Drug treatment


Targeting factor D of the alternative complement pathway reduces geographic atrophy progression secondary to age-related macular degeneration.


Abstract: Geographic atrophy is an advanced form of age-related macular degeneration (AMD) and a leading cause of vision loss for which there are no approved treatments. Genetic studies in AMD patients have implicated dysregulation of the alternative complement pathway in the pathogenesis of geographic atrophy. Lampalizumab is a potential therapeutic that targets complement factor D, a pivotal activator of the alternative complement pathway. The MAHALO phase 2 clinical trial was a multicenter, randomized, controlled study that evaluated lampalizumab administered by intravitreal injection monthly (n = 42) and every other month (n = 41) versus sham control (n = 40) in patients with geographic atrophy secondary to AMD. The primary endpoint was the mean change in lesion area from baseline to month 18 as measured by fundus autofluorescence. Specific AMD-associated genetic polymorphisms were also analyzed. The MAHALO study met its primary efficacy endpoint with an acceptable safety profile; monthly lampalizumab treatment demonstrated a 20% reduction in lesion area progression versus sham control [80% confidence interval (CI), 4 to 37%]. A more substantial monthly treatment benefit of 44% reduction in geographic atrophy area progression versus sham control (95% CI, 15 to 73%) was observed in a subgroup of complement factor I (CFI) risk-allele carriers (57% of the patients analyzed were CFI risk-allele carriers). The MAHALO study shows a potential treatment effect in patients with geographic atrophy and supports therapeutic targeting of the alternative complement pathway for treating AMD pathogenesis.

PMID: 28637922


Treat and extend therapy using aflibercept for neovascular age-related macular degeneration: a prospective clinical trial.

DeCroos FC, Reed D, Adam MK, Salz D, Gupta OP, Ho AC, Regillo CD.

PURPOSE: To determine the efficacy and durability of aflibercept utilized in a treat and extend (TAE) regimen for neovascular age-related macular degeneration (NVAMD).

DESIGN: Multicenter, prospective, open label, non-comparative, interventional study

METHODS: Forty eyes of 40 patients with treatment-naive NVAMD were managed with a TAE regimen of intravitreal aflibercept. The main endpoints were the change in mean and median best-corrected visual acuity from
baseline at years 1 and 2. Other endpoints included mean number of annual injections and treatment intervals.

RESULTS: Thirty five patients (87.5%) and 31 (77.5%) completed year 1 and year 2, respectively. The mean letter gain was 7.2 (p < 0.001) and 2.4 (p = 0.269) letters at 1 and 2 years, respectively, from a mean baseline of 58.9 letters (20/63 - 1 Snellen equivalent). The median visual gain was 11.5 and 7.5 letters at 1 and 2 years, respectively, from a median baseline of 59.0 letters (20/63 - 1 Snellen equivalent). The mean number of injections was 8.0 and 6.5 during the first and second year, respectively. Twelve week or longer treatment intervals were utilized in 35% and 38% of patients during the first and second year time points, respectively.

CONCLUSION: Intravitreal aflibercept TAE therapy led to significant visual improvement in eyes with NVAMD at 1 year, with some loss in the visual gains at the end of year 2 that was not related to loss of exudative control. TAE therapy with aflibercept is a rational strategy to reduce treatments and clinic evaluations over 2 years with satisfactory outcomes.

PMID: 28624325

Eye (Lond). 2017 Jun 23. [Epub ahead of print]

Appropriateness of quality standards for meaningful intercentre comparisons of aflibercept service provision for neovascular age-related macular degeneration.


Purpose: Real-world data give different information on health-care delivery compared with randomised controlled trials. We aimed to evaluate the appropriateness of possible quality standards for intersite comparisons of outcomes of providing Aflibercept for neovascular age-related macular degeneration (nAMD) in clinical practice.

Patients and methods: Retrospective data analysis from an electronic medical record. A consecutive series of treatment-naive patients initiated on aflibercept for nAMD, in the UK from March 2013 to October 2015. Age, visual acuity (VA) at baseline and 1 year, and injection episodes were remotely extracted in an anonymised format.

Results: The mean baseline VA was 54.3 letters, ranging from 51.3 to 58.1 between different centres, in 5620 eyes taken from 12 centres. Out of these, 3360 were initiated on treatment more than a year before. The percentage with <35 letters at baseline was 19.9-3% and that with >70 letters was 24.8-10.7%. Eyes with ≥70 letters at 1 year ranged from 20.2 to 42.9% and those with <35 ranged from 4.5 to 21.6% across different sites. Injection rates in 1 year varied from 5.5 to 8.6, and data available at 1 year also varied from 82.3 to 46.4%.

Conclusions: Significant variation was found between sites attempting to provide the same therapeutic regime. For fair comparisons between sites, we recommend that both VA measures and process measures, such as injection numbers, retention rates, and discharge policies, are used. More work is required to explain the differences. Such real-world data are not generated in the same way as a randomised clinical trial, and maybe best used to help improve service provision.Eye advance online publication, 23 June 2017; doi:10.1038/eye.2017.86.

PMID: 28643799

Ophthalmologica. 2017 Jun 23. [Epub ahead of print]

Long-Term Follow-Up of Choroidal Neovascularization due to Angioid Streaks with pro re nata Intravitreal Anti-VEGF Treatment.

PURPOSE: To evaluate the long-term outcomes of intravitreal anti-vascular endothelial growth factor (VEGF) drugs with a pro re nata (PRN) regimen for the treatment of choroidal neovascularization (CNV) secondary to angiod streaks (AS).

METHODS: This is a retrospective, multicenter, noncomparative case series of consecutive AS eyes affected by treatment-naïve CNV. A complete ophthalmologic examination was performed every 30–45 days after the loading phase, including fluorescein angiography and/or optical coherence tomography.

RESULTS: In all, 52 eyes of 39 patients were treated with intravitreal bevacizumab and/or ranibizumab and followed up for a mean of 33.8 months. The best corrected visual acuity at baseline was 20/40, and it deteriorated by an average of 6.8 ETDRS letters per year (p < 0.001). We performed an average of 5.1, 6.5, and 6.8 injections at the 1-, 2-, and 3-year follow-up, respectively.

CONCLUSIONS: Intravitreal anti-VEGF drugs in a PRN regimen with close monitoring appear to slow the progression of CNV in AS, but they do not prevent the affected eyes from progressive visual loss.

PMID: 28641290

Ophthamic Res. 2017 Jun 23. [Epub ahead of print]

Association of the CFH Y402H Polymorphism with the 1-Year Response of Exudative AMD to Intravitreal Anti-VEGF Treatment in the Brazilian Population.

Medina FMC, Motta AALD, Takahashi WY, Carricondo PC, Motta MMDS, Melo MB, Vasconcellos JPC.

AIM: Evidence of the relationship between the polymorphism of the complement factor H (CFH) gene at position 402 (Y402H) and the response to the treatment of wet AMD is controversial. The aim of this study was to compare the functional and morphological 1-year evolution of patients with exudative AMD treated with antivascular endothelial growth factor (VEGF) drugs with the CFH Y402H polymorphism in the Brazilian population.

METHODS: Forty-six patients treated for wet AMD with bevacizumab or ranibizumab in a pro re nata regimen were included. The evolution of best-corrected visual acuity (BCVA) and central retinal thickness (CRT), and the number of injections over 1 year of follow-up were correlated with CFH genotypes.

RESULTS: The analysis of variance for the difference between the BCVA denoted as logMAR (logarithm of the minimum angle of resolution) values showed an improvement at 1 year when compared to baseline (p = 0.039). Profile contrast analysis showed that this difference was significant only in the group without the C allele (p = 0.049), without significance in patients presenting with the risk allele (p = 0.241). CRT showed a mean reduction at 1 year compared to baseline (p < 0.001). Significant differences in the profile contrast test were found in the group without the C allele (p < 0.001) and in patients with the risk allele (p = 0.002). No difference was found in the number of injections among the different groups (p = 0.787).

CONCLUSIONS: The presence of the risk allele of the Y402H polymorphism in the CFH gene was related to a less favorable evolution over 1 year in this sample of the Brazilian population with exudative AMD who were being treated with anti-VEGF drugs. In agreement with similar previous studies, this study concludes that the CFH risk genotypes may affect the disease response to treatment.

PMID: 28641277


Intravitreal injections service: a patient experience evaluation.

Hasan H, Flockhart S, Qureshi W, Khan S, Ahmed S, Shah N.
INTRODUCTION: This survey has been conducted following the introduction of nurse-led intravitreal injections clinics at the Great Western Hospital. A team of 5 nurses regularly carry out an average of 90 injections per week.

METHODS: A series of 169 consecutive injection patients have been offered the study questionnaire between 28 January 2016 and 28 February 2016; patients with no previous experience with a nurse injector were excluded.

RESULTS: 76.9% strongly agree that the nurse is more friendly and sensitive to their needs. Only 12.4% strongly agree that a doctor will be more suitable to deliver the injections. Seventy-five percent stated that they were very happy with the care, while 0.4% thought a nurse would be unsafe; 69.2% feel more comfortable asking questions when with a nurse injector. Anxiety and nervousness were found to be the main two symptoms experienced by patients around the time of injections (27.8% and 34.9%, respectively).

DISCUSSION: The questionnaire was designed based on the feedback from the local friends and family test. A clear majority of patients gave highly positive feedback about nurse injectors. Considering patients’ individual needs at the time of injections, such as allergies or points that need clarification, helps in overcoming some of the psychological complications of treatment.

PMID: 28640723


Anti-vascular endothelial growth factor for diabetic macular oedema: a network meta-analysis.

Virgili G, Parravano M, Evans JR, Gordon I, Lucenteforte E.

BACKGROUND: Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities can reduce oedema and thereby improve vision and prevent further visual loss. These drugs have replaced laser photocoagulation as the standard of care for people with DMO.

OBJECTIVES: The 2014 update of this review found high-quality evidence of benefit with antiangiogenic therapy with anti-VEGF modalities, compared to laser photocoagulation, for the treatment of DMO. The objective of this updated review is to compare the effectiveness and safety of the different anti-VEGF drugs in preserving and improving vision and quality of life using network meta-analysis methods.

SEARCH METHODS: We searched various electronic databases on 26 April 2017.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) that compared any anti-angiogenic drug with an anti-VEGF mechanism of action versus another anti-VEGF drug, another treatment, sham or no treatment in people with DMO.

DATA COLLECTION AND ANALYSIS: We used standard Cochrane methods for pair-wise meta-analysis and we augmented this evidence using network meta-analysis methods. We focused on the relative efficacy and safety of the three most commonly used drugs as interventions of direct interest for practice: aflibercept and ranibizumab, used on-label; and off-label bevacizumab. We collected data on three efficacy outcomes (gain of 15 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters; mean change in best-corrected visual acuity (BCVA); mean change in central retinal thickness (CRT)), three safety outcomes (all severe systemic adverse events (SSAEs); all-cause death; arterial thromboembolic events) and quality of life. We used Stata ‘network’ meta-analysis package for all analyses. We investigated the risk of bias of mixed comparisons based on the variance contribution of each study, having assigned an overall risk of bias to each study.

MAIN RESULTS: Twenty-four studies included 6007 participants with DMO and moderate vision loss, of which two studies randomised 265 eyes of 230 participants and one was a cross-over study on 56 participants (62 eyes) that was treated as a parallel-arm trial. Data were collected on drugs of direct interest from three studies on aflibercept (975 eyes), eight studies on bevacizumab (515 eyes), and 14 studies on
ranibizumab (1518 eyes). As treatments of indirect interest or legacy treatment we included three studies on pegaptanib (541 eyes), five studies on ranibizumab plus prompt laser (557 eyes), one study on ranibizumab plus deferred laser (188 eyes), 13 studies on laser photocoagulation (936 eyes) and six studies on sham treatment (793 eyes). Aflibercept, bevacizumab and ranibizumab were all more effective than laser for improving vision by 3 or more lines after one year (high-certainty evidence). Approximately one in 10 people improve vision with laser, and about three in 10 people improve with anti-VEGF treatment: risk ratio (RR) versus laser 3.66 (95% confidence interval (CI) 2.79 to 4.79) for aflibercept; RR 2.47 (95% CI 1.81 to 3.37) for bevacizumab; RR 2.76 (95% CI 2.12 to 3.59) for ranibizumab. On average there was no change in visual acuity (VA) with laser after one year, compared with a gain of 1 or 2 lines with anti-VEGF treatment: laser versus aflibercept mean difference (MD) -0.20 (95% CI -0.22 to -0.17) logMAR; versus bevacizumab MD -0.12 (95% CI -0.15 to -0.09) logMAR; versus ranibizumab MD -0.12 (95% CI -0.14 to -0.10) logMAR. The certainty of the evidence was high for the comparison of aflibercept and ranibizumab with laser and moderate for bevacizumab comparison with laser due to inconsistency between the indirect and direct evidence. People receiving ranibizumab were less likely to gain 3 or more lines of VA at one year compared with aflibercept: RR 0.75 (95% CI 0.60 to 0.94), moderate-certainty evidence. For every 1000 people treated with aflibercept, 92 fewer would gain 3 or more lines of VA at one year if treated with ranibizumab (22 to 148 fewer). On average people receiving ranibizumab had worse VA at one year (MD 0.08 logMAR units, 95% CI 0.05 to 0.11), moderate-certainty evidence; and higher CRT (MD 39 µm, 95% CI 2 µm to 76 µm; low-certainty evidence). Ranibizumab and bevacizumab were comparable with respect to aflibercept and did not differ in terms of VA: RR of gain of 3 or more lines of VA at one year 1.11 (95% CI 0.87 to 1.43), moderate-certainty evidence, and difference in change in VA was 0.00 (95% CI -0.02 to 0.03) logMAR, moderate-certainty evidence. CRT reduction favoured ranibizumab by -29 µm (95% CI -58 µm to -1 µm, low-certainty evidence). There was no evidence of overall statistical inconsistency in our analyses. The previous version of this review found moderate-certainty evidence of good safety of antiangiogenic drugs versus control. This update used data at the longest available follow-up (one or two years) and found that aflibercept, ranibizumab and bevacizumab do not differ regarding systemic serious adverse events (SSAEs) (moderate- or high-certainty evidence). However, risk of bias was variable, loop inconsistency could be found and estimates were not precise enough on relative safety regarding less frequent events such as arterial thromboembolic events or death (low- or very low-certainty evidence). Two-year data were available and reported in only four RCTs in this review. Most industry-sponsored studies were open-label after one year. One large publicly-funded study compared the three drugs at two years and found no difference.

AUTHORS’ CONCLUSIONS: Anti-VEGF drugs are effective at improving vision in people with DMO with three to four in every 10 people likely to experience an improvement of 3 or more lines VA at one year. There is moderate-certainty evidence that aflibercept confers some advantage over ranibizumab and bevacizumab in people with DMO at one year in visual and anatomic terms. Relative effects among anti-VEGF drugs at two years are less well known, since most studies were short term. Evidence from RCTs may not apply to real-world practice, where people in need of antiangiogenic treatment are often undertreated and under-monitored. We found no signals of differences in overall safety between the three antiangiogenic drugs that are currently available to treat DMO, but our estimates are imprecise for cardiovascular events and death.

PMID: 28639415


Intravitreal Anti-Vascular Endothelial Growth Factor for Macular Edema due to Complex Retinal Arterial Macroaneurysms.

Bormann C, Heichel J, Hammer U, Habermann A, Hammer T.

INTRODUCTION: Complex retinal arterial macroaneurysms (RAM) are often accompanied by hemorrhage and/or affect the macula. We evaluated the effect of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy using ranibizumab or aflibercept with or without laser photocoagulation in the treatment of macular edema due to RAM.
METHODS: A case report of two patients with secondary macular edema caused by RAM is presented. The first case was a 76-year-old female treated with two 0.5-mg injections of ranibizumab and additional focal laser photocoagulation. This patient presented a solely intraretinal exudation. The second patient was a 96-year-old female, who received one 2.0-mg injection of aflibercept. She showed sub- and intraretinal edema. We documented the clinical courses of these patients based on fundus photography, fluorescein angiography, and spectral-domain optical coherence tomography. Patients were followed-up for 12 months.

RESULTS: Patients were treated successfully using anti-VEGF therapy (ranibizumab or aflibercept) with or without laser photocoagulation. In both cases, we observed a complete regression of the macular edema and an increase in visual acuity.

CONCLUSION: RAM can manifest with heterogeneous findings. Intravitreal anti-VEGF therapy with or without laser photocoagulation may be an effective treatment option in cases of macular edema due to RAM. Aflibercept and ranibizumab seem to be a potent anti-VEGF therapy for RAM. Individualized patient care is needed.

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Mol Pharm. 2017 Jun 20. [Epub ahead of print]

Ocular Pharmacokinetics of Therapeutic Antibodies Given by Intravitreal Injection: Estimation of Retinal Permeabilities Using a 3-Compartment Semi-Mechanistic Model.

Hutton-Smith LA, Gaffney EA, Byrne HM, Maini PK, Gadkar K, Mazer NA.

Abstract: Intravitreally (IVT) injected macromolecules for the treatment of age-related macular degeneration must permeate through the inner limiting membrane (ILM) into the retina and through the retinal pigment epithelium (RPE) to enter the choroid. A quantitative understanding of intraocular transport mechanisms, elimination pathways and the effect of molecular size, is currently incomplete. We present a semi-mechanistic, 3-compartment (retina, vitreous and aqueous) pharmacokinetic (PK) model, expressed using linear ordinary differential equations (ODEs), to describe the molecular concentrations following a single IVT injection. The model was fit to experimental rabbit data, with Fab, Fc, IgG and IgG null antibodies and antibody fragments, to estimate key ocular pharmacokinetic parameters. The model predicts an ocular half-life, t1/2, which is the same for all compartments and dependent on the hydrodynamic radius (Rh) of the respective molecules, consistent with observations from the experimental data. Estimates of the permeabilities of the RPE and ILM are derived for Rh values ranging from 2.5 to 4.9 nm, and are found to be in good agreement with ex-vivo measurements from bovine eyes. We show that the ratio of these permeabilities largely determines the ratio of the molecular concentrations in the retina and vitreal compartments and their dependence on Rh. The model further provides estimates for the ratio of fluxes corresponding to the elimination pathways from the eye, i.e., aqueous humor to retina/choroid, which increase from 5:1 to 7:1 as Rh decreases. Our semi-mechanistic model provides a quantitative framework for interpreting ocular PK and the effects of molecule size on rate-determining parameters. We have shown that intra-ocular permeabilities can be reasonably estimated from 3-compartment ocular PK data and determined how these parameters influence the half-life, retinal permeation and elimination of intravitreally injected molecules from the eye.

PMID: 28631484


Evolution of Geographic Atrophy in Participants Treated with Ranibizumab for Neovascular Age-related Macular Degeneration.

PURPOSE: To evaluate the risk factors, incidence, and rate of progression of geographic atrophy (GA) in eyes with neovascular age-related macular degeneration (nAMD) treated with ranibizumab.

DESIGN: Post-hoc analysis of a prospective clinical study.

PARTICIPANTS: 69 participants with nAMD in at least one eye.

METHODS: Participants were prospectively treated in the study eye with 0.5 mg intravitreal ranibizumab. Study eyes received 4 monthly injections followed by pro re nata injections until a fluid-free macula was achieved on optical coherence tomography. Risk factors assessed included baseline demographics, treatment, and ocular characteristics on imaging. Eyes were evaluated on fundus autofluorescence (FAF) for GA. The rate of GA area growth in study and fellow eyes was analyzed by linear regression of square-root transformed areas.

MAIN OUTCOME MEASURES: Development of new-onset GA and rate of GA area growth measured on ocular imaging, including FAF images of the study eyes.

RESULTS: Sixty-nine participants (mean age 78.8±7.8 years) with an average of 40.0±13.6 months of follow-up were analyzed. Twenty-two of 69 study eyes (32%) were treatment naïve. During their first year of the study, participants received an average of 9.2±3.3 injections in the study eye. Of 63 study eyes with quality baseline images, 22 (35%) had pre-existing GA. Of the remaining 41 eyes, 7 (17%) developed new-onset GA during study follow-up. Those who developed new GA were older (all ≥79 years old) and had received fewer study injections on average (6.9 vs. 10.4 injections at 1 year) compared to those who did not develop new GA. Of the 12 treatment naïve study eyes without GA at baseline, 1 (8.3%) developed new GA during the study. In 21 study eyes with quantifiable GA area, eyes with GA present at baseline (16/21) enlarged by 0.34±0.26 mm/year, compared to 0.19±0.12 mm/year in eyes developing new-onset GA (5/21).

CONCLUSIONS: While 17% of study eyes without GA present at baseline receiving ranibizumab developed new GA, the role of ranibizumab in the development of GA is unclear. Further prospective longitudinal studies are required to determine the eyes most at risk of developing GA in the setting of anti-VEGF treatment.

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Evaluation of Aflibercept Treatment Responses in Eyes with Bevacizumab/Ranibizumab-resistant Wet Age-related Macular Degeneration.


OBJECTIVES: To evaluate anatomic and functional results after switching from intravitreal bevacizumab or ranibizumab treatment to aflibercept for wet (neovascular) age-related macular degeneration.

MATERIALS AND METHODS: This retrospective study included 22 eyes of 22 patients resistant to treatment with at least 6 injections of bevacizumab or ranibizumab. The first three injections had been applied monthly, the others pro re nata (PRN). Outcome measures were follow-up period, injection number, best corrected visual acuity (BCVA), central retinal thickness (CRT) and pigment epithelial detachment (PED) height. Dosing regimen of aflibercept was determined PRN. The patients were examined monthly. In all visits, BCVA and optical coherence tomography results were assessed together and injections were applied according to these findings. Patients with at least three months of follow-up were included in the study.

RESULTS: Twenty-two eyes of 22 patients treated with bevacizumab or ranibizumab were switched to aflibercept therapy. Seven patients had serous PED and 4 patients had fibrovascular PED. The mean follow-up periods for these groups were 20.59±6.76 months and 8.68±3.79 months, respectively. The mean injection numbers were 10.5±3.61 vs 4.54±1.56. Statistically significant reductions were noted in CRT (533.86±164.06 µm vs 412.04±143.86 µm, p<0.05). BCVA levels were almost equal before and after
switching (0.18±0.17 vs 0.18±0.14). Serous and fibrovascular PED heights decreased suboptimally from 460±281.51 µm to 282.42±175.76 µm (p>0.05) for serous PEDs and 251.25±43.85 µm to 225.75±73.09 µm (p>0.05) for fibrovascular PEDs.

CONCLUSION: Switching to aflibercept resulted in significant improvement in CRT, but not in BCVA or PED heights.

PMID: 28630787 PMCID: PMC5468525


Spironolactone as an Adjunctive Treatment in Neovascular Age-Related Macular Degeneration.

Kapoor KG, Sim J.

Abstract: Neovascular age-related macular degeneration (AMD) is a potentially sight-threatening condition. The current standard-of-care treatment regimen is serial intravitreal antivascular endothelial growth factor injections. While these typically have great success, they do carry exceptional treatment burden on the patient, cost burden due to their required frequency of use, and the risk of endophthalmitis, which can be devastating. This case report explores an alternative potential option as a treatment adjunct for neovascular AMD (nAMD), and identifies some of the overlap between nAMD and central serous chorioretinopathy. Future research is needed to better understand the role of mineralocorticoid receptor antagonist treatment in this disease spectrum.

PMID: 28626417 PMCID: PMC5471798

Other treatment & diagnosis


Tissue plasminogen activator-assisted vitrectomy for submacular hemorrhage due to age-related macular degeneration.

Gok M, Karabaş VL, Aslan MS, Kara Ö, Karaman S, Yenihayat F.

PURPOSE: The purpose of this study was to evaluate the treatment efficacy of vitrectomy combined with subretinal recombinant tissue plasminogen activator (r-tPA) and factors affecting visual improvement in patients with submacular hemorrhage (SMH) due to neovascular age-related macular degeneration (nAMD).

MATERIALS AND METHODS: Medical records of 17 consecutive patients diagnosed with SMH secondary to nAMD were retrospectively reviewed. The initial surgical procedure involved a 23-gauge transconjunctival vitrectomy, subretinal r-tPA application through a self-sealing inferior retinotomy, and sulfur hexafluoride gas for tamponade in all patients. The duration, size, and thickness of the hemorrhage and the pre- and post-operative visual acuity (VA) using a Snellen chart were recorded. VA was converted to logMAR for statistical analysis.

RESULTS: The average duration and size of the SMH were 12.8 ± 18.2 days and 8.6 ± 5.3 disc areas, respectively. The mean follow-up time was 16.9 ± 4.7 months. A statistically significant visual improvement was found when comparing initial VA with postoperative best-corrected VA (BCVA) and final BCVA (Wilcoxon rank test, P ≤ 0.01). There was no significant correlation between the size of the hemorrhage and postoperative BCVA and final BCVA (Spearman's rho test). There was no statistically significant correlation between the initial VA and postoperative BCVA and final BCVA (Spearman's rho test). There was no significant correlation between the duration of hemorrhage and postoperative BCVA and final BCVA (Spearman's rho test). The preoperative thickness of hemorrhage (747.5 ± 30 µm) was not correlated with postoperative BCVA or final BCVA (Pearson's test).
CONCLUSIONS: Vitrectomy combined with subretinal r-tPA injection and gas tamponade is an effective surgical intervention to preserve VA in selected patients with apparent SMH.

PMID: 28643713


Comparison of macular pigment optical density in patients with dry and wet age-related macular degeneration.

Ozyurt A, Kocak N, Akan P, Calan OG, Ozturk T, Kaya M, Karahan E, Kaynak S.

AIM: The aim of the study was to evaluate the macular pigment optical density (MPOD) levels in patients with wet age-related macular degeneration (AMD), dry AMD, and also in healthy controls.

SETTINGS AND DESIGN: This study was conducted at Department of Ophthalmology, and the study design was a prospective study.

PATIENTS AND METHODS: Forty-eight patients with wet AMD, 51 patients with dry AMD, and 50 controls were included in the study. All patients were naive to both previous lutein or zeaxanthin administration and any previous intravitreal injections. Fundus reflectance (VISUCAM 500, reflectance of a single 460 nm wavelength) was used to measure the MPOD levels. Three groups were compared regarding age, gender, serum lutein, and zeaxanthin concentrations as well as MPOD levels.

RESULTS: Serum lutein and zeaxanthin levels were significantly higher in control group when compared with wet AMD (Group 1) and dry AMD (Group 2) (P = 0.001 and P< 0.001, respectively). Mean MPOD was found to be similar in all of the three study subgroups (P = 0.630). However, maximum MPOD was significantly higher in control group when compared with Group 1 and 2 (P = 0.003). There was no correlation between serum lutein or zeaxanthin concentrations and mean MPOD levels (P = 0.815, r = 0.014 and P = 0.461, r = 0.043, respectively), but there was a weak correlation between serum zeaxanthin concentration and maximum MPOD level (P = 0.042, r = 0.124). Maximum MPOD level was found to be correlated with the level of AMD (Group 1, 2, and 3; r = 0.184, P = 0.041).

CONCLUSION: Maximum MPOD level was found to be lower in patients with AMD when compared with control cases. Mean MPOD and maximum MPOD levels were similar in wet and dry AMD Groups. These results can be applied clinically keeping in mind that MPOD measurements with one wavelength reflectometry may not be completely reliable.

PMID: 28643712

Ophthalmic Res. 2017 Jun 23. [Epub ahead of print]

7-Hexagon Multifocal Electroretinography for an Objective Functional Assessment of the Macula in 14 Seconds.

Schönbach EM, Chaikitmongkol V, Annam R, McDonnell EC, Wolfson Y, Fletcher E, Scholl HPN.

PURPOSE: We present the multifocal electroretinogram (mfERG) with a 7-hexagon array as an objective test of macular function that can be recorded in 14 s. We provide normal values and investigate its reproducibility and validity.

METHODS: Healthy participants underwent mfERG testing according to International Society for Clinical Electrophysiology of Vision (ISCEV) standards using the Espion Profile/D310 multifocal ERG system (Diagnosys, LLC, Lowell, MA, USA). One standard recording of a 61-hexagon array and 2 repeated recordings of a custom 7-hexagon array were obtained.

RESULTS: A total of 13 subjects (mean age 46.9 years) were included. The median response densities
were 12.5 nV/deg² in the center and 5.2 nV/deg² in the periphery. Intereye correlations were strong in both the center (ρCenter = 0.821; p < 0.0001) and the periphery (ρPeriphery = 0.862; p < 0.0001). Intraeye correlations were even stronger: ρCenter = 0.904 with p < 0.0001 and ρPeriphery = 0.955 with p < 0.0001. Bland-Altman plots demonstrated an acceptable retest mean difference in both the center and periphery, and narrow limits of agreement. We found strong correlations of the center (ρCenter = 0.826; p < 0.0001) and periphery (ρPeriphery = 0.848; p < 0.0001), with recordings obtained by the 61-hexagon method.

CONCLUSIONS: The 7-hexagon mFERG provides reproducible results in agreement with results obtained according to the ISCEV standard.

PMID: 28641302


ASSOCIATION BETWEEN VISUAL FUNCTION AND SUBRETINAL DRUSENOID DEPOSITS IN NORMAL AND EARLY AGE-RELATED MACULAR DEGENERATION EYES.

Neely D, Zarubina AV, Clark ME, Huisingsh CE, Jackson GR, Zhang Y, McGwin G Jr, Curcio CA, Owsey C.

PURPOSE: To examine the association between subretinal drusenoid deposits (SDDs) identified by multimodal retinal imaging and visual function in older eyes with normal macular health or in the earliest phases of age-related macular degeneration (AMD).

METHODS: Age-related macular degeneration status for each eye was defined according to the Age-Related Eye Disease Study (AREDS) 9-step classification system (normal = Step 1, early AMD = Steps 2-4) based on color fundus photographs. Visual functions measured were best-corrected photopic visual acuity, contrast and light sensitivity, mesopic visual acuity, low-luminance deficit, and rod-mediated dark adaptation. Subretinal drusenoid deposits were identified through multimodal imaging (color fundus photographs, infrared reflectance and fundus autofluorescence images, and spectral domain optical coherence tomography).

RESULTS: The sample included 1,202 eyes (958 eyes with normal health and 244 eyes with early AMD). In normal eyes, SDDs were not associated with any visual function evaluated. In eyes with early AMD, dark adaptation was markedly delayed in eyes with SDDs versus no SDD (a 4-minute delay on average), P = 0.0213. However, this association diminished after age adjustment, P = 0.2645. Other visual functions in early AMD eyes were not associated with SDDs.

CONCLUSION: In a study specifically focused on eyes in normal macular health and in the earliest phases of AMD, early AMD eyes with SDDs have slower dark adaptation, largely attributable to the older ages of eyes with SDD; they did not exhibit deficits in other visual functions. Subretinal drusenoid deposits in older eyes in normal macular health are not associated with any visual functions evaluated.

PMID: 28633153


Pfau M, Goerdt L, Schmitz-Valckenberg S, Mauschitz MM, Mishra DK, Holz FG, Lindner M, Fleckenstein M.

PURPOSE: To compare the intermodality and interreader agreement for geographic atrophy (GA) lesion size quantification in green-light fundus autofluorescence (GAF; excitation = 518 nm) versus combined blue-light fundus autofluorescence (BAF; excitation = 488 nm) and near-infrared reflectance (NIR; 820 nm) - based grading.
METHODS: Confocal scanning laser ophthalmoscopy (cSLO) GAF, BAF, and NIR images of 40 eyes from 29 patients (mean age 79.7 years) with GA secondary to AMD were recorded according to a standardized protocol. GA areas were analyzed in GAF, BAF combined with NIR (BAF+NIR), or BAF alone, by four independent readers using semiautomated software (RegionFinder; Heidelberg Engineering, Heidelberg, Germany). A mixed-effects model was used to assess the effect of image modality on the measured square-root lesion area. The coefficient of repeatability (CR) and intraclass correlation coefficient (ICC) were assessed for the square-root lesion area, lesion perimeter, and circularity.

RESULTS: GAF-based measurements were on average 0.062 mm (95% confidence interval [CI] 0.04-0.08 mm) larger than BAF+NIR-based measurements and 0.077 mm (95% CI 0.06 - 0.10 mm) larger than BAF-based measurements. Interreader agreement was highest for GAF-based analysis ([CR, ICC] 0.196 mm, 0.995) followed by BAF+NIR (0.232 mm, 0.992) and BAF alone (0.263 mm, 0.991). The same was noted for the lesion perimeter and circularity. Post hoc review revealed that interreader differences were associated with media opacification interfering with lesion boundary demarcation to a larger extent in BAF than in GAF.

CONCLUSIONS: cSLO-based GAF and combined BAF+NIR imaging with semiautomated lesion delineation allow for an accurate and reproducible quantification of GA. The slightly better interreader agreement using cSLO GAF suggests that its use may be preferable in clinical trials examining the change in lesion size as a clinical endpoint.

PMID: 28632841

Pathogenesis


Loss of Function of P2X7 Receptor Scavenger Activity in Aging Mice: A Novel Model for Investigating the Early Pathogenesis of Age-Related Macular Degeneration.

Vessey KA, Gu BJ, Jobling AI, Phipps JA, Greferath U, Tran MX, Dixon MA, Baird PN, Guymer RH, Wiley JS, Fletcher EL.

Abstract: Age-related macular degeneration (AMD) is a leading cause of irreversible, severe vision loss in Western countries. Recently, we identified a novel pathway involving P2X7 receptor scavenger function expressed on ocular immune cells as a risk factor for advanced AMD. In this study, we investigate the effect of loss of P2X7 receptor function on retinal structure and function during aging. P2X7-null and wild-type C57bl6J mice were investigated at 4, 12, and 18 months of age for macrophage phagocytosis activity, ocular histological changes, and retinal function. Phagocytosis activity of blood-borne macrophages decreased with age at 18 months in the wild-type mouse. Lack of P2X7 receptor function reduced phagocytosis at all ages compared to wild-type mice. At 12 months of age, P2X7-null mice had thickening of Bruch membrane and retinal pigment epithelium dysfunction. By 18 months of age, P2X7-null mice displayed phenotypic characteristics consistent with early AMD, including Bruch membrane thickening, retinal pigment epithelium cell loss, retinal functional deficits, and signs of subretinal inflammation. Our present study shows that loss of function of the P2X7 receptor in mice induces retinal changes representing characteristics of early AMD, providing a valuable model for investigating the role of scavenger receptor function and the immune system in the development of this age-related disease.

PMID: 28628761


Aquaporins: Novel Targets for Age-Related Ocular Disorders.

Abstract: Aquaporins (AQPs), a large family of membrane protein channels that facilitate transport of water and other small solutes, play important roles in physiological functions and human diseases. Up till now, 13 types of AQPs, numbered 0 through 12, have been identified in various mammalian tissues. Homologous genes for AQPs in amphibians, insects, and bacteria highlight the evolutionary conservation and, thus, the importance of these membrane channels. Many members of the AQP family are expressed in the eye. AQP1, which is a water-selective channel, is expressed in the anterior chamber (cornea, ciliary body, trabecular meshwork) and posterior chamber (retina and microvessels in choroid), controlling the fluid homeostasis in the eye. Mice knockout studies have indicated that AQP1 plays an important function in the eye by suggesting its role in aqueous humor dynamics and retina angiogenesis. This review will focus on the role of AQP1 as a novel target for ocular disorders such as glaucoma and age-related macular degeneration, and it will discuss challenges and advances in identifying modulators of AQP1 function that could be useful in clinical applications.

PMID: 28632458

Post-receptor Neuronal Loss in Intermediate Age-Related Macular Degeneration.
Borrelli E, Abdelfattah NS, Uji A, Nittala MG, Boyer DS, Sadda SR.
PURPOSE: To investigate the relationship between ganglion cell complex (GCC) thickness and photoreceptor alterations in eyes with intermediate age-related macular degeneration (AMD).

DESIGN: Retrospective case-control study.

METHODS: We collected data from 68 eyes with intermediate AMD from 68 patients with spectral domain optical coherence tomography (SD-OCT) imaging. A control group of 50 eyes from 50 healthy subjects was included for comparison. Our main outcome measures for comparison between groups were: (i) the average and minimum GCC thickness, and (ii) the "normalized" reflectivity of the ellipsoid zone (EZ) en-face image.

RESULTS: The average and minimum GCC thicknesses were thinner in AMD patients (69.54±9.30 and 63.22±14.11 μm, respectively) than in healthy controls (78.57±6.28 and 76.28±6.85 μm, P< .0001 and P< .0001, respectively). Agreement was found to be excellent in the "normalized" EZ reflectivity assessment (intra-class correlation coefficient=0.986, coefficient of variation=1.11). The EZ "normalized" reflectivity was 0.67±0.11 in controls, and 0.61±0.09 in the AMD group (P=.006). In univariate analysis, EZ "normalized" reflectivity was found to have a significant direct relationship with average (P< .0001) and minimum (P< .0001) GCC thickness in AMD patients, but not in controls (P=.852 and P=.892, respectively).

CONCLUSIONS: Eyes with intermediate AMD exhibit GCC thinning, as well as a reduced EZ "normalized" reflectivity, and these parameters are correlated. This study supports the concept of post-receptor retinal neuronal loss as a contributor to retinal thinning in intermediate AMD.

PMID: 28624323

Epidemiology

Choroidal thickness in patients with coronary artery disease.
Ahmad M, Kaszubski PA, Cobbs L, Reynolds H, Smith RT.
PURPOSE: To evaluate choroidal thickness (CTH) in patients with coronary artery disease (CAD)
compared to healthy controls.

**DESIGN:** Cross-sectional.

**METHODS:** Setting: Ambulatory clinic of a large city hospital. Patient population: Thirty-four patients had documented CAD, defined as history of >50% obstruction in at least one coronary artery on cardiac catheterization, positive stress test, ST elevation myocardial infarction, or revascularization procedure. Twenty-eight age-matched controls had no self-reported history of CAD or diabetes. Patients with high myopia, dense cataracts, and retinal disease were excluded. Observation procedures: Enhanced depth imaging optical coherence tomography and questionnaire regarding medical and ocular history. Main outcome measures: Subfoveal CTh and CTh 2000 μm superior, inferior, nasal, and temporal to the fovea in the left eye, measured by 2 readers.

**RESULTS:** CTh was significantly lower in patients with CAD compared to controls at the subfoveal location (252 vs. 303 μm, P = 0.002) and at all 4 cardinal macular locations. The mean difference in CTh between the 2 groups ranged from 46 to 75 μm and was greatest in the inferior location. Within the CAD group, CTh was significantly lower temporally (P = 0.007) and nasally (P<0.001) than subfoveally, consistent with the pattern observed in controls. On multivariate analysis, CAD was negatively associated with subfoveal CTh (P = 0.006) after controlling for diabetes, hypertension, and hypercholesterolemia.

**CONCLUSIONS AND RELEVANCE:** Patients with CAD have a thinner macular choroid than controls, with preservation of the normal spatial CTh pattern. Decreased CTh might predispose patients with CAD to high-risk phenotypes of age-related macular degeneration such as reticular pseudodrusen and could serve as a potential biomarker of disease in CAD.

PMID: 28632734

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**Genetics**


**Disease-linked mutations in factor H reveal pivotal role of cofactor activity in self surface-selective regulation of complement activation.**


Abstract: Spontaneous activation enables the complement system to respond very rapidly to diverse threats. Activation is efficiently suppressed by complement factor H (CFH) on self surfaces but not foreign surfaces. The surface selectivity of CFH, a soluble protein containing 20 CCP modules (CCPs 1-20), may be compromised by disease-linked mutations. Which of the several functions of CFH drives its self-surface selectivity remains unknown. We made human CFH mutants in Pichia pastoris. In benchmark studies of CCP-1 variants, recombinant I62-CFH (protective against age-related macular degeneration) and V62-CFH functioned equivalently, matching or outperforming plasma-derived CFH while R53H-CFH, linked to atypical haemolytic uraemic syndrome (aHUS), was defective in C3bBb decay-accelerating activity (DAA) and factor I-cofactor activity (CA). The aHUS-linked CCP-19 mutant D1119G-CFH had virtually no CA on (self-like) sheep erythrocytes (ES) but retained measurable DAA. The aHUS-linked CCP-20 mutant S1191L/V1197A-CFH (LA-CFH) had dramatically reduced CA on ES but was less compromised with respect to DAA. D1119G-CFH and LA-CFH performed poorly at preventing complement-mediated haemolysis of ES. PspCN, a CFH-binding Streptococcus pneumoniae protein domain, increases accessibility of CCPs 19-20.

It did not improve the DAA of any CFH variant on ES although it enhanced DAA in surface plasmon-resonance studies. Conversely, PspCN boosted the CA on ES of I62-CFH, R53H-FH and LA-CFH. PspCN also enhanced haemolysis protection by I62-CFH and LA-CFH. We concluded that CCPs 19-20 are critical for efficient CA on self-surfaces but less important for DAA. By exposing CCPs 19-20 and enhancing CA on self-surfaces, PspCN might therapeutically reverse deficiencies in some CFH variants.

PMID: 28637873
Association between polymorphism rs11200638 in the HTRA1 gene and the response to anti-VEGF treatment of exudative AMD: a meta-analysis.

Zhou YL, Chen CL, Wang YX, Tong Y, Fang XL, Li L, Wang ZY.

BACKGROUND: Anti-angiogenesis treatments are the most commonly used treatments for the vision loss caused by exudative age-related macular degeneration (AMD), in which the anti-vascular endothelial growth factor (VEGF) drugs with ranibizumab and bevacizumab are current standard treatments. However, the outcome of anti-VEGF therapeutics is not uniform in all patients.

METHODS: We performed a literature-based meta-analysis including, five published studies relevant to HTRA1 and response to anti-VEGF treatment (bevacizumab or ranibizumab). Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using fixed- and random-effects models. Sensitivity analysis and meta-regression were also performed. Q-statistic test and Egger's test was used to evaluate heterogeneity and publication bias respectively.

RESULTS: Overall, no association between the rs11200638 polymorphism in HTRA1 gene and the anti-VEGF treatment response was found in the genotype GG versus AA (OR = 1.06; 95% CI: 0.77 to 1.48; P = 0.98), genotype GA versus AA (OR = 1.11; 95% CI: 0.83 to 1.47; P = 0.93), genotype GG + GA versus AA (OR = 1.22; 95% CI: 0.94 to 1.57; P = 0.09), and allele G versus A (OR = 0.92; 95% CI: 0.78 to 1.08; P = 0.14). In the subgroup analysis by ethnicity Caucasian population, and a significant association was still not observed in all genetic models. Sensitivity analysis indicated the robustness of our findings, and no publication bias was observed in our meta-analysis.

CONCLUSIONS: This study shows that there was no association between the polymorphism rs11200638 in HTRA1 gene and response to anti-VEGF treatment of exudative AMD. However, more studies are needed to further prove the conclusion of present study, especially well-designed and high quality randomised controlled trials or intervention studies.

PMID: 28637435

Metallothionein polymorphisms in a Northern Spanish population with neovascular and dry forms of age-related macular degeneration.


BACKGROUND: To elucidate the potential role of single nucleotide polymorphisms (SNPs) in the metallothionein (MT) genes in Northern Spanish patients with age-related macular degeneration (AMD).

METHODS: A total of 130 unrelated Northern Spanish natives diagnosed with AMD (46 dry, 35 neovascular, and 49 mixed) and 96 healthy controls, matched by age and ethnicity, were enrolled in a case-control study. DNA was isolated from peripheral blood and genotyped for 14 SNPs located at 5 MT genes (MT1A: rs11076161, rs 11640851, rs8052394, and rs7196890; MT1B: rs8052334, rs964372, and rs7191779; MT1M: rs2270836 and rs936741; MT2A: rs28366003, rs1610216, rs10636, and rs1580833; MT3: rs45570941) using TaqMan probes. The association study was performed using the HaploView 4.0 software.

RESULTS: The allelic and genotypic frequencies analysis revealed that rs28366003 at MT2A gene is significantly associated with dry AMD. The frequency of genotype AG was significantly higher in dry AMD than in control cases (p = 2.65 × 10^-4; AG vs. AA) conferring more than ninefold increased risk to dry AMD (OR = 9.39, 95% CI: 2.11-41.72), whereas the genotype AA confers disease protection (OR = 0.82, 95% CI: 0.71-0.95). No statistically significant differences were observed between AMD subjects and controls in the rest of the 14 SNPs analyzed.
CONCLUSIONS: The present study is the first to investigate the potential association of SNPs at MT genes with susceptibility to AMD. We found a significant association of SNP rs28366003 at MT2A gene with susceptibility to the dry form of AMD in a Northern Spanish population.

PMID: 28635422

Stem cells

Stem Cell Rev. 2017 Jun 22. [Epub ahead of print]

A Promising Tool in Retina Regeneration: Current Perspectives and Challenges When Using Mesenchymal Progenitor Stem Cells in Veterinary and Human Ophthalmological Applications.

Cislo-Pakuluk A, Marycz K.

Abstract: Visual impairment is a common ailment of the current world population, with more exposure to CCD screens and fluorescent lighting, approximately 285 billion people suffer from this deficiency and 13% of those are considered clinically blind. More common causes for visual impairment include age-related macular degeneration (AMD), glaucoma and diabetic retinopathy (Zhu et al. Molecular Medicine Reports, 2015; Kolb et al. 2007; Machalińska et al. Current Eye Research, 34(9),748-760, 2009) among a few. As cases of retinal and optic nerve diseases rise, it is vital to find a treatment, which has led to investigation of the therapeutic potential of various stem cells types (Bull et al. Investigative Ophthalmology & Visual Science, 50(9), 4244, 2009; Bull et al. Investigative Ophthalmology & Visual Science, 49(8), 3449, 2008; Yu et al. Biochemical and Biophysical Research Communications, 344(4), 1071-1079, 2006; Na et al. Graefe's Archive for Clinical and Experimental Ophthalmology, 247(4), 503-514, 2008). In previous studies, some of the stem cell variants used include human Muller SCs and bone marrow derived SCs. Some of the regenerative potential characteristics of mesenchymal progenitor stem cells (MSCs) include their multilineage differentiation potential, their immunomodulatory effects, their high proliferative activity, they can be easily cultured in vitro, and finally their potential to synthesize and secrete membrane derived vesicles rich in growth factors, mRNA and miRNA which possibly aid in regulation of tissue damage regeneration. These facts alone, explain why MSCs are so widely used in clinical trials, 350 up to date (Switonski, Reproductive Biology, 14(1), 44-50, 2014). Animal studies have demonstrated that sub-retinal transplantation of MSCs delays retinal degeneration and preserves retinal function through trophic response (Inoue et al. Experimental Eye Research, 85(2), 234-241, 2007). Umbilical cord derived MSCs (UC/MSCs) have also been shown to contain neuroprotective features of ganglion cells in rat studies (Zwart et al. Experimental Neurology, 216(2), 439-448, 2009). This review aims to present current MSC therapies in practice, as well as their retinal regeneration potential in animal models, and their innovative prospects for treatment of human retinal diseases.

PMID: 28643176


Complement-Mediated Regulation of Apolipoprotein E in Cultured Human RPE Cells.

Yang P, Skiba NP, Tewkesbury GM, Treboschi VM, Baciu P, Jaffe GJ.

PURPOSE: Complement activation is implicated in the pathogenesis of age-related macular degeneration (AMD). Apolipoprotein E (ApoE) and complement activation products such as membrane attack complex (MAC) are present in eyes of individuals with AMD. Herein, we investigated the effect of complement activation on induction of ApoE accumulation in human retinal pigment epithelial (RPE) cells.

METHODS: Cultured human RPE cells were primed with a complement-fixing antibody followed by treatment with C1q-depleted (C1q-Dep) human serum to elicit alternative pathway complement activation. Controls included anti-C5 antibody-treated serum and heat-inactivated C1q-Dep. Total protein was
determined on RPE cell extracts, conditioned media, and extracellular matrix (ECM) by Western blot. ApoE and MAC colocalization was assessed on cultured RPE cells and human eyes by immunofluorescent stain. ApoE mRNA expression was evaluated by quantitative PCR (qPCR).

RESULTS: Complement challenge upregulated cell-associated ApoE, but not apolipoprotein A1. ApoE accumulation was blocked by anti-C5 antibody and enhanced by repetitive complement challenge. ApoE mRNA levels were not affected by complement challenge. ApoE was frequently colocalized with MAC in complement-treated cells and drusen from human eyes. ApoE was released into complement-treated conditioned media after a single complement challenge and accumulated on ECM after repetitive complement challenge.

CONCLUSIONS: Complement challenge induces time-dependent ApoE accumulation in RPE cells. An understanding of the mechanisms by which complement affects RPE ApoE accumulation may help to better explain drusen composition, and provide insights into potential therapeutic targets.

PMID: 28632844


Long-Term Efficacy of GMP Grade Xeno-Free hESC-Derived RPE Cells Following Transplantation.


PURPOSE: Retinal pigment epithelium (RPE) dysfunction underlies the retinal degenerative process in age-related macular degeneration (AMD), and thus RPE cell replacement provides an optimal treatment target. We characterized longitudinally the efficacy of RPE cells derived under xeno-free conditions from clinical and xeno-free grade human embryonic stem cells (OpRegen) following transplantation into the subretinal space of Royal College of Surgeons (RCS) rats.

METHODS: Postnatal (P) day 20 to 25 RCS rats (n = 242) received a single subretinal injection of 25,000 (low), 100,000 (mid), or 200,000 (high)-dose xeno-free RPE cells. BSS+ (balanced salt solution) (vehicle) and unoperated eyes served as controls. Optomotor tracking (OKT) behavior was used to quantify functional efficacy. Histology and immunohistochemistry were used to evaluate photoreceptor rescue and transplanted cell survival at 60, 100, 150, and 200 days of age.

RESULTS: OKT was rescued in a dose-dependent manner. Outer nuclear layer (ONL) was significantly thicker in cell-treated eyes than controls up to P150. Transplanted RPE cells were identified in both the subretinal space and integrated into the host RPE monolayer in animals of all age groups, and often contained internalized photoreceptor outer segments. No pathology was observed.

CONCLUSIONS: OpRegen RPE cells survived, rescued visual function, preserved rod and cone photoreceptors long-term in the RCS rat. Thus, these data support the use of OpRegen RPE cells for the treatment of human RPE cell disorders including AMD.

TRANSLATIONAL RELEVANCE: Our novel xeno-free RPE cells minimize concerns of animal derived contaminants while providing a promising prospective therapy to the diseased retina.

PMID: 28626601 PMCID: PMC5472365


The Immunogenicity and Immune Tolerance of Pluripotent Stem Cell Derivatives.

Liu X, Li W, Fu X, Xu Y.

Abstract: Human embryonic stem cells (hESCs) can undergo unlimited self-renewal and differentiate into all...
cell types in human body, and therefore hold great potential for cell therapy of currently incurable diseases including neural degenerative diseases, heart failure, and macular degeneration. This potential is further underscored by the promising safety and efficacy data from the ongoing clinical trials of hESC-based therapy of macular degeneration. However, one main challenge for the clinical application of hESC-based therapy is the allogeneic immune rejection of hESC-derived cells by the recipient. The breakthrough of the technology to generate autologous-induced pluripotent stem cells (iPSCs) by nuclear reprogramming of patient's somatic cells raised the possibility that autologous iPSC-derived cells can be transplanted into the patients without the concern of immune rejection. However, accumulating data indicate that certain iPSC-derived cells can be immunogenic. In addition, the genomic instability associated with iPSCs raises additional safety concern to use iPSC-derived cells in human cell therapy. In this review, we will discuss the mechanism underlying the immunogenicity of the pluripotent stem cells and recent progress in developing immune tolerance strategies of human pluripotent stem cell (hPSC)-derived allografts. The successful development of safe and effective immune tolerance strategy will greatly facilitate the clinical development of hPSC-based cell therapy.

PMID: 28626459 PMCID: PMC5454078

**Stem Cell Reports. 2017 Jun 13. [Epub ahead of print]**

**The Developmental Stage of Adult Human Stem Cell-Derived Retinal Pigment Epithelium Cells Influences Transplant Efficacy for Vision Rescue.**


Abstract: Age-related macular degeneration (AMD) is a common cause of central visual loss in the elderly. Retinal pigment epithelial (RPE) cell loss occurs early in the course of AMD and RPE cell transplantation holds promise to slow disease progression. We report that subretinal transplantation of RPE stem cell (RPESC)-derived RPE cells (RPESC-RPE) preserved vision in a rat model of RPE cell dysfunction. Importantly, the stage of differentiation that RPESC-RPE acquired prior to transplantation influenced the efficacy of vision rescue. Whereas cells at all stages of differentiation tested rescued photoreceptor layer morphology, an intermediate stage of RPESC-RPE differentiation obtained after 4 weeks of culture was more consistent at vision rescue than progeny that were differentiated for 2 weeks or 8 weeks of culture. Our results indicate that the developmental stage of RPESC-RPE significantly influences the efficacy of RPE cell replacement, which affects the therapeutic application of these cells for AMD.

PMID: 28625537

**Diet, lifestyle & low vision**


**Reading Performance Improvements in Patients with Central Vision Loss without Age-Related Macular Degeneration after Undergoing Personalized Rehabilitation Training.**


PURPOSE: To evaluate the efficacy of a reading rehabilitation program (RRP) in patients with central visual loss (CVL) and assess the impact of the RRP on the quality of life (QoL).

METHODS: The RRP included four in-office and 39 in-home training sessions over 6 weeks. Reading speed, duration, and font size were evaluated during each in-office session. The subjective perception of the QoL was assessed before and after the RRP using the short version of a questionnaire (World Health Organization Quality of Life). A control group who received advice about ocular conditions and low-vision
RESULTS: Seventeen patients with Stargardt's disease (STGD), 11 with adult-onset foveomacular vitelliform dystrophy (AFVD), and eight with myopic macular degeneration (MMD) were included. The control group included five patients each with STGD, AFVD, and MMD. The respective mean corrected distance visual acuities (VAs) in patients with STGD, AFVD, MMD, and the control group were 0.57 ± 0.38, 0.51 ± 0.38, 0.49 ± 0.24, and 0.55 ± 0.25 logarithm of the minimum angle of resolution; the mean corrected near VAs were 0.89 ± 0.20, 1.08 ± 0.17, 0.99 ± 0.34, and 1.18 ± 0.37 (M notation) using low-vision aids. The reading speed, duration, and font size improved in all groups. The RRP groups obtained (p ≤ 0.01) greater improvements than the control group in each reading performance variable assessed. Patients with STGD obtained greater improvements in the subjective evaluation; the control group did not obtain noteworthy improvement in any domain.

CONCLUSIONS: The RRP improved reading performance in patients with CVL and positively impacted the subjective perception of the QoL.

PMID: 28632405

Mol Aspects Med. 2017 Jun 17. [Epub ahead of print]

Many tocopherols, one vitamin E.
Azzi A.

Abstract: Four tocopherols are available in nature and are absorbed with the diet, but only one RRR-α-tocopherol satisfies the criteria of being a vitamin. The biological activity of the different tocopherols studied in the rat by the resorption-gestation test has been inconsistently extrapolated to human beings where the tocopherols have no influence on a successful pregnancy. Diminution of RRR-α-tocopherol intake results in diseases characterized by ataxia, whose pathogenetic mechanism, despite vigorous claims, has not been clarified. The calculation of the Daily Reference Intake (DRI), necessary to prevent disease, is based on an obsolete test, the peroxide-induced erythrocyte hemolysis, called the gold standard, but of highly questioned validity. If many epidemiological studies have given positive results, showing prevention by high vitamin E containing diets of cardiovascular events, neurodegenerative disease, macular degeneration and cancer, the clinical confirmatory intervention studies were mostly negative. On the positive side, besides preventing vitamin E deficiency diseases, vitamin E has shown efficacy as anti-inflammatory and immune boosting compound. It has also shown some efficacy in protecting against nonalcoholic hepato-steatosis. At a molecular level, vitamin E and some of its metabolites have shown capacity of regulating cell signaling and modulating gene transcription.

PMID: 28624327

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