Drug treatment

Eye (Lond). 2017 May 5. [Epub ahead of print]

A systematic review to assess the 'treat-and-extend' dosing regimen for neovascular age-related macular degeneration using ranibizumab.


Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the developed world. Monthly or as-needed (PRN) dosing strategies of intravitreal ranibizumab have been established as efficacious treatment options for neovascular AMD. More recently, the 'treat-and-extend' dosing regimen (TREX) is being adopted in clinical practice as it represents a patient-centric and economical option, reducing treatment burden by extending injection intervals when possible. However, the efficacy of TREX using ranibizumab monotherapy remains to be defined. Therefore, we performed a systematic review to assess the current evidence for TREX using ranibizumab by searching MEDLINE, Embase and PubMed. Of the 1733 articles identified, nine TREX studies were included in our analysis (n=748 eyes). Average patient age was 79.25 (range: 77.34-82.00; SD: 7.27). Baseline BCVA ranged from 48.5-68.9 ETDRS letters. BCVA improvement was 8.92 letters at 1 year (range: 6.5-11.5; SD: 7.54), as a weighted mean accounting for numbers of study eyes. The weighted mean number of injections at one year was 8.60 (range: 7.3-12.0; SD: 1.73). Previously, the landmark ANCHOR and MARINA trials reported gains of 11.3 and 7.2 letters, respectively, using monthly ranibizumab. Chin-Yee et al reported a gain of 3.5 ETDRS letters with 5.3 (S.D. 0.66) PRN ranibizumab injections as weighted means at 1 year in their recent systematic review. Our analysis suggests that TREX delivers visual outcomes superior to PRN and approaches similar efficacy to monthly injections. Further RCTs are needed to fully evaluate the efficacy and economy of TREX in the long-term.

PMID: 28475181


UK AMD/DR EMR REPORT IX: comparative effectiveness of predominantly as needed (PRN) ranibizumab versus continuous aflibercept in UK clinical practice.


AIMS: To compare the effectiveness of continuous aflibercept versus pro re nata (PRN) ranibizumab therapy for neovascular age-related macular degeneration (nAMD).

METHODS: Multicentre, national electronic medical record (EMR) study on treatment naive nAMD eyes undergoing PRN ranibizumab or continuous (fixed or treat and extend (F/TE)) aflibercept from 21 UK
hospitals. Anonymised data were extracted, and eyes were matched on age, gender, starting visual acuity (VA) and year of starting treatment. Primary outcome was change in vision at 1 year.

RESULTS: 1884 eyes (942 eyes in each group) were included. At year 1, patients on PRN ranibizumab gained 1.6 ETDRS (Early Treatment Diabetic Retinopathy Study) letters (95% CI 0.5 to 2.7, p=0.004), while patients on F/TE aflibercept gained 6.1 letters (95% CI 5.1 to 7.1, p=2.2e-16). Change in vision at year 1 of the F/TE aflibercept group was 4.1 letters higher (95% CI 2.5 to 5.8, p=1.3e-06) compared with the PRN ranibizumab group after adjusting for age, starting VA, gender and year of starting therapy. The F/TE aflibercept group had significantly more injections compared with the PRN ranibizumab group (7.0 vs 5.8, p<2.2e-16), but required less clinic visits than the PRN ranibizumab group (10.8 vs 9.0, p<2.2e-16). Cost-effectiveness analysis showed an incremental cost-effectiveness ratio of 58 047.14 GBP/quality-adjusted life year for continuous aflibercept over PRN ranibizumab.

CONCLUSION: Aflibercept achieved greater VA gains at 1 year than ranibizumab. The observed VA differences are small and likely to be related to more frequent treatment with aflibercept, suggesting that ranibizumab should also be delivered by F/TE posology.

PMID: 28478396


Sequential Sterile Intraocular Inflammation Associated With Consecutive Intravitreal Injections of Aflibercept and Ranibizumab.

Grewal DS, Schwartz T, Fekrat S.

Abstract: The authors report the unique response of two patients treated for cystoid macular edema (CME) secondary to central retinal vein occlusion (CRVO) who developed sequential episodes of likely sterile inflammatory responses following separate intravitreal injections of aflibercept (Eylea; Regeneron, Tarrytown, NY) and ranibizumab (Lucentis; Genentech, South San Francisco, CA) despite multiple previous uneventful injections for CME secondary to CRVO. Following the twenty-fifth aflibercept and seventh ranibizumab injection, two patients developed an acute inflammatory response, which was treated empirically with intravitreal antibiotics and topical and oral steroids (in Case 2). After an 8- to 10-week hiatus, they were switched over to ranibizumab and aflibercept, respectively, following which they developed a second episode of intraocular inflammation, treated similarly. Vitreous culture in one and aqueous culture in the other were deemed to represent contamination. Sterile intraocular inflammation, a known risk following injection with either aflibercept or ranibizumab, may develop sequentially in the same patient despite switching the drug.

PMID: 28499055


Safety and Efficacy of Ziv-Aflibercept in the Treatment of Refractory Diabetic Macular Edema.

Ashraf M, Kayal HE, Souka AAR.

BACKGROUND AND OBJECTIVE: To evaluate the safety and efficacy of ziv-aflibercept (Zaltrap; Sanofi-Aventis, Bridgewater, NJ/Regeneron Pharmaceuticals, Tarrytown, NY) in the treatment of refractory diabetic macular edema (DME).

PATIENTS AND METHODS: Retrospective case series looking at the safety of ziv-aflibercept in patients with DME refractory to previous anti-vascular endothelial growth factor (VEGF) therapy. Detailed ophthalmologic examination, best-corrected visual acuity, and optical coherence tomography measurements were performed pre-switch, as well as at each monthly follow-up visit.
RESULTS: The study included 34 eyes of 26 patients. The mean number of ziv-aflibercept injections post-switch was 2.03 injections. Visual acuity improved from a mean of 0.63 logMAR pre-switch to 0.51 logMAR after the first visit and 0.46 logMAR after the second visit post-switch (P < .084). Macular thickness improved from a mean of 513.79 μm to 411.79 μm (P = .006) on the first visit and 426.76 μm (P = .029) after the second visit post-switch. No adverse ocular or systemic side effects were reported on any of the follow visits.

CONCLUSION: Ziv-aflibercept appears to be safe and effective in patients with refractory DME previously treated with other anti-VEGF agents in the short term.

PMID: 28499051

Cornea. 2017 May 9. [Epub ahead of print]

Bilateral Herpetic Keratitis After Bilateral Intravitreal Bevacizumab for Exudative Macular Degeneration.

Derham AM, Chen E, Bunya VY, O’Malley RE.

PURPOSE: To report a case of bilateral herpetic epithelial keratitis after bilateral intravitreal bevacizumab injections for the treatment of exudative age-related macular degeneration.

METHODS: A 66-year-old man with diabetes and an extensive history of bilateral anti-vascular endothelial growth factor treatments for exudative age-related macular degeneration received an intravitreal bevacizumab injection in the right eye and triple therapy (bevacizumab, photodynamic therapy, and triamcinolone acetonide) in the left eye. After 4 days, he presented with pain, photophobia, tearing, and decreased vision in both eyes. Slit-lamp examination revealed bilateral dendritic epithelial lesions with terminal bulbs, and he was diagnosed with bilateral herpes simplex epithelial keratitis.

RESULTS: The patient was treated with ganciclovir ophthalmic ointment and oral acyclovir with resolution of signs and symptoms.

CONCLUSIONS: To our knowledge, this is the first documented account of bilateral herpetic epithelial keratitis after bilateral intravitreal bevacizumab injections.

PMID: 28489722

Retina. 2017 May 9. [Epub ahead of print]

TREATMENT OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION PATIENTS WITH VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS IN EVERYDAY PRACTICE: Identification of Health Care Constraints in Germany-The PONS Study.

Ehiken C, Wilke T, Bauer-Steinhusen U, Agostini HT, Hasanbasic Z, Müller S.

PURPOSE: The PONS study was conceived to analyze the extent of nonpersistence (NP) and nonadherence (NA) in the treatment of patients with neovascular age-related macular degeneration in everyday clinical practice in Germany. Further objectives were to identify factors that can affect NP and NA and to analyze clinical outcomes under everyday conditions.

METHODS: Nonpersistence (no contact with doctor for at least 3 months) and NA (no treatment or follow-up for at least 6 weeks) as well as clinical data were analyzed up to 24 months retrospectively and 12 months prospectively in 480 patients with neovascular age-related macular degeneration in 23 treatment centers. Patients were interviewed for factors possibly affecting NP and NA.

RESULTS: One third of patients fulfilled criteria of NA in the first 3 months and two thirds after 6 months. The NP was 18.8% after 12 months. Treatment exclusively at one center, a higher number of patients with
neovascular age-related macular degeneration at the treating center, and fixed appointments were associated with a lower risk for NP. An initial gain in visual acuity after upload was not preserved after 12 months (mean change -0.5 Early Treatment Diabetic Retinopathy Study letters). Whereas visual acuity declined by 7.5 Early Treatment Diabetic Retinopathy Study letters in patients with good baseline visual acuity ≥20/40, visual acuity improved by 8.5 letters in patients with baseline visual acuity of ≤20/200. Only 7.5% of patients underwent an optical coherence tomography scan after 3 upload injections, and only 2.0 optical coherence tomographies were performed in the first 12 months.

CONCLUSION: The NP and NA were high in our study population and are likely to have contributed to a suboptimal clinical outcome compared with randomized clinical trials. Shortcomings in the management of patients with neovascular age-related macular degeneration, including restrictions in the timely and adequate follow-up (including optical coherence tomography) and retreatment, appear to be constraining factors in Germany.

PMID: 28489692


Response of eyes with age-related macular degeneration to anti-VEGF drugs and implications for therapy planning.

Miyamoto N, Mandai M, Kojima H, Kameda T, Shimozono M, Nishida A, Kurimoto Y.

PURPOSE: To evaluate the response to and dependence on aflibercept or ranibizumab in patients with age-related macular degeneration (AMD).

METHODS: We retrospectively reviewed AMD patients who received induction therapy with aflibercept or ranibizumab for the following parameters: whether complete resolution of the retinal fluid ("good response") was achieved and whether recurrence was observed within 3 months ("dependent") after the induction treatment. With aflibercept treatment, treatment-naïve eyes with a good response/non-dependence were recommended a pro re nata regimen, and other eyes were recommended a proactive bimonthly regimen, followed by monitoring of visual acuity (VA) for 12 months. The measured values of the groups were compared using one-way analysis of variance with Tukey's test to evaluate the difference between baseline and postinjection VA.

RESULTS: Among the treatment-naïve eyes, 76% had a good response to aflibercept and 37% of these were aflibercept-dependent, while 58% had a good response to ranibizumab but 51% of these were ranibizumab-dependent. Among the eyes that converted from ranibizumab treatment, 92% of the good responders to ranibizumab with dependence and 76% of the poor responders on ranibizumab had a good response to aflibercept. With aflibercept treatment, the mean VA of treatment-naïve patients was significantly better than the baseline VA over 12 months (P<0.001), and the VA of the converted group improved significantly with proactive treatment and the improvement was continuously maintained from 6 to 12 months.

CONCLUSION: The evaluation of response to and dependence on anti-vascular endothelial growth factor therapies in AMD was useful and practical in managing therapeutic protocols to obtain a good VA.

PMID: 28496299 PMCID: PMC5417657


Recent advances in the management and understanding of macular degeneration.

Bahadorani S, Singer M.

Abstract: Current management of age-related macular degeneration (AMD) is directed at intravitreal
injection of vascular endothelial growth factor (VEGF) inhibitors for the treatment of wet AMD and supplementation with oral antioxidants for the treatment of dry AMD. In this article, we will review recent clinical trials for the treatment of dry and wet AMD.

PMID: 28491291 PMCID: PMC5399962

Eur J Ophthalmol. 2017 May 10:0. [Epub ahead of print]

Author’s reply to comments to: Visual and anatomic outcomes after conversion to aflibercept in neovascular age-related macular degeneration: 12-month results.

Abri Aghdam K, Framme C, Pielen A, Junker B.

Author information
PMID: 28497459


Cost-effectiveness of Intravitreous Ranibizumab Compared With Panretinal Photocoagulation for Proliferative Diabetic Retinopathy: Secondary Analysis From a Diabetic Retinopathy Clinical Research Network Randomized Clinical Trial.

Hutton DW, Stein JD, Bressler NM, Jampol LM, Browning D, Glassman AR; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: The Diabetic Retinopathy Clinical Research Network Protocol S randomized clinical trial results suggest that ranibizumab is a reasonable treatment alternative to panretinal photocoagulation (PRP) when managing proliferative diabetic retinopathy (PDR), with or without concomitant baseline diabetic macular edema (DME). However, ranibizumab injections are costly. Thus, it would be useful to examine the relative cost-effectiveness of these 2 treatment modalities.

OBJECTIVE: To evaluate incremental cost-effectiveness ratios of 0.5-mg ranibizumab therapy vs PRP for PDR.

DESIGN, SETTING, AND PARTICIPANTS: Preplanned secondary analysis using efficacy, safety, and resource utilization data through 2 years of follow-up at 55 US sites for 213 adults with PDR. Data were collected from February 2012 to January 2015.

INTERVENTIONS: Intravitreous 0.5-mg ranibizumab at baseline and as frequently as every 4 weeks based on a structured retreatment protocol or PRP at baseline for PDR. Eyes in both groups could receive ranibizumab for concomitant DME.

MAIN OUTCOMES AND MEASURES: Incremental cost-effectiveness ratios of ranibizumab compared with PRP evaluated within 2 prespecified subgroups for the study eye: with baseline vision-impairing (Snellen equivalent 20/32 or worse) DME and without baseline vision-impairing DME.

RESULTS: The study included 305 adults with PDR, the mean age was 52 years, 44% were women, and 52% were white. Of the 46 participants with PDR and vision-impairing DME at baseline, 21 were assigned to the ranibizumab group and 25 to the PRP group (plus ranibizumab for DME). Among the remaining participants without baseline vision-impairing DME, 80 and 87 were in the ranibizumab and PRP groups, respectively. For participants with and without baseline vision-impairing DME, the incremental cost-effectiveness ratios of ranibizumab therapy compared with PRP were $55 568/quality-adjusted life-year and $662 978/quality-adjusted life-year, respectively, over 2 years.

CONCLUSIONS AND RELEVANCE: Over 2 years, compared with PRP, 0.5-mg ranibizumab as given in this trial is within the $50 000/quality-adjusted life-year to $150 000/quality-adjusted life-year range.
frequently cited as cost-effective in the United States for eyes presenting with PDR and vision-imparing DME, but not for those with PDR without vision-imparing DME.

PMID: 28492920

**JAMA. 2017 May 9. [Epub ahead of print]**

**Effect of Bevacizumab vs Aflibercept on Visual Acuity Among Patients With Macular Edema Due to Central Retinal Vein Occlusion: The SCORE2 Randomized Clinical Trial.**

Scott IU, VanVeldhuisen PC, Ip MS, Blodi BA, Oden NL, Awh CC, Kunimoto DY, Marcus DM, Wroblewski JJ, King J; SCORE2 Investigator Group.

IMPORTANCE: Studies have established the efficacy and safety of aflibercept for the treatment of macular edema due to central retinal vein occlusion. Bevacizumab is used off-label to treat this condition despite the absence of supporting data.

OBJECTIVE: To investigate whether bevacizumab is noninferior to aflibercept for the treatment of macular edema secondary to central retinal or hemiretinal vein occlusion.

DESIGN, SETTING, AND PARTICIPANTS: The SCORE2 randomized noninferiority clinical trial was conducted at 66 private practice or academic centers in the United States, and included 362 patients with macular edema due to central retinal or hemiretinal vein occlusion who were randomized 1:1 to receive aflibercept or bevacizumab. The first participant was randomized on September 17, 2014, and the last month 6 visit occurred on May 6, 2016. Analyses included data available as of December 30, 2016.

INTERVENTIONS: Eyes were randomized to receive intravitreal injection of bevacizumab (1.25 mg; n = 182) or aflibercept (2.0 mg; n = 180) every 4 weeks through month 6.

MAIN OUTCOMES AND MEASURES: The primary outcome was mean change in visual acuity (VA) letter score (VALS) from the randomization visit to the 6-month follow-up visit, based on the best-corrected electronic Early Treatment Diabetic Retinopathy Study VALS (scores range from 0-100; higher scores indicate better VA). The noninferiority margin was 5 letters, and statistical testing for noninferiority was based on a 1-sided 97.5% confidence interval.

RESULTS: Among 362 randomized participants (mean [SD] age, 69 [12] years; 157 [43.4%] women; mean [SD] VALS at baseline, 50.3 [15.2] [approximate Snellen VA 20/100]), 348 (96.1%) completed the month 6 follow-up visit. At month 6, the mean VALS was 69.3 (a mean increase from baseline of 18.6) in the bevacizumab group and 69.3 (a mean increase from baseline of 18.9) in the aflibercept group (model-based estimate of between-group difference, -0.14; 97.5% CI, -3.07 to ∞; P = .001 for noninferiority), meeting criteria for noninferiority. Ocular adverse events in the aflibercept group included 4 participants with intraocular pressure (IOP) more than 10 mm Hg greater than baseline; ocular adverse events in the bevacizumab group included 1 participant with endophthalmitis (culture negative), 9 with IOP more than 10 mm Hg greater than baseline, 2 with IOP higher than 35 mm Hg, and 1 with angle-closure glaucoma not attributed to the study drug or procedure.

CONCLUSIONS AND RELEVANCE: Among patients with macular edema due to central retinal or hemiretinal vein occlusion, intravitreal bevacizumab was noninferior to aflibercept with respect to visual acuity after 6 months of treatment.

PMID: 28492910

**JAMA Ophthalmol. 2017 May 9. [Epub ahead of print]**

**Baseline Factors Associated With 6-Month Visual Acuity and Retinal Thickness Outcomes in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion or Hemiretinal Vein**

Scott IU, VanVeldhuisen PC, Ip MS, Blodi BA, Oden NL, King J, Antoszyk AN, Peters MA, Tolentino M; SCORE2 Investigator Group.

IMPORTANCE: Macular edema (ME) is the leading cause of decreased visual acuity (VA) associated with retinal vein occlusion (RVO). Identifying factors associated with better outcomes in RVO eyes treated with anti-vascular endothelial growth factor (VEGF) therapy may provide information useful in counseling patients.

OBJECTIVE: To investigate baseline characteristics associated with 6-month VA and central subfield thickness (CST) outcomes in participants in the Study of Comparative Treatments for Retinal Vein Occlusion 2 (SCORE2).

DESIGN, SETTING, AND PARTICIPANTS: A total of 362 patients with central RVO or hemi-RVO were enrolled between September 17, 2014, and November 18, 2015, and randomized 1:1 in a masked fashion to receive bevacizumab or aflibercept. At month 6, 348 participants (96%) had VA outcomes measured and 335 participants (93%) had spectral domain optical coherence tomography outcomes measured. The current data analysis was conducted from February 27, 2017, to April 7, 2017.

INTERVENTIONS: Eyes were randomly assigned to receive an intravitreal injection of bevacizumab, 1.25 mg, or aflibercept, 2.0 mg, at baseline and every 4 weeks, with the primary outcome measured at 6 months.

MAIN OUTCOMES AND MEASURES: Change from baseline in VA letter score (VALS), VALS gain of 15 or more, change from baseline in CST, CST less than 300 µm, and resolution of ME. Baseline factors associated with 6-month outcome at the 0.05 level in univariate regressions were included in multivariate regressions, with those significant after multiplicity control by the Hochberg method reported.

RESULTS: The mean (SD) age of patients was 69 (12) years, and 43% were women. Younger patient age (odds ratio [OR], 0.95 per year of age; 95% CI, 0.93-0.98; P = .007) and lower baseline VALS (OR, 0.96 per letter; 95% CI, 0.94-0.98; P < .001) were associated with a 6-month VALS gain of 15 or greater. Compared with bevacizumab, aflibercept treatment was associated with a higher odds of ME resolution (OR, 3.59; 95% CI, 2.22-5.80; P < .001) and CST less than 300 µm (OR, 5.30; 95% CI, 2.40-11.67; P = .001), but not with a better VA outcome. Macular edema was less likely to resolve in eyes that received anti-VEGF treatment prior to study participation (OR, 0.33; 95% CI, 0.17-0.64; P = .03).

CONCLUSIONS AND RELEVANCE: In eyes treated with bevacizumab or aflibercept, younger age and worse baseline VALS were associated with better 6-month VA outcomes. Aflibercept treatment was associated with more favorable spectral domain optical coherence tomography outcomes but not VA outcomes. These findings may be useful in assessing expected response at month 6 after monthly injection of anti-VEGF agents for treating ME due to CRVO and HRVO.

PMID: 28492860

Adv Ther. 2017 May 8. [Epub ahead of print]


Dervenis N, Mikropoulou AM, Tranos P, Dervenis P.

Abstract: Diabetic retinopathy (more specifically diabetic macular edema, DME) is the most common cause of loss of vision in the working population in developed countries. Anti-vascular endothelial growth factor (anti-VEGF) agents considerably changed the treatment algorithms and improved prognosis of center-involving DME. Ranibizumab was the first approved anti-VEGF agent that revolutionized DME treatment. The vast increase in the number of patients undergoing intravitreal treatment and the role of anti-VEGF pharmacotherapy as the mainstay of DME treatment have triggered several challenges. Among them, of considerable interest is the quest for an optimal dosing scheme and the search for combination therapies.
Although a significant body of research is directed towards other molecules that could potentially be new therapeutic targets, VEGF inhibition is expected to play an important long-term role in the treatment of DME considering the pathogenesis of the disease. Finally, recent studies revealed that ranibizumab may constitute a significant treatment modality in the management of other diabetic vision-threatening complications including proliferative diabetic retinopathy.

PMID: 28484955


Short-term outcomes in patients with branch retinal vein occlusion who received intravitreal aflibercept with or without intravitreal ranibizumab.

Sakanishi Y, Usui-Ouchi A, Tamaki K, Mashimo K, Ito R, Ebihara N.

PURPOSE: The purpose of this study was to determine the short-term outcomes for patients who received intravitreal aflibercept (IVA) with or without intravitreal ranibizumab (IVR) for macular edema (ME) due to branch retinal vein occlusion (BRVO).

PATIENTS AND METHODS: Patients received IVA for ME due to BRVO. Patients who initially received IVA were defined as the treatment-naïve group and those who were switched from IVR to IVA after ME recurrence were defined as the switching group. Patient outcomes were examined at 1 week and 1 month postinjection.

RESULTS: Both groups comprised 27 eyes from 27 patients. There was a significant decrease in central macular thickness (CMT) at 1 week and 1 month postinjection in both groups. There was also a significant improvement in best-corrected visual acuity (BCVA) at 1 week and 1 month postinjection in the treatment-naïve group and 1 month in the switching group. Younger age was associated with a good BCVA at 1 month postinjection in the switching group, and the absence of epiretinal membrane was associated with a reduction in CMT at 1 month postinjection in the switching group.

CONCLUSION: IVA is temporarily effective for treating ME due to BRVO regardless of a history of IVR use.

PMID: 28496301 PMCID: PMC5422553

Retina. 2017 May 10. [Epub ahead of print]

CLINICAL FINDINGS OF EYES WITH MACULAR EDEMA ASSOCIATED WITH BRANCH RETINAL VEIN OCCLUSION REFRACTORY TO RANIBIZUMAB.

Hasegawa T, Kawano T, Maruko I, Koizumi H, Iida T.

PURPOSE: To determine the relationship between the clinical findings and the response to ranibizumab therapy in eyes with macular edema associated with branch retinal vein occlusion.

METHODS: We reviewed the medical records of 68 patients with macular edema associated with a branch retinal vein occlusion. The patients were placed in the refractory group if the central foveal thickness remained more than 250 μm throughout the 6-month study period despite the ranibizumab therapy; otherwise, they were placed in the responsive group.

RESULTS: Sixty (88.2%) of 68 eyes were placed in the responsive group and the other 8 eyes (11.8%) were placed in the refractory group. At the pretreatment examination, fluorescein angiography showed extensive leakage from occluded vessels in 52 (86.7%) of the 60 eyes in the responsive group and focal leakages from microaneurysms or dilated capillaries in the other 8 eyes (13.3%). In the refractory group, 7 (87.5%) of 8 eyes had only focal leakage and 1 eye (12.5%) had extensive leakage (P < 0.0001). The mean initial subfoveal choroidal thickness in the eyes with branch retinal vein occlusion in the responsive
group was significantly thicker than that in the fellow eyes (278.0 ± 90.5 μm, 249.9 ± 94.4 μm; P < 0.0001). On the other hand, the mean initial subfoveal choroidal thickness in the refractory group was not significantly different from that of the fellow eyes (P = 0.4002).

CONCLUSION: The dye leakage pattern in the fluorescein angiography images and choroidal thickness may be associated with response to ranibizumab therapy.

PMID: 28492435

Ranibizumab versus aflibercept for macular edema due to central retinal vein occlusion.
Chatziralli I, Theodossiadis G, Theodossiadis P.
PMID: 28484833

Other treatment & diagnosis

Urinary Isoprostane Levels and Age-Related Macular Degeneration.
PURPOSE: Oxidative stress, characterized by an excessive production of reactive oxygen intermediates has been suggested to play a role in the pathogenesis of age-related macular degeneration (AMD). We examined the association of urinary F2-isoprostanes (F2-IsoPs), a marker of lipid peroxidation and the most reliable marker of oxidative damage with AMD.

METHODS: We included 238 adults with AMD and 390 age- and sex-matched controls without AMD who participated in a population-based cross-sectional study in Singapore (Singapore Chinese Eye Study, 2009-2011). AMD was graded from retinal photographs using the Wisconsin Age-Related Maculopathy Grading System. Urinary-free F2-IsoPs (pmol/mmol of creatinine) were measured by gas chromatography mass spectrometry (GC-MS). The association between F2-IsoPs and AMD was examined using unconditional logistic regression models adjusted for potential confounders including smoking, body mass index (BMI), blood pressure, total and high-density lipoprotein cholesterol, and history of cardiovascular disease.

RESULTS: Higher levels of F2-IsoPs were associated with AMD independent of potential confounders. Compared to quartile 1 (Q1) of F2-IsoPs, the multivariable odds ratio (95% confidence interval) of AMD in quartiles 2, 3, and 4 were 2.05 (1.26-3.32), 1.80 (1.10-2.94), and 1.76 (1.06-2.94), respectively. In subgroup analyses comparing Q4 to Q1, this association was stronger in women, those with BMI less than 25 kg/m2 and those with hypertension, but no significant interaction was found (P interaction > 0.1 for each strata).

CONCLUSIONS: Higher levels of urinary F2-IsoPs levels were associated with AMD independent of potential confounders in Chinese adults.

PMID: 28492872

Retina. 2017 May 10. [Epub ahead of print]
LONGITUDINAL CHANGE OF OUTER NUCLEAR LAYER AFTER RETINAL PIGMENT EPITHELIAL TEAR SECONDARY TO AGE-RELATED MACULAR DEGENERATION.
Oishi A, Fang PP, Thiele S, Holz FG, Krohne TU.

PURPOSE: To investigate longitudinal changes of outer nuclear layer (ONL) thickness in patients with retinal pigment epithelium tears secondary to neovascular age-related macular degeneration.

METHODS: This is an institutional retrospective interventional case series. Twenty-six eyes of 22 patients with retinal pigment epithelium tears identified between April 2009 and March 2015. The patients underwent intravitreal injection of anti-vascular endothelial growth factor agents as needed. Volume scans of optical coherence tomography at first diagnosis of tear (baseline) and after 12 months were analyzed. Outer nuclear layer was segmented, and average ONL thickness inside the tear area, at the border of the tear, and in areas outside the tear was measured. Change of ONL thickness. We also explored several factors for their association with ONL thinning including tear area, number of treatments, and the duration with persistent subretinal fluid.

RESULTS: Thinning of ONL was found in all the investigated areas (P < 0.01, respectively). Among the investigated factors, larger tear area was associated with greater ONL thinning outside the tear area (standardized β = -0.37, P = 0.030), and younger age was associated with greater ONL thinning inside the tear area (standardized β = 0.37, P = 0.041).

CONCLUSION: After an retinal pigment epithelium tear, thinning of ONL occurs in the area devoid of retinal pigment epithelium and also in adjacent areas. Few factors were predictive for the degree of ONL thinning. These results provide new insight in disease progression of this particular neovascular age-related macular degeneration subphenotype.

PMID: 28492434

Retina. 2017 May 10. [Epub ahead of print]

QUANTITATIVE OPTICAL COHERENCE TOMOGRAPHY ANALYSIS OF RETINAL DEGENERATIVE CHANGES IN DIABETIC MACULAR EDEMA AND NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Boiko EV, Maltsev DS.

PURPOSE: To investigate the relationship of the pre-anti-vascular endothelial growth factor (VEGF) retinal tissue area (RTA) and optical density (ODRT) of the retinal optical slice portion located in the central subfield, and their ratio (RTA/ODRT), in the presence of diabetic macular edema or of intraretinal cystic fluid in neovascular age-related macular degeneration, to central retinal thickness and best-corrected visual acuity after anti-VEGF treatment with ME resolution.

METHODS: The optical coherence tomography images and medical records of 33 patients (41 eyes) with neovascular age-related macular degeneration, 15 (21 eyes) with diabetic macular edema and 9 healthy individuals (15 eyes) were retrospectively analyzed. RTA, ODRT, and RTA/ODRT were calculated on pre-anti-VEGF B-scan images. Spearman rank correlation was used to assess the relationship of central retinal thickness and best-corrected visual acuity after anti-VEGF treatment with the variables under study.

RESULTS: Pre-anti-VEGF RTA was positively correlated with post-anti-VEGF central retinal thickness (ρ = 0.76; P < 0.001) and best-corrected visual acuity (ρ = 0.67; P < 0.001), whereas pre-anti-VEGF ODRT was moderately negatively correlated (ρ = -0.26; P = 0.049 and ρ = -0.48; P = 0.001, respectively) and pre-anti-VEGF RTA/ODRT ratio was strongly positively correlated (ρ = 0.75; P < 0.001 and ρ = 0.85; P < 0.001, respectively). The area under curve for RTA/ODRT ratio was 0.93 (P < 0.001), and the cut-off value for post-anti-VEGF LogMAR best-corrected visual acuity of 0.4 (20/50 Snellen equivalent) or worse was 1,406.7 μm/U (sensitivity: 0.94; specificity: 0.78).

CONCLUSION: Both RTA and ODRT, or, preferably, RTA/ODRT ratio alone can be used as predictors of functional and anatomic outcomes in patients with diabetic macular edema or neovascular age-related macular degeneration treated with anti-VEGF therapy.

PMID: 28492427
Correlation between retinal function and microstructural foveal changes in intermediate age related macular degeneration.

Fragiotta S, Carnevale C, Cutini A, Vingolo EM.

PURPOSE: To assess foveal microstructural changes influencing retinal sensitivity (RS) and fixation stability using microperimeter MP-1 in intermediate age-related macular degeneration (AMD).

METHODS: In this cross-sectional study, 22 eyes of 22 patients (mean age: 75 ± 9.02 years) with intermediate AMD were enrolled. Retinal sensitivity and bivariate contour ellipse area (BCEA) were obtained by microperimetry MP-1 (Humphrey 10-2 68-loci grid) under mesopic conditions. Drusen type, drusenoid pigment epithelial detachment, hyperreflective foci (HF), integrity of external limiting membrane (ELM), inner ellipsoid zone (ISel), RPE/Bruch's membrane complex (RPE/B) and subfoveal choroidal thickness were analyzed in the foveal region and compared with RS and BCEA. Spearman's rank correlation coefficient was used to evaluate the relationship between variables. Logistic regression analysis was also used to assess morphological predictor influencing RS or BCEA.

RESULTS: RS was strongly and inversely related with the presence of HF (r = -0.66, P = 0.001), integrity of ELM (r = -0.70, P < 0.001), ellipsoid zone (r = -0.45, P = 0.03). Instead, BCEA is positively related to the ellipsoid zone integrity (r = 0.45, P = 0.03). Logistic regression analysis confirmed that disruption of ISel influenced fixation stability (ExpB: 9.69, P = 0.04) but not RS. Instead, the presence of HF and disruption of ELM predicted RS reduction (ExpB: 0.55, P = 0.02 and ExpB: 0.29, P = 0.04, respectively).

CONCLUSIONS: The integrity of ELM and the presence of HF are both predictors of RS. The ELM status may be considered a new biomarker of retinal function together with HF. Instead, the integrity of ISel band seems to be a more selective predictor of BCEA than RS.

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Choroidal structure determined by binarizing optical coherence tomography images in eyes with reticular pseudodrusen.

Masuda N, Kojima M, Yamashita M, Nishi T, Ogata N.

PURPOSE: To compare the choroidal structure beneath the macular area in eyes with reticular pseudodrusen (RPD) and age-matched controls.

METHODS: This study was performed at Nara Medical University Hospital, Japan. Twenty eyes of 14 patients (82.3±4.2 years, mean ± standard deviation) with RPD and 35 eyes of 20 age-matched controls (81.5±6.0 years) were studied. The choroidal structure was determined by binarizing the images obtained by enhanced depth imaging optical coherence tomography in all patients and controls. The total, luminal, and stromal choroidal areas were quantified by the binarization method.

RESULTS: The total choroidal area of the eyes with RPD was significantly smaller than that of control eyes (P=0.001, unpaired t-test). Both the luminal and stromal areas in eyes with RPD were significantly smaller than that of control eyes (P=0.001, paired t-test), but there was no significant difference in the luminal/stromal ratio between eyes with RPD and control eyes.

CONCLUSION: The total, luminal, and stromal choroidal areas in eyes with RPD were smaller than those of the control eyes. The reduction of the choroidal luminal and stromal areas may be due to a loss of the oxygen demand of the choroid due to RPE dysfunction.

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Exp Eye Res. 2017 May 5. [Epub ahead of print]

In vivo two-photon imaging of retina in rabbits and rats.

Jayabalan GS, Wu YK, Bille JF, Kim S, Mao XW, Gimbel HV, Rauser ME, Fan JT.

Abstract: The purpose of this study was to evaluate the retina using near-infrared (NIR) two-photon scanning laser ophthalmoscopy. New Zealand white rabbits, albino rats, and brown Norway rats were used in this study. An autofluorescence image of the retina, including the retinal cells and its associated vasculatures was obtained by a real-time scan using the ophthalmoscope. Furthermore, the retinal vessels, nerve fiber layers and the non-pigmented retina were recorded with two-photon fluorescein angiography (FA); and the choroidal vasculatures were recorded using two-photon indocyanine green angiography (ICGA). Two-photon ICGA was achieved by exciting a second singlet state at ∼398 nm. Simultaneous two-photon FA and two-photon ICGA were performed to characterize the retinal and choroidal vessels with a single injection. The minimum laser power threshold required to elicit two-photon fluorescence was determined. The two-photon ophthalmoscope could serve as a promising tool to detect and monitor the disease progression in animal models. Moreover, these high-resolution images of retinal and choroidal vessels can be acquired in a real-time scan with a single light source, requiring no additional filters for FA or ICGA. The combination of FA and ICGA using the two-photon ophthalmoscope will help researchers to characterize the retinal diseases in animal models, and also to classify the types (classic, occult or mixed) of choroidal neovascularization (CNV) in macular degeneration. Furthermore, the prototype can be adapted to image the retina of rodents and rabbits.

PMID: 28483661


Combined Fundus Autofluorescence and Near Infrared Reflectance as Prognostic Biomarkers for Visual Acuity in Foveal-Sparing Geographic Atrophy.


PURPOSE: To identify predictors of best corrected visual acuity (BCVA) in eyes with foveal-sparing geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

METHODS: Best corrected visual acuity (Early Treatment Diabetic Retinopathy Study charts); serial fundus autofluorescence; and near-infrared reflectance images of patients participating in the FAM (NCT00393692) and DSGA (NCT02051998) studies were analyzed. The sizes of GA and spared fovea, and the minimal linear dimension of intact retinal pigment epithelium ("bridge") between the residual foveal island and the surrounding retina were quantified and associations with BCVA were assessed by local regression curves and mixed effects models.

RESULTS: A total of 65 eyes (51 patients, aged 75.68 ± 8.41 years) were included. Median time between baseline and last visit with detectable foveal sparing was 18 (quartiles: 12, 33) months. Median BCVA was 0.30 (0.20, 0.52) logMAR at baseline and 0.4 (0.3, 0.7) logMAR at follow-up. Local regression curves suggested no linear association of BCVA with GA size, sparing size or bridge size. Most contrasting values for BCVA were observed for >1.5 mm² foveal-sparing size and for 400 μm bridge size. Employing these values as cutoff levels, mixed effects modeling revealed that both anatomic parameters, but not time, significantly impacted BCVA.

CONCLUSIONS: During the review period eyes with foveal-sparing GA were likely to maintain the baseline BCVA. There was no linear correlation of BCVA with foveal-sparing size. Yet, BCVA was worse if the spared foveal area was <1.5 mm² or if the bridge was smaller than 400 μm in width. These findings add to the understanding of the natural history of foveal-sparing GA and may support future clinical trial designs.

PMID: 28475704
Impact of eye-tracking technology on OCT-angiography imaging quality in age-related macular degeneration.

Lauermann JL, Treder M, Heiduschka P, Clemens CR, Eter N, Alten F.

OBJECTIVE: To evaluate the impact of eye-tracking (ET) technology on optical coherence tomography angiography (OCT-A) image quality and manifestation of motion artifacts in patients with age-related macular degeneration (AMD).

METHODS: In a prospective trial, multimodal retinal imaging including OCT-A was performed in 30 patients (78.97 ± 9.7 years) affected by different stages of AMD. Central 3 x 3 mm² OCT-A imaging was performed four times consecutively in each patient, twice with active, and twice with inactive ET. Parameters for image evaluation were signal strength index (SSI), variability of foveal vessel density (VD), acquisition time, presence of motion artifacts caused by eye movement (blink lines, displacement) and by software correction of eye movement (quilting, stretch artifacts, vessel doubling). Images were evaluated by two independent readers with subsequent senior reader arbitration for presence of artifacts, and an OCT-A motion artifact score (MAS) was calculated.

RESULTS: Eight patients had early and eight patients had intermediate stages of AMD. Four patients had an atrophic late stage and ten patients an exudative stage of the disease. SSI was 53.55 with inactive and 57.18 with active ET (p = 0.0005). Coefficients of variability of VD between the first and second measurement were 8.9% with inactive and 5.7% with active ET. Mean image acquisition time was 15.97 s (active ET: 22.88 s, p < 0.001). Presence of motion artifacts was significantly higher with inactive ET (mean MAS 3.27 vs. 1.93; p < 0.0001). MAS correlated with AMD disease stage [p = 0.0031 (inactive ET) and p < 0.0001 (active ET)] and with SSI (p = 0.0072 and p = 0.0006).

CONCLUSIONS: In patients with AMD, active ET technology offers an improved image quality in OCT-A imaging regarding presence of motion artifacts at the expense of higher acquisition time.

PMID: 28474129

Pathogenesis

Oncotarget. 2017 Apr 19. [Epub ahead of print]

Anti-complement component 5 antibody targeting MG4 domain inhibits choroidal neovascularization.


Abstract: Age-related macular degeneration (AMD) is one of the main causes of visual impairment in adults. Visual deterioration is more prominent in neovascular AMD with choroidal neovascularization (CNV). Clinical and postmortem studies suggested that complement system activation might induce CNV. In this study, we demonstrated that an anti-mouse complement component 5 (C5) antibody targeting MG4 domain of β chain effectively inhibited CNV which was induced by laser photocoagulation in mice. The targeted epitope of this anti-C5 antibody was different from that of currently utilized anti-C5 antibody (eculizumab) in the MG7 domain in which a single nucleotide polymorphism (R885H/C) results in poor response to eculizumab. Even with targeting MG4 domain, this anti-C5 antibody reduced production of C5a, monocyte chemoattractant protein-1 and vascular endothelial growth factor to prevent infiltration of F4/80-positive cells into CNV lesions and formation of CNV. Furthermore, anti-C5 antibody targeting MG4 domain induced no definite toxicity in normal retina. These results demonstrated that anti-C5 antibody targeting MG4 domain inhibited CNV in neovascular AMD.

PMID: 28477014
Involvement of Nrf2 in Ocular Diseases.

Batliwala S, Xavier C, Liu Y, Wu H, Pang IH.

Abstract: The human body harbors within it an intricate and delicate balance between oxidants and antioxidants. Any disruption in this checks-and-balances system can lead to harmful consequences in various organs and tissues, such as the eye. This review focuses on the effects of oxidative stress and the role of a particular antioxidant system—the Keap1-Nrf2-ARE pathway—on ocular diseases, specifically age-related macular degeneration, cataracts, diabetic retinopathy, and glaucoma. Together, they are the major causes of blindness in the world.

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Epidemiology


Incidence of Intermediate-Stage Age-Related Macular Degeneration in Patients with the Acquired Immunodeficiency Syndrome.

Jabs DA, Van Natta ML, Pak JW, Danis RP, Hunt PW.

PURPOSE: To evaluate the incidence of intermediate-stage age-related macular degeneration (AMD) in patients with the acquired immunodeficiency syndrome (AIDS).

DESIGN: Cohort study.

METHODS: Patients enrolled in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) underwent 5- and 10-year follow-up retinal photographs. Intermediate-stage AMD (AREDS stage 3) was determined from these photographs by graders at a centralized Reading Center, using the Age-Related Eye Disease Study-2 grading system. The incidence of AMD in LSOCA was compared to that in the Multi-Ethnic Study of Atherosclerosis (MESA), a Human Immunodeficiency Virus (HIV)-uninfected cohort, which used a similar photographic methodology.

RESULTS: The incidence of AMD in LSOCA was 0.65/100 person-years (PY). In a multivariate analysis the only significant risk factor for AMD in LSOCA was smoking; the relative risk vs never smokers was 3.4 for former smokers (95% confidence interval [CI] 1.3, 9.5; P=0.02) and 3.3 for current smokers (95% CI 1.1, 9.7; P=0.03). Compared to the MESA cohort, the race/ethnicity- and gender-adjusted risk of AMD in LSOCA was 1.75 (95% CI 1.16, 2.64; P=0.008), despite the fact that the mean age of the MESA cohort was 17 years greater than the LSOCA cohort (61 + 9 years vs 44 + 8 years).

CONCLUSIONS: Patients with AIDS have a 1.75-fold increased race- and gender-adjusted incidence of intermediate-stage AMD compared with that found in an HIV-uninfected cohort. This increased incidence is consistent with the increased incidence of other age-related diseases in antiretroviral-treated, immune-restored, HIV-infected persons when compared to HIV-uninfected persons.

PMID: 28499708


Six-Year Incidence and Progression of Age-Related Macular Degeneration in Kenya: Nakuru Eye Disease Cohort Study.

IMPORTANCE: The incidence of age-related macular degeneration (AMD) is unknown in Africa.

OBJECTIVE: To estimate the 6-year cumulative incidence and progression of AMD in older adults (≥50 years old) in Nakuru, Kenya.

DESIGN, SETTING, AND PARTICIPANTS: This study assessed a population-based cohort with 6-year follow-up of 4414 participants who had a complete assessment. Random cluster sampling with probability proportionate to size procedures was used to select a representative, cross-sectional sample of adults 50 years and older from January 26, 2007, through November 11, 2008. A 6-year follow-up was undertaken from January 7, 2013, through March 12, 2014. On both occasions, a comprehensive ophthalmic examination was performed that included logMAR visual acuity, digital retinal photography, and grading of images at Moorfields Eye Hospital Reading Centre. Data were collected on general health and risk factors.

MAIN OUTCOMES AND MEASURES: Incident AMD in participants with no AMD at baseline and progression from early to late AMD.

RESULTS: A total of 1453 of the 2900 individuals (50.1%) at risk for AMD were followed up after 6 years (mean [SD] age, 60.7 [8.2] years; 635 female [49.5%]; 799 Kikuyu [62.3%], 324 Kalenjin [25.3%], and 159 other [12.4%]); 1282 had data on AMD status at follow-up. Of these, 202 developed early AMD, and no participants developed late AMD. The 6-year weighted (for loss to follow-up) cumulative incidence of early AMD was 164.2 per 1000 persons (95% CI, 136.7-195.9 per 1000 persons). Two individuals with baseline early AMD from the 142 at risk had developed late AMD at follow-up, with a 6-year cumulative incidence of progression from early to late AMD of 24.5 per 1000 persons (95% CI, 5.0-111.7 per 1000 persons). Cumulative incidence of AMD increased with age (≥80 years old vs 50-59 years old: 1.8; 95% CI, 0.9-3.5) and was higher in women (female vs male: 1.6; 95% CI, 1.2-2.1) and persons with diabetes (diabetes vs no diabetes: 1.7; 95% CI, 1.0-2.8).

CONCLUSIONS AND RELEVANCE: In Kenya, more than 100 000 estimated new cases of AMD, mainly early AMD, will develop every year in individuals 50 years or older, although a 50% loss to follow-up and wide CIs for progression to late AMD limit definitive conclusions from these findings.

PMID: 28494075

Genetics


From Compliment to Insult- Genetics of the Complement System in Physiology and Disease in the Human Retina.

Mullins RF, Warwick AN, Sohn EH, Lotery AJ.

Abstract: Age-related macular degeneration (AMD) is a major cause of visual impairment that affects the central retina. Genome wide association studies and candidate gene screens have identified members of the complement pathway as contributing to the risk of AMD. In this review, we discuss the complement system, its importance in retinal development and normal physiology, how its dysregulation may contribute to disease, and how it might be targeted to prevent damage to the aging choriocapillaris in AMD.

PMID: 28482029

Stem cells

Stem Cells Transl Med. 2017 May 5. [Epub ahead of print]

Connective Tissue Growth Factor Promotes Efficient Generation of Human induced pluripotent stem cell-Derived Choroidal Endothelium.

Abstract: Age-related macular degeneration (AMD) is a leading cause of irreversible blindness in the Western world. Although, the majority of stem cell research to date has focused on production of retinal pigment epithelial (RPE) and photoreceptor cells for the purpose of evaluating disease pathophysiology and cell replacement, there is strong evidence that the choroidal endothelial cells (CECs) that form the choriocapillaris vessels are the first to be lost in this disease. As such, to accurately evaluate disease pathophysiology and develop an effective treatment, production of patient-specific, stem cell-derived CECs will be required. In this study, we report for the first time a stepwise differentiation protocol suitable for generating human iPSC-derived CEC-like cells. RNA-seq analysis of the monkey CEC line, RF/6A, combined with two statistical screens allowed us to develop media comprised of various protein combinations. In both screens, connective tissue growth factor (CTGF) was identified as the key component required for driving CEC development. A second factor tumor necrosis factor (TNF)-related weak inducer of apoptosis receptor was also found to promote iPSC to CEC differentiation by inducing endogenous CTGF secretion. CTGF-driven iPSC-derived CEC-like cells formed capillary tube-like vascular networks, and expressed the EC-specific markers CD31, ICAM1, PLVAP, vWF, and the CEC-restricted marker CA4. In combination with RPE and photoreceptor cells, patient-specific iPSC derived CEC-like cells will enable scientists to accurately evaluate AMD pathophysiology and develop effective cell replacement therapies.

PMID: 28474838


Eyeing the Fountain of Youth.

Saint-Geniez M, Rosales MAB.

Abstract: Stem cell-based disease modeling is an emerging technology for the mechanistic study and therapeutic screening of complex ocular pathologies. In this issue of Cell Stem Cell, Saini et al. (2017) show that iPSC-derived RPE cells from age-related macular degeneration patients express increased levels of pro-inflammatory factors that can be normalized by the anti-aging drug nicotinamide.

PMID: 28475881


Progress of stem/progenitor cell-based therapy for retinal degeneration.


Abstract Retinal degeneration (RD), such as age-related macular degeneration (AMD) and retinitis pigmentosa, is one of the leading causes of blindness. Presently, no satisfactory therapeutic options are available for these diseases principally because the retina and retinal pigmented epithelium (RPE) do not regenerate, although wet AMD can be prevented from further progression by anti-vascular endothelial growth factor therapy. Nevertheless, stem/progenitor cell approaches exhibit enormous potential for RD treatment using strategies mainly aimed at the rescue and replacement of photoreceptors and RPE. The sources of stem/progenitor cells are classified into two broad categories in this review, which are (1) ocular-derived progenitor cells, such as retinal progenitor cells, and (2) non-ocular-derived stem cells, including embryonic stem cells, induced pluripotent stem cells, and mesenchymal stromal cells. Here, we discuss in detail the progress in the study of four predominant stem/progenitor cell types used in animal models of RD. A short overview of clinical trials involving the stem/progenitor cells is also presented. Currently, stem/progenitor cell therapies for RD still have some drawbacks such as inhibited proliferation and/or differentiation in vitro (with the exception of the RPE) and limited long-term survival and function of grafts in
vivo. Despite these challenges, stem/progenitor cells represent the most promising strategy for RD treatment in the near future.

PMID: 28486987 PMCID: PMC5424366

Acta Biomater. 2017 May 5. [Epub ahead of print]

Preparation and evaluation of human choroid extracellular matrix scaffolds for the study of cell replacement strategies.


Abstract: Endothelial cells (ECs) of the choriocapillaris are one of the first cell types lost during age-related macular degeneration (AMD), and cell replacement therapy is currently a very promising option for patients with advanced AMD. We sought to develop a reliable method for the production of human choroidal extracellular matrix (ECM) scaffolds, which will allow for the study of choroidal EC (CEC) replacement strategies in an environment that closely resembles the native tissue. Human RPE/choroid tissue was treated sequentially with Triton X-100, SDS, and DNase to remove all native cells. While all cells were successfully removed from the tissue, collagen IV, elastin, and laminin remained, with preserved architecture of the acellular vascular tubes. The ECM scaffolds were then co-cultured with exogenous ECs to determine if the tissue can support cell growth and allow EC reintegration into the decellularized choroidal vasculature. Both monkey and human ECs took up residence in the choriocapillary tubes of the decellularized tissue. Together, these data suggest that our decellularization methods are sufficient to remove all cellular material yet gentle enough to preserve tissue structure and allow for the optimization of cell replacement strategies.

STATEMENT OF SIGNIFICANCE:

Age-related macular degeneration (AMD) is a devastating disease affecting more than 600 million people worldwide. Endothelial cells of the choriocapillaris (CECs) are among the first cell types lost in early AMD, and cell replacement therapy is currently the most promising option for restoring vision in patients with advanced AMD. In order to study CEC replacement strategies we have generated a 3D choroid scaffold using a novel decellularization method in human RPE/choroid tissue. To our knowledge, this is the first report describing decellularization of human RPE/choroid, as well as recellularization of a choroid scaffold with CECs. This work will aid in our development and optimization of cell replacement strategies using a tissue scaffold that is similar to the in vivo environment.

PMID: 28483697

J Cell Physiol. 2017 May 8. [Epub ahead of print]

The influence of rAAV2-mediated SOX2 delivery into neonatal and adult human RPE cells; a comparative study.

Ezati R, Etemadzadeh A, Soheili ZS, Samiei S, Pirmardan ER, Davari M, Najafabadi HS.

Abstract: Cell replacement is a promising therapy for degenerative diseases like age-related macular degeneration (AMD). Since the human retina lacks regeneration capacity, much attention has been directed towards persuading for cells that can differentiate into retinal neurons. In this report we have investigated reprogramming of the human RPE cells and concerned the effect of donor age on the cellular fate as a critical determinant in reprogramming competence. We evaluated the effect of SOX2 over-expression in human neonatal and adult RPE cells in cultures. The coding region of human SOX2 gene was cloned into Adeno-Associated virus (AAV2) and primary culture of human neonatal/adult RPE cells were infected by recombinant virus. De-differentiation of RPE to neural/retinal progenitor cells was investigated by quantitative real time PCR and ICC for neural/ retinal progenitor cells' markers. Gene expression analysis
showed 80 fold and 12 fold over-expression for SOX2 gene in infected neonatal and adult hRPE cells respectively. The fold of increase for Nestin in neonatal and adult hRPE cells was 3.8 fold and 2.5 fold respectively. PAX6 expression was increased 3 fold and 2.5 fold in neonatal/adult treated cultures. Howbeit we could not detect rhodopsin, and CHX10 expression in neonatal hRPE cultures and expression of rhodopsin in adult hRPE cells. Results showed SOX2 induced human neonatal/adult RPE cells to de-differentiate toward retinal progenitor cells. However, the increased number of PAX6, CHX10, Thy1 and rhodopsin positive cells in adult hRPE treated cultures clearly indicated the considerable generation of neuro-retinal terminally differentiated cells.

PMID: 28480968

**Diet, lifestyle and low vision**

*Ophthalmologica.* 2017 May 6. [Epub ahead of print]

**Nutrition, Genes, and Age-Related Macular Degeneration: What Have We Learned from the Trials?**

Chew EY.

Abstract: The Age-Related Eye Disease Study (AREDS) and AREDS2 provided evidence for treating persons with age-related macular degeneration (AMD) with antioxidant vitamins and minerals to reduce the risk of development of late AMD. The AREDS2 data suggest that the beta-carotene in the original AREDS supplements be replaced by lutein and zeaxanthin, providing a safer drug for those who are smokers or former smokers. Even though consuming fish reduced the risk of AMD in observational studies, the AREDS2 results showed that omega-3 long-chain polyunsaturated fatty acids (docosahexaenoic acid/ eicosapentaenoic acid) had no beneficial effect on AMD. Despite the major progress in the discovery of gene variants associated with AMD, the use of genetic testing to predict disease has not been clinically useful. The use of genetic testing prior to AMD therapies such as administering AREDS supplements is not recommended by the American Academy of Ophthalmology and other organizations.

PMID: 28478452


**Effects of Magnification on Emotion Perception in Patients With Age-Related Macular Degeneration.**

Johnson AP, Woods-Fry H, Wittich W.

PURPOSE: Individuals with low vision often experience difficulties in performing tasks of daily living, such as face perception. This leads them to having difficulties with social interactions, as they can no longer correctly perceive the emotion of others. The present study investigated the effects of magnification on face perception in participants with age-related macular degeneration (AMD), and their ability to detect and categorize emotions. It was hypothesized that patients with AMD would be less accurate in comparison to healthy controls, but that magnification would improve their performance to that of controls.

METHODS: Faces containing happy, angry, or neutral emotion were both doubled (equivalent of arm's length distance) and decreased by half in size (equivalent of across the street). The ability to detect and to discriminate emotional content was compared between 20 AMD patients and 7 age-matched controls. Eye movements were recorded while conducting both tasks.

RESULTS: Regardless of stimulus size, when compared to controls, we observed that individuals with AMD consistently performed with lower accuracy in both emotion detection and categorization tasks. Moreover, having images undergo a 2-fold increase in size did improve performance, but did not equate AMD participants' performance to that of the controls in either the emotion detection or categorization task. Eye movements in AMD participants were highly variable in position compared to controls.
CONCLUSIONS: The data suggest that magnification alone does not appear to be the answer for improving emotion perception within individuals with low vision. Next steps should include an evaluation of the effects of viewing strategy.

PMID: 28492869