed central GA. Among 265 eyes without any GA on baseline CP, 70 (26.4%) developed CP-visible GA. Final multivariate models were adjusted for age. In the model for GA, the independent predicting SD OCT factors (P < 0.001-0.03) were: hyperreflective foci and retinal pigment epithelium (RPE) layer atrophy or absence, followed by choroid thickness in absence of subretinal drusenoid deposits, photoreceptor outer segment loss, RPE drusen complex volume, and RPE drusen complex abnormal thinning volume. For central GA, the factors (P < 0.001) were RPE drusen complex abnormal thinning volume, intraretinal fluid or cystoid spaces, hyperreflective foci, and RPE layer atrophy or absence. The models yielded a calculator that computes the probabilities of CP-visible, new-onset GA and central GA after 1 to 5 years.

CONCLUSIONS: For AMD eyes with large drusen and no advanced disease, we built a novel risk assessment model-based on age and SD OCT segmentation, drusen characteristics, and retinal pathology-for progression to CP-visible GA over up to 5 years. This calculator may simplify SD OCT grading and with future validation has a promising role as a clinical prognostic tool.

PMID: 28847641


[Patient-Reported Treatment Satisfaction with Stereotactic Radiotherapy in Neovascular Age-Related Macular Degeneration]. [Article in German]

Kurz M, Rudolf M, Holzhey A, Neubauer AS, Grisanti S, Ranjbar M.

Background: Stereotactic radiotherapy (SRT) in conjunction with the common intravitreal injections (IVI) is a new adjuvant approach in neovascular age-related macular degeneration (AMD) patients. The aim of our study was to investigate factors influencing patient satisfaction one year after SRT.

Methods: A questionnaire was administered to 35 AMD patients who had consecutively undergone SRT using the iRay®-device at the Department of Ophthalmology, University of Lübeck. In addition to descriptive statistics, responses were evaluated by correlation analysis. Moreover, subgroup analyses were performed, using a classification of IVI responders (annual injection rate after SRT ≤ 3), visual acuity (VA) responders (VA improvement ≥ 0.2 logMAR) and double responders (annual injection rate after SRT ≤ 3 as well as VA improvement ≥ 0.2 logMAR).

Results: The response rate was 86%. With respect to their treatment expectations, twice as many patients hoped to receive less injections instead of a better vision. Those hoping for less injections were significantly more satisfied with their clinical outcome. In addition, IVI-responders were significantly more satisfied than IVI-non-responders, while VA-responders were not, compared to VA-non-responders.

Conclusions: Patient satisfaction seems to depend on patients’ comprehension of how SRT affects their disease and what kinds of expectations were set. It is of utmost importance to provide the patients with adequate and comprehensible education and to define realistic goals prior to SRT.

PMID: 28837976

Detection of Early Loss of Color Vision in Age-Related Macular Degeneration - With Emphasis on Drusen and Reticular Pseudodrusen.

Vemala R, Sivaprasad S, Barbur JL.

PURPOSE: To evaluate chromatic sensitivity in patients with age-related macular degeneration (AMD) characterized by drusen and reticular pseudodrusen. To investigate whether the severity of color vision loss can distinguish between various stages of AMD and hence be used as an index of progression toward advanced AMD.

METHODS: Chromatic sensitivity was measured by using the Color Assessment and Diagnosis (CAD) test in asymptomatic individuals with early and intermediate AMD and compared to normative data. All study participants had logMAR visual acuity of 0.3 or better. The CAD thresholds measured in eyes with and without reticular pseudodrusen were also compared and related to central macular thickness (CMT). Student's t-test P values < 0.05 were considered significant.

RESULTS: All early- and intermediate-AMD eyes (n = 90) had chromatic sensitivity loss in either RG (red/green) or YB (yellow/blue), or both (P < 0.0001) as compared to age-matched normal subjects. The eyes exhibited a range of CAD thresholds affecting both color mechanisms, but YB color thresholds were in general higher than RG thresholds (P < 0.001). Intermediate-AMD patients exhibited large intersubject variability. In general, eyes with reticular pseudodrusen and eyes with CMT < 200 μm had significantly higher CAD thresholds.

CONCLUSIONS: The anatomic integrity of cone photoreceptors remains relatively unaffected in early and intermediate stages of AMD. The processing of cone signals in the retina can, however, be heavily disrupted with subsequent loss of both YB and RG chromatic sensitivity. The greatest losses were observed in eyes with reticular pseudodrusen.

PMID: 28846119

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

CLASSIFICATION AND QUANTITATIVE ANALYSIS OF GEOGRAPHIC ATROPHY JUNCTIONAL ZONE USING SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Qu J, Velaga SB, Hariri AH, Nittala MG, Sadda S.

PURPOSE: The junctional zone at the border of areas of geographic atrophy (GA) in eyes with nonneovascular age-related macular degeneration is an important target region for future therapeutic strategies. The goal of this study was to perform a detailed classification and quantitative characterization of the junctional zone using spectral domain optical coherence tomography.

METHODS: Spectral domain optical coherence tomography volume cube scans (Spectralis OCT, 1024 × 37, Automatic Real Time > 9) were obtained from 15 eyes of 11 patients with GA because of nonneovascular age-related macular degeneration. Volume optical coherence tomography data were imported into previously described validated grading software (3D-OCTOR), and manual segmentation of the retinal pigment epithelium (RPE) and photoreceptor layers was performed on all B-scans (total of 555). Retinal pigment epithelium and photoreceptor defect maps were produced for each case. The borders of the photoreceptor defect area and RPE defect area were delineated individually on separate annotation layers. The two outlines were then superimposed to compare the areas of overlap and nonoverlap. The perimeter of the RPE defect area was calculated by the software in pixels. The superimposed outline of the photoreceptor defect area and the RPE defect area was scrutinized to classify the overlap configuration of the junctional zone into one of three categories: Type 0, exact correspondence between the edge of the RPE defect and photoreceptor defect; Type 1, loss of photoreceptors outside and beyond the edge of the
RPE defect; Type 2, preservation of photoreceptors beyond the edge of the RPE defect. The relative proportion of the various border configurations was expressed as a percentage of the perimeter of the RPE defect. Each configuration was then classified into four subgroups according to irregularity of the RPE band and the presence of debris.

RESULTS: Fifteen eyes of 11 patients (mean age: 79.3 ± 4.3 years; range: 79-94 years) were included in this study. Seventeen GA lesions were analyzed. Two hundred and thirty-two B-scans were found to pass through the GA lesions, yielding 612 individual GA borders which were separately analyzed and classified. The mean area of the RPE defect was 4.0 ± 4.4 mm, which was significantly smaller than that of the photoreceptor defect which measured 4.4 ± 4.1 mm (paired t test, P = 0.037). On average, 18.0 ± 9.6% (range, 2.3-36.6%) of the junctional zone was of the Type 0 configuration, 57.3 ± 19.0% (range, 21.3-96.8%) was Type 1, and 24.7 ± 18.0% (range, 0.9-64.4%) was Type 2. Type 1 was more prevalent than Type 0 and 2 (analysis of variance, P = 0.000). Debris was present at the margin of the defect in 24.3% (149 of 612) of all assessed junctional zones; 20.0% (14 of 70) of Type 0 junctions, 28.7% (120 of 418) of Type 1, and 12.1% (15 of 124) of Type 2. Debris was more common in Type 1 than Type 2 junctions (P < 0.001). Retinal pigment epithelial irregularity was present at the margin of the defect in 34.8% (213 of 612) of all assessed junctional zones; 52.9% (37 of 70) of Type 0 junctions, 38.0% (159 of 418) of Type 1, and 13.7% (17 of 124) of Type 2. Retinal pigment epithelial irregularity was present more often at Type 0 and Type 1 than at Type 2 junctions (P < 0.001 for both).

CONCLUSION: The size of the optical coherence tomography-visible RPE and photoreceptor defect in GA lesions differ significantly. There were significant areas where the photoreceptor outer segments were preserved despite the absence of visible RPE cells, and also areas of photoreceptor outer segment loss despite apparent RPE preservation. These findings have implications for development of therapeutic strategies, particularly cell-replacement approaches.

PMID: 28834947

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


Graham KW, Chakravarthy U, Hogg RE, Muldrew KA, Young IS, Kee F.

PURPOSE: To compare multicolor (MC) and traditional color fundus photography (CFP) in their ability to detect features of early and late age-related macular degeneration (AMD).

METHODS: Study design: Observational case series.

PARTICIPANTS: Fundus images captured using standard CFP and MC imaging from 33 patients attending hospital clinics and 26 participants from the pilot phase of the Northern Ireland Cohort for the Longitudinal Study of Ageing (NICOLA). Systematic grading of early and late AMD features; (hard drusen, soft drusen, reticular pseudodrusen, pigment clumping, non-geographic atrophy hypopigmentation, atrophy, hemorrhage, and fibrosis) on CFP and MC.

RESULTS: There were 105 eyes with gradable images for comparison. Using CFP as the gold standard, sensitivity values for MC ranged from 100% for atrophy, non-geographic atrophy hypopigmentation, and fibrosis to 69.7% for pigment clumping. Specificity values were high: >80% for all features. On using MC as the comparator, CFP had lower sensitivity for the detection of early AMD features (27.8% for reticular drusen to 77.8% for non-geographic atrophy hypopigmentation). Analysis of OCT in discrepant cases showed better agreement with MC for all AMD lesions, except hemorrhage and non-geographic atrophy hypopigmentation. For pigment clumping, CFP and MC were in equal agreement with OCT.

CONCLUSION: Multicolor retinal imaging allowed for improved detection and definition of AMD features.

PMID: 28834946

Kolomeyer AM, Traband A, VanderBeek BL.

PMID: 28823357

Pathogenesis


Melatonin Modulates Prohibitin and Cytoskeleton in the Retinal Pigment Epithelium.

Sripathi SR, Prigge CL, Elledge B, He W, Offor J, Gutsaeva DR, Jahng WJ.

Abstract: The retinal pigment epithelium (RPE) plays imperative roles in normal retinal function by photoreceptor protection from light and phagocytosis of rod and cone outer segments during disc shedding. Melatonin is the free radical scavenger and circadian determinant to protect the RPE and retina from oxidative stress and regulate the circadian clock. The current study tested the hypothesis whether melatonin could affect cytoskeletal structure within RPE. Our Western blot analysis demonstrated that melatonin treatment up-regulated prohibitin 3-fold compared to control. β-tubulin levels were also up-regulated by melatonin but to a lesser extent. Initial cell shape of ARPE-19 is epitheloid, however, after 30-minute treatment with melatonin, RPE cells undergo a morphological change to a fusiform shape with spindle outgrowth. Cells return to epitheloid shape after 12 hours in untreated medium. Melatonin treated cells showed increased and dissimilar distribution of prohibitin and β-tubulin compared to non-treated cells, thus altered cytoskeletal and mitochondrial structure in the RPE. Our data implies that melatonin may play a protective role under oxidative stress, which is shown by the marker prohibitin in terms of increased expression and nuclear distribution. During the protective process, cells change their morphology. Our results suggest that melatonin treatment could be beneficial to protect mitochondria under oxidative stress and treat certain ocular diseases, including age-related macular degeneration.

PMID: 28845390


Retinal and choroidal angiogenesis: a review of new targets.

Cabral T, Mello LGM, Lima LH, Polido J, Regatieri CV, Belfort R Jr, Mahajan VB.

Abstract: Retinal and choroidal neovascularization are a major cause of significant visual impairment, worldwide. Understanding the various factors involved in the accompanying physiopathology is vital for development of novel treatments, and most important, for preserving patient vision. The intraocular use of anti-vascular endothelial growth factor therapeutics has improved management of the retinal and choroidal neovascularization but some patients do not respond, suggesting other vascular mediators may also contribute to ocular angiogenesis. Several recent studies examined possible new targets for future anti-angiogenic therapies. Potential targets of retinal and choroidal neovascularization therapy include members of the platelet-derived growth factor family, vascular endothelial growth factor sub-family, epidermal growth factor family, fibroblast growth factor family, transforming growth factor-β superfamily (TGF-β1, activins, follistatin and bone morphogenetic proteins), angiopoietin-like family, galectins family, integrin superfamily, as well as pigment epithelium derived factor, hepatocyte growth factor, angiopoietins, endothelins, hypoxia-inducible factors, insulin-like growth factors, cytokines, matrix metalloproteinases and their inhibitors and glycosylation proteins. This review highlights current antiangiogenic therapies under development, and
discusses future retinal and choroidal pro- and anti-angiogenic targets as well as the importance of developing of new drugs.

PMID: 28835854 PMCID: PMC5563895

Am J Pathol. 2017 Aug 17. [Epub ahead of print]

Deletion of Endothelial TGF-β Signaling Leads to Choroidal Neovascularization.

Schlecht A, Leimbeck SV, Jägle H, Feuchtinger A, Tamm ER, Braunger BM.

Abstract: The molecular pathogenesis of choroidal neovascularization (CNV), an angiogenic process that critically contributes to vision loss in age-related macular degeneration (AMD) is unclear. Here we analyzed the role of transforming growth factor (TGF)-β signaling for CNV formation by generating a series of mutant mouse models with induced conditional deletion of TGF-β signaling in the entire eye, the retinal pigment epithelium (RPE) or the vascular endothelium. Deletion of TGF-β signaling in the eye caused CNV, irrespectively if it was ablated in newborn or three-week-old mice. Areas of CNV showed photoreceptor degeneration, multilayered RPE, basal lamina deposits and accumulations of monocytes/macrophages. The changes progressed leading to marked structural and functional alterations of the retina. While the specific deletion of TGF-β signaling in the RPE caused no obvious changes, specific deletion in vascular endothelial cells caused CNV and a phenotype quite similar to that observed after the deletion in the entire eye. We conclude that impairment of TGF-β signaling in the vascular endothelium of the eye is sufficient to trigger CNV formation. Our findings highlight the importance of TGF-β signaling as key player in the development of ocular neovascularization and indicate a fundamental role of TGF-β signaling in the pathogenesis of AMD.

PMID: 28823871

Epidemiology


Prevalence of age-related macular degeneration in rural southern China: the Yangxi Eye Study.


PURPOSE: To describe the prevalence of age-related macular degeneration (AMD) among older adults in rural southern mainland China.

METHODS: Eligible persons aged 50 years or over were identified by geographically defined cluster sampling from Yangxi County, Guangdong Province, China. Participants underwent a standardised interview and comprehensive eye examinations from August to November in 2014. Digital retinal photographs were graded for AMD lesions using the Clinical Classification of Age-Related Macular Degeneration developed by the Beckman Initiative for Macular Research Classification Committee. Age-standardised prevalence of AMD and AMD lesions was calculated using the 2010 world population data and compared with those of other populations.

RESULTS: Of 5825 subjects who participated (90.7% response rate), 4881 (83.8%) had fundus photographs gradable for AMD. Early, intermediate and late AMD were present in 2003 (41.0%), 879 (18.0%) and 42 (0.86%) participants. The age-standardised prevalence of early, intermediate and late AMD was 40.4% (95% CI 39.6% to 41.2%), 17.6% (95% CI 17.0% to 18.2%) and 0.79% (95% CI 0.65% to 0.95%), respectively. Total AMD was more prevalent in men than in women (62.8% vs 57.1%).

CONCLUSIONS: AMD is an important public health concern for rural southern China, and the prevalence of AMD was higher in men than in women.

PMID: 28848023

Visual impairment and blindness in Hungary.


AIM: The aim of this study was to estimate the prevalence and causes of blindness, severe visual impairment (SVI), moderate visual impairment (MVI), and early visual impairment (EVI) and its causes in an established market economy of Europe.

DESIGN: A cross-sectional population-based survey.

METHODS: A sample size of 3675 was calculated using the standard Rapid Assessment of Avoidable Blindness (RAAB) software in Hungary. A total of 105 clusters of 35 people aged 50 years or older were randomly selected with probability proportionate to size by the Hungarian Central Statistical Office. Households within the clusters were selected using compact segment sampling. Visual acuity (VA) was assessed with a Snellen tumbling E-chart with or without a pinhole in the households.

RESULTS: The adjusted prevalences of bilateral blindness, SVI, MVI and EVI were 0.9% (95% CI: 0.6-1.2), 0.5% (95% CI: 0.2-0.7), 5.1% (95% CI: 4.3-5.9) and 6.9% (95% CI: 5.9-7.9), respectively. The major causes of blindness in Hungary were age-related macular degeneration (AMD; 27.3%) and other posterior segment diseases (27.3%) and cataract (21.2%) and glaucoma (12.1%). Cataract was the main cause of SVI, MVI and EVI. Cataract surgical coverage (CSC) was 90.7%. Of all bilateral blindness in Hungary, 45.5% was considered avoidable.

CONCLUSION: This study proved that RAAB methodology can be successfully conducted in industrialized countries, which often lack reliable epidemiologic data. The prevalence of blindness was relatively low, with AMD and other posterior segment diseases being the leading causes, and cataract is still a significant cause of visual impairment.

PMID: 28834193


Evaluation of coronary artery disease as a risk factor for reticular pseudodrusen.

McCarter RV, McKay GJ, Quinn NB, Chakravarthy U, MacGillivray TJ, Robertson G, Pellegrini E, Trucco E, Williams MC, Peto T, Dhillon B, van Beek EJ, Newby DE, Kee F, Young IS, Hogg RE.

PURPOSE: Reticular pseudodrusen (RPD) are a risk factor for late age-related macular degeneration (AMD). Associations between RPD and coronary artery disease (CAD) have been reported from small case-control studies. This study investigated the association of RPD within a predominantly CAD cohort.

METHODS: A subgroup of subjects from a multicentre randomised controlled trial of CT coronary angiography (CTCA) underwent ultrawide field (UWF) retinal imaging CAD determined by CTCA and was categorised as normal, non-obstructive or obstructive. Specific AMD features in UWF images were graded. Standardised grids were used to record the spatial location of AMD features, including RPD. Multivariate confounder adjusted regression models assessed the association between RPD and CAD.

RESULTS: The 534 participants were aged 27-75 years (mean 58±9 years; 425 (80%) ≥50 years) with a male preponderance (56%). Within the study sample, 178 (33%) had no CAD, 351 (66%) had CAD. RPD was detected in 30 participants (5.6%) and bilaterally in 23. Most participants with bilateral RPD had intermediate AMD 17 (74%). After adjustment for potential confounders (age, sex, drusen >125 µm, smoking status), multivariate analysis found no significant association between CAD and RPD (OR 1.31; 95% CI (0.57 to 3.01); p=0.52). A significant association was identified between RPD and intermediate AMD (OR 3.18; 95% CI (1.61 to 6.27); p=0.001).
CONCLUSION: We found no evidence to support an association between CAD and RPD. RPD was strongly associated with intermediate AMD features.

PMID: 28822985

**Genetics & gene therapy**

**Ophthalmic Genet. 2017 Aug 28;1-5. [Epub ahead of print]**

**Association of HTRA1 rs11200638 with age-related macular degeneration (AMD) in Brazilian patients.**

Lana TP, da Silva Costa SM, Ananina G, Hirata FE, Rim PHH, Medina FM, de Vasconcellos JPC, de Melo MB.

Abstract: Age-related macular degeneration is a multifactorial disease that can lead to vision impairment in older individuals. Although the etiology of age-related macular degeneration remains unknown, risk factors include age, ethnicity, smoking, hypertension, obesity, and genetic factors. Two main loci have been identified through genome-wide association studies, on chromosomes 1 and 10. Among the variants located at the 10q26 region, rs11200638, located at the HTRA1 gene promoter, has been associated with age-related macular degeneration in several populations and is considered the main polymorphism. We conducted a replication case-control study to analyze the frequency and participation of rs11200638 in the etiology of age-related macular degeneration in a sample of patients and controls from the State of São Paulo, Brazil, through polymerase chain reaction and enzymatic digestion. The frequency of the A allele was 57.60% in patients with age-related macular degeneration and 36.45% in controls (p value < 1e-07), representing a 2.369-fold higher risk factor for the disease. Both the AA and AG genotypes were observed more frequently in the age-related macular degeneration group compared to the control group (p = 1.21e-07 and 0.0357, respectively). No statistically significant results were observed after stratification in dry versus wet types or advanced versus non-advanced forms. To our knowledge, this is the first time the association between rs11200638 and overall age-related macular degeneration has been reported in South America.

PMID: 28846052

**Acta Med Litu. 2017;24(2):75-82.**

**Associations between CYP2C8 rs10509681 and rs11572080 gene polymorphisms and age-related macular degeneration.**


BACKGROUND: Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in industrialized countries. Early symptoms of AMD include drusen and changes in retinal pigment epithelium. However, the etiology of AMD and drusen formation is not fully understood. Recent studies suggest that CYP2C8-related metabolic processes might play an important role in the development of AMD. The aim of our study is to investigate CYP2C8 rs10509681 and CYP2C8 rs11572080 genotype frequencies in patients with early AMD and to compare them with healthy controls.

MATERIALS AND METHODS: The study enrolled 305 patients with early AMD and 300 healthy controls. The genotyping of CYP2C8 rs10509681 and CYP2C8 rs11572080 was carried out using the real-time PCR method.

RESULTS: The analysis of studied CYP2C8 polymorphisms did not reveal any statistically significant differences between the AMD and the control groups. For the CYP2C8 rs10509681 gene polymorphism the
distribution of T/T, T/C, and C/C genotypes was 83.3%, 16.7%, and 0% vs. 83.7%, 15.7%, and 0.7%, p = 0.343. For the CYP2C8 rs11572080 gene polymorphism the distribution of C/C, T/C and T/T and genotypes was 84.9%, 15.1%, and 0% vs. 82.3%, 17.3%, and 0.3%, p = 0.447.

CONCLUSION: The study revealed that there were no statistically significant differences in the distribution of CYP2C8 rs10509681 and CYP2C8 rs11572080 genotypes in patients with early AMD and in healthy controls.

PMID: 28845124 PMCID: PMC5566945


A Scalable Bayesian Method for Integrating Functional Information in Genome-wide Association Studies.


Abstract: Genome-wide association studies (GWASs) have identified many complex loci. However, most loci reside in noncoding regions and have unknown biological functions. Integrative analysis that incorporates known functional information into GWASs can help elucidate the underlying biological mechanisms and prioritize important functional variants. Hence, we develop a flexible Bayesian variable selection model with efficient computational techniques for such integrative analysis. Different from previous approaches, our method models the effect-size distribution and probability of causality for variants with different annotations and jointly models genome-wide variants to account for linkage disequilibrium (LD), thus prioritizing associations based on the quantification of the annotations and allowing for multiple associated variants per locus. Our method dramatically improves both computational speed and posterior sampling convergence by taking advantage of the block-wise LD structures in human genomes. In simulations, our method accurately quantifies the functional enrichment and performs more powerfully for prioritizing the true associations than alternative methods, where the power gain is especially apparent when multiple associated variants in LD reside in the same locus. We applied our method to an in-depth GWAS of age-related macular degeneration with 33,976 individuals and 9,857,286 variants. We find the strongest enrichment for causality among non-synonymous variants (54× more likely to be causal, 1.4× larger effect sizes) and variants in transcription, repressed Polycomb, and enhancer regions, as well as identify five additional candidate loci beyond the 32 known AMD risk loci. In conclusion, our method is shown to efficiently integrate functional information in GWASs, helping identify functional associated-variants and underlying biology.

PMID: 28844487


Shared genetic variants for polypoidal choroidal vasculopathy and typical neovascular age-related macular degeneration in East Asians.


Abstract: Polypoidal choroidal vasculopathy (PCV), a subtype of age-related macular degeneration (AMD) more frequently seen in East Asians, has both common and distinct clinical manifestations with typical neovascular AMD (tAMD). We aim to examine the extent to which common genetic variants are shared between these two subtypes. We performed the meta-analysis of association in a total of 1062 PCV patients, 1157 tAMD patients and 5275 controls of East Asian descent from the Genetics of AMD in Asians Consortium at the 34 known AMD loci. A total of eight loci were significantly associated with PCV, including
age-related maculopathy susceptibility 2 (ARMS2)-HtrA serine peptidase 1 (HTRA1), complement factor H (CFH), C2-CFB-SKIV2L, CETP, VEGFA, ADAMTS9-AS2 and TGFBR1 (P<5 × 10^{-4}) from the single-nucleotide polymorphism-based test and COL4A3 from the gene-based tests (P_{gene}=2.02 × 10^{-4}). PCV and tAMD are genetically highly correlated (r_{g}=0.69, P=4.68 × 10^{-3}), with AMD known loci accounting for up to 36% variation. Weaker association for PCV was observed at ARMS2-HTRA1 (P_{dif}=4.39 × 10^{-4}) and KMT2E-SRPK2 (P_{dif}=4.43 × 10^{-3}), compared with tAMD. Variants at CFH, CETP and VEGFA exhibited different association signals in East Asians, in contrast to those in European individuals. Our data suggest a substantially shared genetic susceptibility for PCV and tAMD, while also highlight the unique associations for PCV, which is useful in understanding the pathogenesis of PCV. Journal of Human Genetics advance online publication, 24 August 2017; doi:10.1038/jhg.2017.83.

PMID: 28835638


Adult-Onset Vitelliform Macular Dystrophy caused by BEST1 p.Ile38Ser Mutation is a Mild Form of Best Vitelliform Macular Dystrophy.


Abstract: Adult-onset vitelliform macular dystrophy (AVMD) is a common and benign macular degeneration which can be caused by BEST1 mutation. Here, we investigated the clinical characteristics associated with a newly identified BEST1 mutation, p.Ile38Ser and confirmed the associated physiological functional defects. The 51-year-old patient presented bilateral small subretinal yellow deposits. Consistent with AVMD, the corresponding lesions showed hyperautofluorescence, late staining in fluorescein angiography, and subretinal hyper-reflective materials in spectral-domain optical coherence tomography. Genetic analysis demonstrated that the patient presented with a heterozygous p.Ile38Ser BEST1 mutation. Surface biotinylation and patch clamp experiments were performed in transfected HEK293T cells. Although, the identified BEST1 mutant maintains normal membrane expression, p.Ile38Ser mutant showed significantly smaller currents than wild type (WT). However, it showed larger currents than other BEST1 mutants, p.Trp93Cys, causing autosomal dominant best vitelliform macular dystrophy (BVMD), and p.Ala195Val, causing autosomal recessive bestrophinopathy (ARB). The cells expressing both WT and each BEST1 mutant showed that the functional defect of p.Ile38ser was milder than that of p.Trp93Cys, whereas combination of p.Ala195Val with WT showed good current. We identified and described the phenotype and in vitro functions of a novel BEST1 mutation causing AVMD. AVMD induced by p.Ile38Ser BEST1 mutation is a mild form of BVMD.

PMID: 28831140


Restoring vision in mice with retinal degeneration using multicharacteristic opsin.

Wright W, Gajjeraman S, Batabyal S, Pradhan S, Bhattacharya S, Mahapatra V, Tripathy A, Mohanty S.

Abstract: Retinal degenerative diseases, such as retinitis pigmentosa (RP) and dry age-related macular degeneration, have led to loss of vision in millions of individuals. Currently, no surgical or medical treatment is available, although optogenetic therapies are in clinical development. We demonstrate vision restoration using multicharacteristics opsin (MCO1) in animal models with degenerated retina. MCO1 is reliably delivered to specific retinal cells via intravitreal injection of adeno-associated virus (vMCO1), leading to significant improvement in visually guided behavior conducted using a radial arm water maze. The time to reach the platform and the number of error arms decreased significantly after delivery of MCO1. Notably, the improvement in visually guided behavior was observed even at light intensity levels orders of magnitude lower than that required for channelrhodopsin-2 opsin. Viability of vMCO1-treated retina is not
compromised by chronic light exposure. Safe virus-mediated MCO1 delivery has potential for effective gene therapy of diverse retinal degenerations in patients.

PMID: 28840163 PMCID: PMC5561766


Comparative gene expression study and pathway analysis of the human iris- and the retinal pigment epithelium.

Bennis A, Ten Brink JB, Moerland PD, Heine VM, Bergen AA.

BACKGROUND: The retinal pigment epithelium (RPE) is a neural monolayer lining the back of the eye. Degeneration of the RPE leads to severe vision loss in, so far incurable, diseases such as age-related macular degeneration and some forms of retinitis pigmentosa. A promising future replacement therapy may be autologous iris epithelial cell transdifferentiation into RPE in vitro and, subsequently, transplantation. In this study we compared the gene expression profiles of the iris epithelium (IE) and the RPE.

METHODS: We collected both primary RPE- and IE cells from 5 freshly frozen human donor eyes, using respectively laser dissection microscopy and excision. We performed whole-genome expression profiling using 44k Agilent human microarrays. We investigated the gene expression profiles on both gene and functional network level, using R and the knowledge database Ingenuity.

RESULTS: The major molecular pathways related to the RPE and IE were quite similar and yielded basic neuro-epithelial cell functions. Nonetheless, we also found major specific differences: For example, genes and molecular pathways, related to the visual cycle and retinol biosynthesis are significantly higher expressed in the RPE than in the IE. Interestingly, Wnt and aryl hydrocarbon receptor (AhR-) signaling pathways are much higher expressed in the IE than in the RPE, suggesting, respectively, a possible pluripotent and high detoxification state of the IE.

CONCLUSIONS: This study provides a valuation of the similarities and differences between the expression profiles of the RPE and IE. Our data combined with that of the literature, represent a most comprehensive perspective on transcriptional variation, which may support future research in the development of therapeutic transplantation of IE.

PMID: 28827822 PMCID: PMC5565104


MicroRNA Expression Analysis in Serum of Patients with Congenital Hemochromatosis and Age-Related Macular Degeneration (AMD).

Szemraj M, Oszajca K, Szemraj J, Jurowski P.

BACKGROUND: Congenital hemochromatosis is a disorder caused by mutations of genes involved in iron metabolism, leading to increased levels of iron concentration in tissues and serum. High concentrations of iron can lead to the development of AMD. The aim of this study was to analyze circulating miRNAs in the serum of congenital hemochromatosis patients with AMD and their correlation with the expression of genes involved in iron metabolism.

MATERIAL AND METHODS: Peripheral blood monolayer cells and serum were obtained from patients with congenital hemochromatosis, congenital hemochromatosis and AMD, AMD patients without congenital hemochromatosis, and healthy controls. Serum miRNAs expressions were analyzed by RT-PCR (qRT-PCR) using TaqMan MicroRNA probes, and proteins levels were measured by ELSA kits. Gene polymorphisms in TF and TFRC genes were determined using the TaqMan discrimination assay.
RESULTS: Statistical analysis of the miRNAs expressions selected for further study the miR-31, miR-133a, miR-141, miR-145, miR-149, and miR-182, which are involved in the posttranscriptional expression of iron-related genes: TF, TFRI, DMT1, FTL, and FPN1. It was discovered that the observed changes in the expressions of the miRNAs was correlated with the level of protein in the serum of the analyzed genes. There were no statistically significant differences in the distribution of genotype and allele frequencies in TF and TFRC genes between analyzed groups of patients.

CONCLUSIONS: The differences studied in the miRNA serum profile, in conjunction with the changes in the analyzed protein levels, may be useful in the early detection of congenital hemochromatosis in patients who may develop AMD disease.

PMID: 28827515


Cytochrome P450 monooxygenase lipid metabolites are significant second messengers in the resolution of choroidal neovascularization.


Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness for individuals age 50 and above in the developed world. Abnormal growth of choroidal blood vessels, or choroidal neovascularization (CNV), is a hallmark of the neovascular (wet) form of advanced AMD and leads to significant vision loss. A growing body of evidence supports a strong link between neovascular disease and inflammation. Metabolites of long-chain polyunsaturated fatty acids derived from the cytochrome P450 (CYP) monooxygenase pathway serve as vital second messengers that regulate a number of hormones and growth factors involved in inflammation and vascular function. Using transgenic mice with altered CYP lipid biosynthetic pathways in a mouse model of laser-induced CNV, we characterized the role of these lipid metabolites in regulating neovascular disease. We discovered that the CYP-derived lipid metabolites epoxydocosapentaenoic acids (EDPs) and epoxyeicosatetraenoic acids (EEQs) are vital in dampening CNV severity. Specifically, overexpression of the monooxygenase CYP2C8 or genetic ablation or inhibition of the soluble epoxide hydrolase (sEH) enzyme led to increased levels of EDP and EEQ with attenuated CNV development. In contrast, when we promoted the degradation of these CYP-derived metabolites by transgenic overexpression of sEH, the protective effect against CNV was lost. We found that these molecules work in part through their ability to regulate the expression of key leukocyte adhesion molecules, on both leukocytes and endothelial cells, thereby mediating leukocyte recruitment. These results suggest that CYP lipid signaling molecules and their regulators are potential therapeutic targets in neovascular diseases.

PMID: 28827330

Stem cells


Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration.

Souied E, Pulido J, Staurenghi G.

Comment on


PMID: 28836423
Development of a Refined Protocol for Trans-scleral Subretinal Transplantation of Human Retinal Pigment Epithelial Cells into Rat Eyes.
Zhao C, Boles NC, Miller JD, Kawola S, Temple S, Davis RJ, Stern JH.

Abstract: Degenerative retinal diseases such as age-related macular degeneration (AMD) are the leading cause of irreversible vision loss worldwide. AMD is characterized by the degeneration of retinal pigment epithelial (RPE) cells, which are a monolayer of cells functionally supporting and anatomically wrapping around the neural retina. Current pharmacological treatments for the non-neovascular AMD (dry AMD) only slow down the disease progression but cannot restore vision, necessitating studies aimed at identifying novel therapeutic strategies. Replacing the degenerative RPE cells with healthy cells holds promise to treat dry AMD in the future. Extensive preclinical studies of stem cell replacement therapies for AMD involve the transplantation of stem cell-derived RPE cells into the subretinal space of animal models, in which the subretinal injection technique is applied. The approach most frequently used in these preclinical animal studies is through the trans-scleral route, which is made difficult by the lack of direct visualization of the needle end and can often result in retinal damage. An alternative approach through the vitreous allows for direct observation of the needle end position, but it carries a high risk of surgical traumas as more eye tissues are disturbed. We have developed a less risky and reproducible modified trans-scleral injection method that uses defined needle angles and depths to successfully and consistently deliver RPE cells into the rat subretinal space and avoid excessive retinal damage. Cells delivered in this manner have been previously demonstrated to be efficacious in the Royal College of Surgeons (RCS) rat for at least 2 months. This technique can be used not only for cell transplantation but also for delivery of small molecules or gene therapies.

PMID: 28829422

Autologous Induced Stem-Cell-Derived Retinal Cells for Macular Degeneration.
Mandai M, Kurimoto Y, Takahashi M.

Comment on
PMID: 28834478

Diet, lifestyle & low vision
Cost-effectiveness of age-related macular degeneration study supplements in the UK: combined trial and real-world outcomes data.
Lee AY, Butt T, Chew E, Agron E, Clemons TE, Egan CA, Lee CS, Tufail A; UK EMR AMD Research Group.

AIMS: To evaluate the cost-effectiveness of Age-Related Eye Disease Study (AREDS) 1 & 2 supplements in patients with either bilateral intermediate age-related macular degeneration, AREDS category 3, or unilateral neovascular age-related macular degeneration AMD (nAMD), AREDS category 4.

METHODS: A patient-level health state transition model based on levels of visual acuity in the better-seeing
eye was constructed to simulate the costs and consequences of patients taking AREDS vitamin supplements.

SETTING: UK National Health Service (NHS). The model was populated with data from AREDS and real-world outcomes and resource use from a prospective multicentre national nAMD database study containing 92,976 ranibizumab treatment episodes.

INTERVENTIONS: Two treatment approaches were compared: immediate intervention with AREDS supplements or no supplements.

MAIN OUTCOME MEASURES: quality-adjusted life years (QALYs) and healthcare costs were accrued for each strategy, and incremental costs and QALYs were calculated for the lifetime of the patient. One-way and probabilistic sensitivity analyses were employed to test the uncertainty of the model.

RESULTS: For AREDS category 3, the incremental cost-effectiveness ratio was £30,197. For AREDS category 4 compared with no intervention, AREDS supplements are more effective (10.59 vs 10.43 QALYs) and less costly (£52,074 vs 54,900) over the lifetime of the patient.

CONCLUSIONS: The recommendation to publicly fund AREDS supplements to category 3 patients would depend on the healthcare system willingness to pay. In contrast, initiating AREDS supplements in AREDS category 4 patients is both cost saving and more effective than no supplement use and should therefore be considered in public health policy.

PMID: 28835423

Arq Bras Oftalmol. 2017 Jun;80(3):159-164.

Vision status, ophthalmic assessment, and quality of life in the very old.


PURPOSE: To determine the vision status, ophthalmic findings, and quality of life among the very elderly.

METHODS: This was a cross-sectional observational study of individuals aged 80 years and above. A comprehensive ophthalmic exam was performed with measurement of both the presenting (PVA) and best-corrected visual acuity. The Quality of Life Short Form-36 (SF-36) and the Visual Function Questionnaire (VFQ-25) were also administered.

RESULTS: A total of 150 non-institutionalized participants were assigned to three age groups: 80-89 years (n=70), 90-99 years (n=50), and 100 years and older (n=30). PVA and best-corrected visual acuity were normal (≥20/30) in 20 (13.3%) and 37 participants (24.7%), respectively. Regarding PVA, mild visual impairment (<20/30 to ≥20/60) was found in in 53 (35.4%), moderate visual impairment (<20/60 to ≥20/200) in 50 (33.3%), severe visual impairment (<20/200 to ≥20/400) in 8 (5.3%), and blindness (<20/400) in 19 (12.7%) participants. Regarding best-corrected visual acuity, mild, moderate, and severe visual impairments were present in 55 (36.7%), 38 (25.3%), and 5 (3.3%) participants, respectively, and blindness was present in 15 (10%). The main causes of visual impairment/blindness were cataract (43.8%), refractive errors (21.5%), age-related macular degeneration (17.7%), and myopic degeneration (3.8%). SF-36 scores were worse in those with low visual acuity, while VFQ-25 domain scores were poorer in those with vision impairment/blindness.

CONCLUSION: Vision impairment and blindness was present in three-quarters of this sample, but it was notable that adequate correction with spectacles improved visual acuity. This reinforces the need for regular ophthalmic care in elderly patients to improve their quality of life by optimizing vision.

PMID: 28832732
Ophthalmologe. 2017 Aug 22. [Epub ahead of print]

[Ophthalmological health care of the institutionalized elderly : The OVIS study]. [Article in German]


BACKGROUND: Due to demographic change and societal transformation the number of elderly persons living in retirement homes is growing in Germany. Access to health care is more complicated in the setting of nursing homes. Different regional studies suggest unmet ophthalmological health care needs in institutionalized elderly people. This study assessed the current ophthalmological health care structure and supply status in nursing homes in Germany.

METHODS: This prospective, multicenter cross-sectional study was conducted by 14 study centers in Germany. Elderly people living in 32 nursing homes were included after approval by the local institutional review boards. A standardized examination was performed which included a detailed medical and ocular history, refraction, visual acuity testing, tonometry, biomicroscopy and dilated funduscopy. Unmet ophthalmological health care needs were documented and the data were analyzed descriptively and via logistic regression modelling.

RESULTS: A total of 600 participants (434 women and 166 men) aged 50-104 years were examined of which 368 (61%) had ophthalmological conditions requiring treatment. The most prevalent findings were cataracts (315; 53%), disorders of the eyelids (127; 21%), dry eye disease (57; 10%) and posterior capsule opacification (43; 7%). In 63 (11%) of the participants glaucoma was suspected and 55 (9%) of the examined population had a known diagnosis of glaucoma, of whom one third was not on any or on insufficient anti-glaucomatous therapy. 236 (39%) showed signs of age-related macular degeneration (AMD). Only 52% of the examined cohort had been examined by an ophthalmologist within the last 5 years and 39% stated that they would currently not be able to consult an ophthalmologist. Reported barriers were mainly transport and lack of support.

CONCLUSION: This study demonstrates considerable unmet ophthalmological health care needs of the institutionalized elderly in Germany. Novel and reformed models of specialist care provision have to be developed.

PMID: 28831559


The Charles Bonnet Syndrome in Patients With Neovascular Age-Related Macular Degeneration: Association With Proton Pump Inhibitors.


PURPOSE: We investigate the prevalence of the Charles Bonnet syndrome (CBS) in patients with neovascular age-related macular degeneration (AMD) and analyze the role of oral proton pump inhibitors (PPIs) and other potential risk factors.

METHODS: A total of 510 consecutive patients with neovascular-AMD followed at a single tertiary center in Portugal were screened for CBS. Using a structured questionnaire, psychiatrically healthy individuals were interviewed systematically and divided into a CBS group and a non-CBS group. Demographic data, current medication, and ocular risk factors were collected and compared between the two groups.

RESULTS: A total of 500 patients met the inclusion criteria and 471 with complete data were included in the final analysis. The prevalence of CBS was 9.0% (45/500). Using a binary logistic regression model, correlations were found between older age (P = 0.002), PPI intake (P = 0.022), poor visual acuity (P =
0.004), and development of CBS. PPIs doubled the risk of CBS from 7% (20/304) to 15% (25/167), with an odds ratio of 2.154. The increased risk for visual hallucinations caused by PPIs was independent of age (P = 0.598) and visual acuity (P = 0.739).

CONCLUSIONS: The prevalence of CBS in neovascular-AMD patients is high and mainly affects older individuals with poor visual acuity. PPIs seem to increase the risk of development of hallucinations independently of the degree of visual loss.

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