Drug treatment

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Consistent Long-Term Therapy of Neovascular Age-Related Macular Degeneration Managed by 50 or More Anti-VEGF Injections Using a Treat-Extend-Stop Protocol.

Adrean SD, Chaili S, Ramkumar H, Pirouz A, Grant S.

PURPOSE: To examine the clinical results for patients with neovascular age-related macular degeneration (nAMD) who were managed with a treat-extend-stop (TES) protocol and received 50 or more injections of anti-vascular endothelial growth factor (VEGF) agents.

DESIGN: Retrospective case study.

PARTICIPANTS: Data for patients from a private retina practice meeting the following criteria were included: diagnosis of nAMD and having received 50 or more intravitreal injections of anti-VEGF agents.

METHODS: The patients’ baseline visual acuity (VA; obtained using Snellen charts and converted to Early Treatment Diabetic Retinopathy Study [ETDRS] letters), age, length of follow-up, anti-VEGF agents used, and interval between treatments were obtained. These data were examined through the 51st injection and at the last follow-up examination. Patients were excluded if they lost significant vision because of a diagnosis unrelated to AMD during therapy.

MAIN OUTCOME MEASURES: Visual acuity and complications.

RESULTS: Sixty-seven eyes of 71 patients were identified who met inclusion criteria. The mean age of patients was 83.0 years. Women made up 58.2% of the study population, whereas men constituted 41.8%. The mean initial VA was 55.6 ETDRS letters. The mean duration of follow-up at the 51st visit for an injection was 6.4 years, and the mean duration of follow-up at the last visit was 8 years. The mean number of injections at final follow-up was 63.7. The mean interval between treatments at the 51st follow-up was 5.4 weeks, and the mean follow-up at the last examination was 6.4 weeks. Mean VA at the 51st injection was 65.3 letters, and the mean change from baseline was 9.7 letters (P < 0.001, Student paired t test). The mean vision gained at last follow-up was 8.7 letters from baseline (P < 0.001), or 64.3 letters.

CONCLUSIONS: In this study, patients gained a mean of 2 ETDRS lines after 50 injections. This study had a mean follow-up of 8 years, and 35.2% of eyes had a 3-line or more gain in VA at the last follow-up examination. Patients who require consistent long-term anti-VEGF therapy, managed with a TES protocol, are likely able to maintain or improve their vision.

PMID: 29439828
Klin Monbl Augenheilkd. 2018 Feb 16. [Epub ahead of print]

[Cost Comparison of Licensed Intravitreal Therapies for Insufficiently Anti-VEGF Responding Fovea Involving Diabetic Macular Edema in Germany]. [Article in German]

Neubauer AS, Haritoglou C, Ulbig MW.

BACKGROUND: In the treatment of center-involving diabetic macular edema, despite initial therapy with an anti-VEGF compound, an insufficient response may occur. Further therapy options include a switch of anti-VEGF products or to corticosteroid implants, such as Fluocinolone acetonide or Dexamethasone.

OBJECTIVES: Firstly, to investigate systematically which evidence-based study data are available describing the efficacy of in-label treatments after primary anti-VEGF treatment, secondly, to investigate which costs go along for the healthcare provider.

METHODS: A systematic literature review (SLR) for randomized controlled trials (RCT) was performed in Medline and Embase. A short-term cost-effect model was built in MS Excel with a 3 year time horizon to compare in-label intravitreal options Ranibizumab (Lucentis®), Aflibercept (Eylea®), Fluocinolone acetonide implant (Iluvien®), and Dexamethasone implant (Ozurdex®). Cost components comprised of drug and injection costs, optical coherence tomography (OCT) procedures, and adverse events such as endophthalmitis, IOP-lowering drugs and surgery and cataract surgery.

RESULTS: A total of 42 publications of 20 RCTs were identified. No study had a clearly defined population after first line anti-VEGF treatment, thus no direct efficacy comparison was possible. In the short-term cost-effect model total costs were 17,542 € for Ranibizumab, 15,896 € for Aflibercept, 10,826 € for Fluocinolone acetonide implant and 12,365 € for Dexamethasone implant. For all treatment regimens, drug costs were the predominant cost component, followed by injection costs (with variations dependent on the specific drug) and OCT costs. In the uni- and multivariate sensitivity analyses, the results obtained were robust to changes of model inputs.

CONCLUSIONS: In summary, the short-term cost-effect comparison demonstrates that steroid implants can provide significant cost savings versus in-label anti-VEGF treatment for center-involving diabetic macular edema. Single application of the long-lasting Fluocinolone acetonide implant is the most cost-efficient in-label treatment option.

PMID: 29452450


Intravitreal Aflibercept Versus Ranibizumab for Wet Age-Related Macular Degeneration: A Cost-effectiveness Analysis.


BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of vision loss in the United States. The most severe vision loss occurs in patients with neovascular AMD, known as wet AMD (wAMD). The most commonly used antivascular endothelial growth factor (VEGF) therapies approved by the FDA to treat patients with wAMD are ranibizumab, 0.5 mg administered by intravitreal injection once a month (approximately every 28 days), and intravitreal aflibercept injection (IAI), 2 mg every 4 weeks (monthly) for the first 12 weeks (3 months), followed by IAI 2 mg once every 8 weeks (2 months). Given the similar efficacy and safety profiles between IAI and ranibizumab, their associated costs and comparative cost-effectiveness are key factors in determining which one represents a more rational investment of scarce health care resources to help address the increasing cost of prescription drugs in the United States, a source of concern for patients, prescribers, payers, and policymakers.

OBJECTIVE: To assess the cost-effectiveness of intravitreal aflibercept injection 2 mg every 8 weeks after
3 initial monthly doses (IAI 2q8) versus ranibizumab 0.5 mg monthly (Rq4) and pro re nata (PRN) in the treatment of patients with wAMD from a U.S. payer perspective.

METHODS: A Markov cohort model was developed to estimate the lifetime quality-adjusted life-years (QALYs) and costs of treating patients with wAMD with IAI 2q8, Rq4, and ranibizumab PRN. The model considered changes in best-corrected visual acuity in the affected and fellow eyes over time, and the effect of blindness on mortality. Efficacy for IAI 2q8 and Rq4 was from VIEW 1 and VIEW 2 studies and from the Comparison of AMD Treatments Trials for ranibizumab PRN. Utilities and costs (in 2016 U.S. dollars) were from published literature. Health outcomes and costs were discounted at an annual rate of 3%.

RESULTS: Over a lifetime, IAI 2q8 provided equal health benefits with Rq4 (5.44 QALYs) at a lower total cost ($33,795 vs. $48,031) as a result of fewer injections. IAI 2q8 yielded slightly greater QALYs versus ranibizumab PRN (5.44 vs. 5.40) at a slightly higher cost ($33,795 vs. $33,652), with an incremental cost per QALY gained of $2,583. Results were sensitive to variations in drug acquisition costs and number of injections of both drugs and the baseline age of the cohort.

CONCLUSIONS: IAI 2q8 can be cost saving and cost-effective compared with Rq4 and ranibizumab PRN for the treatment of wAMD in the United States.

PMID: 29451077


Incidence of ocular hypertension after intravitreal injection of anti-VEGF agents in the treatment of neovascular AMD.

Moraru A, Pînzaru G, Moţoc A, Costin D, Brănişteanu D.

Purpose: The assessment of the incidence of ocular hypertension over a period of 1 year in patients treated with multiple intravitreal injections of anti-VEGF agents for neovascular AMD.

Methods: The study comprised 58 eyes diagnosed with neovascular age-related macular degeneration and receiving PRN intravitreal treatment with anti-VEGF agents (bevacizumab or aflibercept). The follow-up period was 1 year. Intraocular pressure was measured by using the Goldmann applanation tonometry before the intravitreal injection, at 24 hours after the administration of the anti-VEGF agent and at 1 and 4 weeks. Patients diagnosed with glaucoma or who underwent ophthalmic surgery were excluded.

Results: The patients received an average of 7.54 intravitreal injections. The mean baseline intraocular pressure was 15.3 mm Hg; 19.8 mm Hg at 24 hours; 17.4 mmHg at 1 week and 14.8 mmHg at 4 weeks after the administration of the anti-VEGF agent. 4 patients required long-term topical hypotensive treatment. Raised intraocular pressure was related to increased frequency of treatment. At 1 year follow up, an average difference of 2.1 mmHg compared to baseline was registered in the cases that have received more than 6 intravitreal injections. By comparison, in the cases treated with a reduced number of doses of intravitreal anti VEGF agent, the difference from baseline was 0.9 mmHg. There were no significant differences in mean IOP depending on the anti VEGF (bevacizumab or aflibercept) agent used.

Conclusions: Intravitreal treatment with anti VEGF agents produces a transient increase in intraocular pressure, predominantly immediately following administration, without causing long-term increased values.

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Aflibercept Versus Bevacizumab and/or Ranibizumab for Recurrent Macular Edema Secondary to Central Retinal Vein Occlusion.
Ozgonul C, Dedania VS, Besirli CG.

PURPOSE: To compare functional and anatomic outcomes of treatment with intravitreal aflibercept versus bevacizumab and/or ranibizumab in patients with recurrent macular edema (ME) secondary to central retinal vein occlusion (CRVO).

METHODS: Retrospective, comparative case series of patients with recurrent ME in the setting of CRVO. Patients with recurrent ME received treatment with aflibercept (Group 1, G1) or bevacizumab and/or ranibizumab (Group 2, G2). Primary outcome measures were best-corrected visual acuity (BCVA) and central foveal thickness (CFT).

RESULTS: Of the 20 eyes (20 patients) with recurrent ME included in the study, 9 received aflibercept (G1) and 11 received bevacizumab and/or ranibizumab (G2). Median BCVA at recurrence of ME and at most recent follow-up was 20/60 (G1) and 20/80 (G2) and 20/40 (G1) and 20/50 (G2, P > 0.05 for all comparisons), respectively. Median CFT at recurrence of ME and at most recent follow-up was 492 μm (G1) and 448 μm (G2) and 291 μm (G1) and 295 μm (G2, P > 0.05 for all comparisons), respectively. Complete resolution of ME for at least 4 months was found in 78% (G1) and 55% (G2) of patients with a median injection free interval of 11 (G1) and 13 (G2) months (P > 0.05).

CONCLUSIONS: In patients with recurrent ME secondary to CRVO, there was improvement in BCVA and CFT in all groups, although patients treated with aflibercept showed a trend toward better anatomical outcomes decreased need for recurrent injections.

PMID: 29447089

Retin Cases Brief Rep. 2018 Feb 13.[Epub ahead of print]

PROGRESSION OF RETINAL ISCHEMIA IN A CASE OF MACULAR TELANGIECTASIA TYPE 1 AFTER RANIBIZUMAB INJECTION: OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY FINDINGS.

Lorusso M, Zito R, Nikolopoulou E, Micelli Ferrari L, Cicinelli MV, Querques G, Micelli Ferrari T.

PURPOSE: To describe a case of a 68-year-old man with macular telangiectasia (MacTel) Type 1 in the right eye, showing an increase in capillary ischemia after intravitreal ranibizumab.

METHODS: The patient underwent complete ophthalmologic evaluation, including best-corrected visual acuity, intraocular pressure, anterior segment and fundus examination, optical coherence tomography (OCT), and OCT angiography at baseline and on each visit. Fluorescein angiography was performed at baseline. The patient was followed up on monthly bases for 22 months.

RESULTS: The patient presented a best-corrected visual acuity of 20/80 in the right eye and of 20/25 in the left eye at baseline. In the right eye, the fluorescein angiography images showed perifoveal capillary ectasia, late-frames dye leakage, and enlargement of the foveal avascular zone. The OCT showed intraretinal pseudocysts and microaneurysms, and the OCT angiography showed vascular rarefaction, capillary dropout, and capillary ectasia of the superficial plexus. After 16 months of follow-up and four ranibizumab injections, the best-corrected visual acuity was 20/60, and the OCT angiography disclosed a further enlargement of the foveal avascular zone area and increased capillary obliteration in the perifoveal nasal area.

CONCLUSION: Optical coherence tomography angiography may represent an indispensable diagnostic technique, complementary to traditional imaging, in the evaluation of the effects of anti-vascular endothelial growth factor therapy in patients with MacTel Type 1.

PMID: 29443804

Low-Energy Stereotactic Radiotherapy for Treatment of Exudative Age-Related Macular Degeneration in a Treat-and-Extend Regimen.


BACKGROUND AND OBJECTIVE: To evaluate the effectiveness and safety of low-energy stereotactic radiotherapy (SRT) combined with anti-vascular endothelial growth factor (VEGF) treatment following a treat-and-extend regimen (TER) in wet age-related macular degeneration (AMD).

PATIENTS AND METHODS: Before/after SRT, the authors compared retrospective consecutive case series of 50 patients requiring frequent anti-VEGF treatment (every 4 or 6 weeks) in wet AMD, treated with a single session of SRT and TER (same manner pre/post-SRT). Outcomes were visual acuity (VA), recurrence-free interval, and central retinal thickness (CRT).

RESULTS: After SRT, CRT was reduced from baseline (407.3 μm ± 153.2 μm) to 12 months (320.2 μm ± 112.1 μm; P < .001), with statistical significance from month 2 onward. VA was stable for 12 months (64.0 letters ± 15.1 letters vs. 63.6 letters ± 16.2 letters). The mean recurrence-free interval increased from 4.24 weeks ± 0.66 weeks to 7.52 weeks ± 3.05 weeks at 12 months (P < .001). No severe side effects were observed.

CONCLUSION: Low-energy SRT, combined with anti-VEGF TER, was associated with reduced injection frequency and preserved VA during 12 months of follow-up.

PMID: 29443357


Mortality associated with bevacizumab intravitreal injections in age-related macular degeneration patients after acute myocardial infarct: a retrospective population-based survival analysis.

Hanhart J, Comaneshter DS, Freier-Dror Y, Vinker S.

BACKGROUND: Intraocular injections of antivascular endothelial growth factor (VEGF) agents are currently the main therapy in age-related macular degeneration (AMD). The safety of bevacizumab, an anti-VEGF compound frequently delivered off label, is debated, particularly for high-group risks. We aim to analyze the mortality associated with intravitreal injections of bevacizumab for AMD in patients previously diagnosed with acute myocardial infarct (MI).

METHODS: In a national database, we identified bevacizumab-treated AMD patients with a diagnosis of MI prior to their first bevacizumab injection, delivered between September 2008 and October 2014 (n = 2100). We then generated sub-groups of patients treated within 3 months (n = 11), 6 months (n = 24), 12 months (n = 52), and 24 months (n = 124) after MI. Those patients were compared to age- and gender-matched members that had a MI at the same time and had never been exposed to anti-VEGF. Survival analysis was performed using propensity score-adjusted Cox regression.

RESULTS: Bevacizumab-treated patients were slightly and insignificantly older than controls (mean age 83.25 vs 83.19 year, P = .75). Gender distribution was similar. In a Cox regression adjusted with propensity score, the following differences in mortality were found: within 3 months between MI and initiation of bevacizumab treatment, OR = 6.22 (95% C.I 1.08-35.97, P < .05); within 6 months, OR = 2.37 (95% C.I 0.93-6.02, P = .071); within 12 months, OR = 3.00 (95% C.I 1.44-6.28, P < .01); within 24 months after MI, OR = 2.24 (95% C.I 1.35-3.70, P < .01); and MI any time prior to first bevacizumab injection, OR = 1.71 (95% C.I 1.53-1.92, P < .001).

CONCLUSIONS: We report increased mortality associated with the use of intravitreal bevacizumab in AMD
patients after MI, compared to age- and gender-matched post-MI patients with no exposure to any anti-VEGF agent. Caution should be taken while offering bevacizumab to AMD patients after MI.

PMID: 29429131


Bevacizumab in the treatment of acute central/hemicentral retinal vein occlusions.

Călugăru D, Călugăru M, Țălu Ş.

Abstract: Even if bevacizumab is unlicensed, a majority of retina specialists still currently recommends it in retinal vein occlusion-related macular edema. For the first time, the results of our studies showed evidence suggesting that an early treatment administered immediately after the onset of venous occlusion, provided a significant and sustained improvement in visual acuity and foveal thickness, with inactive disease (dry retina and stable visual acuity for at least 6 months after the last injection) in most phakic patients with acute central/ hemicentral retinal vein occlusions, making this treatment option a rational and viable therapeutic strategy. Central/ hemicentral retinal vein occlusion has to be considered an ophthalmic emergency. The highlighting of the ocular conditions most frequently associated with central/ hemicentral retinal vein occlusion (ocular hypertension, primary open angle glaucoma, primary angle closure suspect, primary angle closure, and primary angle closure glaucoma) is mandatory. Regardless of the anti-vascular endothelial growth factor agents used (bevacizumab/ ranibizumab/ aflibercept), and regardless of the treatment approaches chosen (treat-and-extend/ pro re nata algorithm), the efficacy of therapy depends primarily on the precociousness of the therapy after the diagnosis of central/ hemicentral retinal vein occlusion. Any delay in the treatment will adversely influence the restoration of visual functions, which are difficult to correct even with subsequent treatment.

PMID: 29450339 PMCID: PMC5720126


Aflibercept efficacy in refractory choroidal neovascularization.

Brănișteanu DC, Bîlhă A, Moraru A.

Abstract: The aim of the report is to evaluate the short-term efficacy and safety of aflibercept (EYLEA®) in patients with choroidal neovascularization (CNV) transformed into refractory during treatment with bevacizumab (AVASTIN®).

METHODS: Clinical, morphological, and functional changes were retrospectively evaluated in cases with refractory CNVs to monthly 1.25 mg bevacizumab intravitreal injections (AVASTIN®) and switched to 3 monthly 2.0 mg intravitreal injections of aflibercept (EYLEA®).

RESULTS: In this pilot evaluation, 8 cases of CNVs that become refractory to intravitreal treatment with 1.25 mg intravitreal bevacizumab (AVASTIN®), were switched to 2.0 mg intravitreal aflibercept (EYLEA®) and evaluated. The mean age of patients was 67.6 years (54-74 years). In 7 cases, CNV was associated to age related macular degeneration and in 1 case to angioid streaks. The mean number of previous intravitreal bevacizumab (AVASTIN®) administrations was 9.32 (7-12). In all cases, the last 3 intravitreal injections of bevacizumab were performed at an interval of maximum 6 weeks. The refractory status was confirmed by the lack of improvement or worsening of the clinical features as revealed by SD-OCT. A slowly anatomical improvement was noticed in 5 out of 8 cases (62.5%) since the first aflibercept administration. The anatomical improvement was stable after 3 monthly administrations. During the treatment, only 3 out of 5 cases (60%) showing anatomical improvement had a minor visual benefit (one line of VA gain). In 3 cases, the treatment change was unremarkable. No side effects were noticed.
CONCLUSIONS: The anatomical improvement confirms previous reports regarding the efficacy and safety of aflibercept (EYLEA®) in some cases of CNV that became refractory during conventional anti-VEGF therapy. The improvement can be, at least partially, explained by the more complex features of aflibercept. Unfortunately, a minor visual benefit was noticed in a limited number of cases.

PMID: 29450330 PMCID: PMC5711372


Intravitreal ranibizumab injection combined with photodynamic therapy for polypoidal choroidal vasculopathy.

Li J, Sun J, Li B, Liu Z.

Abstract: The aim of the present study was to evaluate the efficacy of combination treatment with intravitreal ranibizumab (IVR) injection and photodynamic therapy (PDT) for polypoidal choroidal vasculopathy (PCV). A total of 64 patients with PCV were included in the present study, which were divided into the IVR monotherapy group (Group A) and combination treatment groups (Groups B-D) with different treatment intervals. All subjects were followed-up at 1, 3, 6 and 12 months following treatment, and subjected to the detection of best-corrected visual acuity (BCVA) and central foveal thickness (CFT). Compared with the monotherapy group, more significant BCVA improvement was observed for the combination treatment groups, with the most evident effect exhibited in Group C. At the end of the follow-up period, visual acuity improvement rates were markedly elevated in the combination treatment groups, as compared with the monotherapy group. According to optical coherence tomography, the CFT for the combination treatment groups was thinner than the monotherapy group. Among the combination groups, CFT improvement for Group C was superior to other groups. Fundus angiography demonstrated that, compared with monotherapy, combination treatment may significantly promote the regression and prevent the recurrence of polyps and BVN. The most efficient effectiveness was observed for Group C. In addition, combination treatment may significantly reduce the IVR injection numbers required to treat PCV. Patients receiving combination treatment with IVR injection and PDT have greater vision improvements, reduced macular degeneration and decreased injection numbers. Combination therapy may therefore, represent an effective and safe therapeutic strategy for PCV clinical treatment.

PMID: 29434739 PMCID: PMC5776170


Anti-vascular endothelial growth factor indications in ocular disease.

Cornel S, Adriana ID, Mihaela TC, Speranta S, Algerino S, Mehdi B, Jalaladin HR.

Abstract: The purpose of this systemic review was to investigate the indications of anti-vascular endothelial growth factor (anti-VEGF) in the treatment of ocular diseases. For this, a comprehensive literature research was performed exploring the current use of anti-VEGF in a variety of retinal or anterior segment diseases and highlighting the visual outcome for these patients. The anti-VEGF therapy is now commonly used for a wide range of pathologies like age-related macular degeneration, retinal vein occlusion or diabetic retinopathy. Pathological processes such as abnormal neovascularization, ocular angiogenesis and macular edema which can greatly reduce visual acuity are now targeted by anti-VEGF treatment, having a major impact on vision.

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Other treatment & diagnosis


Optometry-facilitated teleophthalmology: an audit of the first year in Western Australia.

Bartnik SE, Copeland SP, Aicken AJ, Turner AW.

BACKGROUND: Lions Outback Vision has run a state-wide teleophthalmology service since 2011. In September 2015 the Australian federal government introduced a Medicare reimbursement for optometry-facilitated teleophthalmology consultations under specific circumstances. This audit demonstrates the first 12 months experience with this scheme. We aim to provide practical insights for others looking to embed a telemedicine program as part of delivering outreach clinical services.

METHODS: A 12-month retrospective audit was performed between September 2015 and August 2016, inclusive. A research officer used a specifically designed data extraction tool to record information from all teleophthalmology consultations performed in the time period. The primary outcome was the diagnosis at the end of the teleophthalmology consultation. Secondary outcome measures included the number of teleconsultations, cataract surgery rate, remoteness area of patients referred and imaging accompanying the referral.

RESULTS: In the 12-month period, 709 patients were referred resulting in 683 teleophthalmology teleconsultations. Cataract was the most frequent diagnosis (n = 287, 42.7 per cent), followed by glaucoma (n = 77, 11 per cent), age-related macular degeneration (n = 30, 4.4 per cent) and diabetic retinopathy (n = 26, 3.8 per cent). Of those who had teleconsultations, 98.6 per cent were from Outer Regional, Remote or Very Remote Australia. One or more accompanying images or investigations were part of 349 (49 per cent) teleconsultations, most commonly optical coherence tomography (215, 30 per cent) and fundus photography (148, 21 per cent). Face-to-face consultations were undertaken at an outreach clinic in 23 (3.4 per cent) cases, to determine the diagnosis. There were no statistically significant factors associated with attendance at teleophthalmology consultation, or for successfully undergoing cataract surgery.

CONCLUSION: Teleophthalmology is a valuable adjunct to regional outreach ophthalmology services, providing patients with increased access to specialist care for a wide range of ophthalmic conditions, and more efficient access to surgical care.

PMID: 29444552


Early changes in macular optical coherence tomography parameters after Ranibizumab intravitreal injection in patients with exudative age-related macular degeneration.

de Almeida NA, de Souza OF.

BACKGROUND: Evaluation of the impact of different macular optical coherence parameters on visual acuity as early as 1 day after injection of ranibizumab in patients with subfoveal exudative age-related macular degeneration.

METHODS: This was an interventional, non randomized, open label prospective study, where we evaluated 20 eyes of 20 patients affected by exudative age-related macular degeneration. These patients were treated with injections of ranibizumab between February 2013 and January 2015. The primary endpoint of this study was to evaluate the early changes in optical coherence tomography parameters (retinal thickness, central and total retinal volume) and impact on best-corrected visual acuity (BCVA) obtained by logarithm of minimum resolution using ETDRS protocol in patients treated with a single dose intravitreal injection of ranibizumab (0.5 mg/0.05 mL) during the first month of follow. The patients were evaluated on the first day, then at 7 and 30 days after the treatment. The National Eye Institute Visual Functioning
Questionnaire was applied during the study period to assess early perception of ranibizumab injection effectiveness. The adverse events were monitored throughout the study.

RESULTS: Central retinal thickness values at 1 (464.0 ± 97.8 µm), 7 (379.9 ± 107.8 µm) and 30 days (365.5 ± 95.1 µm) after ranibizumab injection showed a statically significant reduction when compared with baseline results (P = 0.01, P = 0.001, P = 0.001, respectively). Similar alterations were observed in central and total retinal volume, which were detected early on the first day of evaluation, after the measurement at baseline (central: 0.36 ± 0.07 vs. 0.40 ± 0.10 mm3, P = 0.01; total: 9.62 ± 1.10 vs. 9.99 ± 2.56 mm3, P = 0.002) and remained steady at 7 (P = 0.001, P = 0.002, respectively) and 30 days (P = 0.001, P = 0.004, respectively) with slight variations without losing their gains in these parameters. The best-corrected logarithm of minimum angle of resolution (logMAR) showed a statistically significant difference when compared to the baseline. (0.81 ± 0.16 vs. 0.67 ± 0.24, P = 0.005). The NEI-VFQ-25 questionnaire demonstrate statically significant results after treatment. When patients were asked about the subjective improvement in visual quality, over 80% reported early improvement. Throughout the period of follow-up visits, no serious adverse events were reported.

CONCLUSION: Intravitreal injection of ranibizumab can produce early changes in optical coherence tomography parameters and an improvement in perceived visual quality of patients with subfoveal exudative age-related macular degeneration.

PMID: 29445522 PMCID: PMC5798187


Relationship of Area of Soft Drusen in Retina with Cerebral Amyloid-β Accumulation and Blood Amyloid-β Level in the Elderly.

Shoda C, Kitagawa Y, Shimada H, Yuzawa M, Tateno A, Okubo Y.

BACKGROUND: Histopathological studies have confirmed that soft drusen contains amyloid-β (Aβ).

OBJECTIVE: To examine the relationship between the area of soft drusen in the macular area and cerebral Aβ accumulation or plasma Aβ level in elderly persons without dementia.

METHODS: Fourteen consecutive patients (18 eyes) aged ≥50 years with macular soft drusen were studied prospectively. From color fundus photographs, the area of soft drusen (pixel) within a 6,000 µm diameter with the macula as center was measured. Standard uptake value ratio (SUVR) was obtained from positron emission tomography using florbetapir, which indicates the ratio of cerebral cortical-to-cerebellar Aβ accumulation. Ratio of plasma Aβ1-42 to Aβ1-40 level was calculated.

RESULTS: Mean age was 73.3±7.6 years. The soft drusen area was 4.32±2.42 mm2. The SUVR was 1.08±0.15. Plasma Aβ1-42/Aβ1-40 ratio was 0.17±0.08. When SUVR ≥1.10 was defined as positive and <1.10 as negative, the soft drusen area in SUVR-positive patients (6.19±1.14 mm2) was significantly (p=0.0043) larger than that in SUVR-negative patients (3.13±2.27 mm2). Multivariate regression analysis showed that SUVR positivity correlated with soft drusen area (p=0.0484) and with Voxel-based Specific Regional Analysis System for Alzheimer’s Disease score (p=0.0360). However, there was no correlation with gender (p=0.1921), age (p=0.2361), Alzheimer’s Disease Assessment Scale score (p=0.6310), Mini-Mental State Examination score (p=0.4246), or plasma Aβ1-42/Aβ1-40 ratio (p=0.8398).

CONCLUSION: Among elderly persons without dementia, the area of soft drusen was larger in those with more extensive cerebral Aβ accumulation. The area of soft drusen may be a biomarker of cerebral Aβ accumulation.

PMID: 29439351
Type 2 choroidal neovascularisation in polypoidal choroidal vasculopathy: a retrospective case series.

Liang S, Shi X, Rosenfeld PJ, Li X.

BACKGROUND AND OBJECTIVE: To demonstrate the coexistence of polypoidal choroidal vasculopathy (PCV) with type 2 neovascularisation (NV), we used multimodal imaging, including spectral-domain optical coherence tomography angiography (SD-OCTA), to identify both types of lesions in the same eye.

STUDY DESIGN: This retrospective case series reviewed patients with PCV diagnosed with indocyanine green angiography (ICGA), fluorescein angiography (FA), SD-OCT and SD-OCTA.

RESULTS: 15 eyes of 14 patients were imaged and diagnosed with PCV by ICGA. ICGA identified polyps in all these eyes, while SD-OCTA imaging identified polypoidal lesions in only 11 (73%) of these eyes with PCV. Branching vascular networks (BVNs) were detected in 12 eyes (80%) by ICGA and SD-OCTA. Type 2 NV was detected in four eyes (27%) by FA and SD-OCTA. In these eyes, a combination of polyps, BVNs and type 2 NV were detected using FA, ICGA and SD-OCTA.

CONCLUSION: BVN and type 2 NV can coexist in the same PCV eye and communicate with each other. This suggests that polyps may represent a structural variant of neovascular tissue rather than a distinct pathogenic process in NV.

PMID: 29436399

Diagnosis of non-exudative (DRY) age related macular degeneration by non-invasive photon-correlation spectroscopy.

Fankhauser FI, Ott M, Munteanu M.

PURPOSE: Photon-correlation spectroscopy (PCS) (quasi-elastic light scattering spectroscopy, dynamic light scattering spectroscopy) allows the non-invasively reveal of local dynamics and local heterogeneities of macromolecular systems. The capability of this technique to diagnose the retinal pathologies by in-vivo investigations of spatial anomalies of retinas displaying non-exudative senile macular degeneration was evaluated. Further, the potential use of the technique for the diagnosis of the macular degeneration was analyzed and displayed by the Receiver Operating Curve (ROC).

METHODS: The maculae and the peripheral retina of 73 normal eyes and of 26 eyes afflicted by an early stage of non-exudative senile macular degeneration were characterized by time-correlation functions and analyzed in terms of characteristic decay times and apparent size distributions.

RESULTS: The characteristics of the obtained time-correlation functions of the eyes afflicted with nonexudative macular degeneration and of normal eyes differed significantly, which could be referred to a significant change of the nano- and microstructure of the investigated pathologic maculas.

CONCLUSIONS: Photon-correlation spectroscopy is able to assess the macromolecular and microstructural aberrations in the macula afflicted by non-exudative, senile macular degeneration. It has been demonstrated that macromolecules of this disease show a characteristic abnormal behavior in the macula.

PMID: 29450328 PMCID: PMC5711370

Use of Optical Coherence Tomography Angiography in Masqueraders of Wet Age-Related Macular Degeneration and Choroidal Neovascularization.

Schechet S, Hariprasad SM, Movahedan A, Skondra D.

PMID: 29443356


Comparison of ICare tonometry to Goldman tonometry for the measurement of intraocular pressure changes following intravitreal anti-VEGF injection.

Hui M, Raniga A, Fraser-Bell S, Salem W, Clement C.

Abstract: In developed countries, age-related macular degeneration (AMD) is a leading cause of visual impairment, particularly in its neovascular form. Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) is the standard of care for wet AMD. Inspite of the small intravitreal bolus of 0.05ml, many studies have reported a rise in intraocular pressure (IOP) immediately post injection.1-3.

PMID: 29442417

Pathogenesis

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In Vivo Multimodal Imaging and Analysis of Mouse Laser-Induced Choroidal Neovascularization Model.

Ragauskas S, Kielczewski E, Vance J, Kaja S, Kalesnykas G.

Abstract: Laser-induced choroidal neovascularization (CNV) is a well-established model to mimic the wet form of age-related macular degeneration (AMD). In this protocol, we aim to guide the reader not simply through the technical considerations of generating laser-induced lesions to trigger neovascular processes, but rather focus on the powerful information that can be obtained from multimodal longitudinal in vivo imaging throughout the follow-up period. The laser-induced mouse CNV model was generated by a diode laser administration. Multimodal in vivo imaging techniques were used to monitor CNV induction, progression and regression. First, spectral domain optical coherence tomography (SD-OCT) was performed immediately after the lasering to verify a break of Bruch’s membrane. Subsequent in vivo imaging using fluorescein angiography (FA) confirmed successful damage of Bruch’s membrane from serial images acquired at the choroidal level. Longitudinal follow-up of CNV proliferation and regression on days 5, 10, and 14 after the lasering was performed using both SD-OCT and FA. Simple and reliable grading of leaky CNV lesions from FA images is presented. Automated segmentation for measurement of total retinal thickness, combined with manual caliber application for measurement of retinal thickness at CNV sites, allow unbiased evaluation of the presence of edema. Finally, histological verification of CNV is performed using isolectin GS-IB4 staining on choroidal flatmounts. The staining is thresholded, and the isolectin-positive area is calculated with ImageJ. This protocol is especially useful in therapeutics studies requiring high-throughput-like screening of CNV pathology as it allows fast, multimodal, and reliable classification of CNV pathology and retinal edema. In addition, high resolution SD-OCT enables the recording of other pathological hallmarks, such as the accumulation of subretinal or intraretinal fluid. However, this method does not provide a possibility to automate CNV volume analysis from SD-OCT images, which has to be performed manually.

PMID: 29443029
Induction of Ocular Complement Activation by Inflammatory Stimuli and Intraocular Inhibition of Complement Factor D in Animal Models.

Crowley MA, Delgado O, Will-Orrego A, Buchanan NM, Anderson K, Jaffee BD, Dryja TP, Liao SM.

PURPOSE: Genome-wide association studies suggest a role for the complement system in age-related macular degeneration (AMD). We characterized ocular complement activation and evaluated a complement factor D (FD) neutralizing antibody.

METHODS: Mice were treated with toll-like receptor (TLR) ligands, intravitreal injection (IVT), or corneal debridement. Levels of complement proteins and mRNA were measured. A FD neutralizing antibody was administered IVT into eyes of rabbits that were challenged with LPS (lipopolysaccharide) administered intravenously.

RESULTS: Levels of C3 and factor B (FB) mRNA and protein in the eye were increased following intraperitoneal injection of TLR4 ligand LPS. Increased levels of C3 and FB breakdown products were observed in both eye tissues and plasma. Complement activation products were markedly reduced in C3-/- and Cfb-/- mice challenged with LPS. Ocular complement levels were also elevated in mice treated systemically with TLR2 and -3 ligands, injured by IVT injection or corneal debridement, or even in normal aging. IVT administration of a complement FD neutralizing antibody in rabbits inhibited LPS-induced complement activation in the posterior segment of the eye, but not in the anterior segment of the eye or in plasma.

CONCLUSIONS: Systemic TLR stimulation and eye tissue injury induced time-dependent alternative complement pathway activation in the eye. Ocular complement levels were also gradually elevated during aging. An anti-FD antibody IVT potently inhibited LPS-induced complement activation in the posterior segment of the eye. This study provides insights into the dynamic profile of ocular complement activation, which is valuable for complement research in eye diseases and for developing complement therapeutics for AMD.

PMID: 29450541

Anti-neovascularization effects of DMBT in age-related macular degeneration by inhibition of VEGF secretion through ROS-dependent signaling pathway.

Chen S, Zhou Y, Zhou L, Guan Y, Zhang Y, Han X.

Abstract: Choroidal neovascularization (CNV) is the hallmark of late-staged wet age-related macular degeneration (AMD). Vascular endothelial growth factor (VEGF) is a key component in the development and progression of wet AMD. DMBT, 6,6'-bis(2,3-dimethoxybenzoyl)-α,α-D-trehalose, had been proved that it could suppress tumor angiogenesis and metastasis by inhibiting production of VEGF. But the effects of DMBT on CNV were not known. This study was to investigate effects and mechanisms of DMBT on CNV in vitro and in vivo. Results showed that DMBT could inhibit migration and tube formation of RF/6A cells under ARPE-19 hypoxia conditioned medium. DMBT could reduce lesion area in laser-induced CNV model mice. ELISA and Western blotting assay showed that DMBT markedly inhibited secretion of VEGF in vitro and in vivo. Furthermore, DMBT restrained ROS level under hypoxia via suppressing Nrf2/HO-1 pathway. DMBT effectively suppressed hypoxia-induced the up-regulation of p-Akt, p-NF-κB, and HIF-1α. These results suggest that DMBT can inhibit CNV by down-regulation of VEGF in retina through Akt/NF-κB/HIF-1α and ERK/Nrf2/HO-1/HIF-1α pathway. DMBT might be a promising lead molecule for anti-CNv and serve as a therapeutic agent to inhibit CNV.

PMID: 29446046

A model to study complement involvement in experimental retinal degeneration.


BACKGROUND: The complement system (CS) plays a role in the pathogenesis of a number of ocular diseases, including diabetic retinopathy (DR), glaucoma, uveitis, and age-related macular degeneration (AMD). Given that many of the complex eye-related degenerative diseases have limited treatment opportunities, we aimed to mimic the in vivo retinal degenerative process by developing a relevant co-culture system.

METHOD AND MATERIALS: The adult porcine retina was co-cultured with the spontaneously arising human retinal pigment epithelial cells-19 (ARPE-19).

RESULTS: Inflammatory activity was found after culture and included migrating microglial cells, gliosis, cell death, and CS activation (demonstrated by a minor increase in the secreted anaphylatoxin C3a in co-culture). CS components, including C1q, C3, C4, soluble C5b-9, and the C5a receptor, were expressed in the retina and/or ARPE cells after culture. C1q, C3, and CS regulators such as C4 binding protein (C4BP), factor H (CFH), and factor I (CFI) were secreted after culture.

DISCUSSION: Thus, our research indicates that this co-culturing system may be useful for investigations of the CS and its involvement in experimental neurodegenerative diseases.

PMID: 29436895

Epidemiology


Prevalence of age-related macular degeneration associated genetic risk factors and 4-year progression data in the Irish population.

Connolly E, Rhatigan M, O’Halloran AM, Muldrew KA, Chakravarthy U, Cahill M, Kenny RA, Doyle SL.

BACKGROUND/AIMS: Age-related macular degeneration (AMD) is estimated to affect 196 million people >50 years old globally. Prevalence of AMD-associated genetic risk factors and rate of disease progression are unknown in Ireland.

METHODS: Prevalence of AMD-associated genetic risk variants, complement factor H (CFH) rs1061170, age-related maculopathy susceptibility 2 (ARMS2) rs10490924, component 3 (C3) rs2230199, complement factor B (CFB) rs641153 and superkiller viralicidic activity 2-like (SKIV2L) rs429608 and 4-year progression data in a population-representative cohort (The Irish Longitudinal study on Ageing (TILDA)) were assessed. 4473 participants ≥50 years were assessed. 4173 had no disease n=1843; 44% male and n=2330; 56% female, mean age 60±9.0, 300 had AMD n=136; 45% male and n=164; 55% female, mean age 64±9.0. A 4-year follow-up was undertaken with 66% of AMD cases attending. Progression and regression from early to late AMD were measured. Genetic association as indicators of disease and as predictors of progression were assessed by multinomial logistic regression.

RESULTS: Older age and the presence of CFH and ARMS2 risk alleles are two main risk factors associated with the prevalence of AMD in the TILDA cohort. 23% progressed to a higher grade of AMD. Carriers of CFH risk allele showed a strong association for disease progression. Heterozygosity for ARMS2 risk allele predicted progression to late AMD. 75% of those who progressed from early to late disease had soft drusen and hyperpigmentation at baseline.

CONCLUSIONS: The prevalence of risk-associated genes and 4-year progression rates of AMD in this
The Association of Serum Iron-Binding Proteins and Antioxidant Parameter Levels in Age-related Macular Degeneration.

Čolak E, Žorić L, Radosavljević A, Ignjatović S.

PURPOSE: Age-related macular degeneration (AMD) is the leading cause of the irreversible central visual loss among the elderly in the developed countries. Iron is considered a potent generator of the oxidative damage whose levels increase with age, potentially exacerbating the age-related diseases. The aim of this study was to assess the serum values of iron, and iron-binding proteins (transferrin, ferritin, and haptoglobin) in patients with AMD along with the parameters of the antioxidant defense: superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase, and total antioxidant status (TAS), in order to analyze the possible impact of iron and iron-binding proteins to the development of oxidative stress in AMD patients, and the association of the selected parameters with the AMD. In addition, the aim was to examine the gender differences and calculate the cutoff points of tested parameters that could be associated with AMD.

MATERIAL AND METHODS: A cross-sectional study included 55 AMD patients aged 71.7 ± 7.36 years and 65 aged-matched control subjects aged 70.25 ± 6.46 years.

RESULTS: Significantly lower ferritin (P = 0.025), SOD (P = 0.026), GPx (P = 0.019), and TAS (P < 0.004) values were found in patients with AMD compared to the controls (P < 0.05). Significant association of GPx < 27 U/gHb (odds ratio [OR]: 1.13; 95% confidence interval [CI] 0.78-2.10; P = 0.049), TAS < 1.25 mmol/L (OR: 5.77; 95% CI 0.98-367.0; P < 0.000), ferritin < 84.8 pg/mL (OR: 2.52; 95% CI 1.37-4.62; P = 0.002), and haptoglobin < 1.51 g/L (OR: 1.94; 95% CI 1.05-3.56; P = 0.031) was found with the AMD. According to receiver operating characteristic curve analysis, ferritin concentration < 84.8 pg/L, GPx < 27 U/gHb, and TAS < 1.25 mmol/L have sufficient predictive ability for AMD.

CONCLUSION: Significantly reduced capacity of the antioxidant defense system and iron-binding storage proteins (ferritin) found in AMD could have an important role in the development of increase oxidative stress in AMD patients.

PMID: 29448841
epidemiological studies to derive incidence, and Office for National Statistics data on mortality and migration overseas.

RESULTS: By 2023, >900 new cases of each of ‘wet’ (neovascular) and ‘dry’ age-related macular degeneration, >1200 cases of primary open angle glaucoma and almost 15 000 cases of cataracts are expected to have accrued in the subcohort of 68 500 participants who had ocular assessment at baseline, with around seven times as many cases of each disease in the whole cohort of 500 000 participants. These predicted incident case numbers generate good or substantial statistical power for a range of nested case-control studies of potential genetic, lifestyle and environmental determinants of disease.

CONCLUSIONS: Over the next few years, UK Biobank is expected to generate sufficient numbers of new cases for statistically well-powered studies of the determinants of the major causes of sight loss: age-related macular degeneration, vision-impairing cataract and glaucoma.

PMID: 29437582


Decreased severity of age-related macular degeneration in amblyopic eyes.

Storey PP, Aziz HA, O’Keefe GAD, Borchert M, Lam LA, Puliafito CA, Olmos de Koo LC.

AIM: To evaluate whether people with age-related macular degeneration (AMD) and a history of amblyopia have equal severity of AMD in both eyes.

METHODS: Billing records were used to locate all people with a history of amblyopia and AMD evaluated between 1 January 2003 and 1 June 2015 at a single ophthalmology institute. Two ophthalmic graders blinded to amblyopia status determined the severity of AMD in each eye using fundus photos and a validated grading scale.

RESULTS: A total of 14 people were found to have AMD and a documented history of amblyopia. Average patient age was 77.0 years and average best corrected visual acuity was 20/160 in eyes with a history of amblyopia and 20/40 in fellow eyes without amblyopia. Eyes with a history of amblyopia were found to have a lower AMD severity score (mean lower score: -1.38; paired t-test P=0.019). Of the 11 people with asymmetric disease severity, 10 individuals had worse AMD in the non-amblyopic eye while one person had worse AMD in the amblyopic eye (P=0.0067).

CONCLUSIONS: Our pilot study suggests that eyes with a history of amblyopia may manifest decreased severity of AMD compared with non-amblyopic eyes in the same patient. Further research is warranted to investigate this clinical observation.

PMID: 29437581


Association of Retinal Vascular Caliber and 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 relationship between retinal vascular caliber and AMD in patients with AIDS.

METHODS: Participants enrolled in the Longitudinal Study of the Ocular Complications of AIDS had retinal photographs taken at enrollment. Retinal vascular caliber (central retinal artery equivalent [CRAE] and central retinal vein equivalent [CRVE]) and intermediate-stage AMD were determined from these retinal
photographs. Photographs were evaluated by graders at a centralized reading center, using the Age-Related Eye Disease Study grading system for AMD and semiautomated techniques for evaluating retinal vascular caliber.

RESULTS: Of the 1171 participants evaluated, 110 (9.4%) had AMD and 1061 (90.6%) did not. Compared with participants without AMD, participants with AMD had larger mean CRAEs (151 ± 16 μm versus 147 ± 16 μm; P = 0.009) and mean CRVEs (228 ± 24 μm versus 223 ± 25 μm; P = 0.02). The unadjusted differences were: CRAE, 4.3 μm (95% confidence interval [CI] 1.1-7.5; P = 0.009) and CRVE, 5.5 μm (95% CI 0.7-10.3; P = 0.02). After adjustment for age, race/ethnicity, sex, human immunodeficiency syndrome (HIV) transmission category, smoking, enrollment and nadir CD4+ T cells, and enrollment and maximum HIV load, the differences between patients with and without AMD were as follows: CRAE, 5.4 μm (95% CI 2.3-8.5; P = 0.001) and CRVE, 6.0 μm (95% CI 1.4-10.6; P = 0.01).

CONCLUSIONS: In patients with AIDS, AMD is associated with greater retinal arteriolar and venular calibers, suggesting a role for shared pathogenic mechanisms, such as persistent systemic inflammation.

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Genetics & gene therapy


Complete Transcriptome Profiling of Normal and Age-Related Macular Degeneration Eye Tissues Reveals Dysregulation of Anti-Sense Transcription.

Kim EJ, Grant GR, Bowman AS, Haider N, Gudiseva HV, Chavali VRM.

Abstract: Age-related macular degeneration (AMD) predominantly affects the retina and retinal pigment epithelium in the posterior eye. While there are numerous studies investigating the non-coding transcriptome of retina and RPE, few significant differences between AMD and normal tissues have been reported. Strand specific RNA sequencing of both peripheral retina (PR) and RPE-choroid-sclera (PRCS), in both AMD and matched normal controls were generated. The transcriptome analysis reveals a highly significant and consistent impact on anti-sense transcription as well as moderate changes in the regulation of non-coding (sense) RNA. Hundreds of genes that do not express anti-sense transcripts in normal PR and PRCS demonstrate significant anti-sense expression in AMD in all patient samples. Several pathways are highly enriched in the upregulated anti-sense transcripts-in particular the EIF2 signaling pathway. These results call for a deeper exploration into anti-sense and noncoding RNA regulation in AMD and their potential as therapeutic targets.

PMID: 29445097

Stem cells


Tissue engineering of retina and Bruch’s membrane: a review of cells, materials and processes.

Tan YSE, Shi PJ, Choo CJ, Laude A, Yeong WY.

Abstract: The biological, structural and functional configuration of Bruch's membrane (BM) is significantly relevant to age-related macular degeneration (AMD) and other chorioretinal diseases, and AMD is one of the leading causes of blindness in the elderly worldwide. The configuration may worsen along with the ageing of retinal pigment epithelium and BM that finally leads to AMD. Thus, the scaffold-based tissue-engineered retina provides an innovative alternative for retinal tissue repair. The cell and material
requirements for retinal repair are discussed including cell sheet engineering, decellularised membrane and tissue-engineered membranes. Further, the challenges and potential in realising a whole tissue model construct for retinal regeneration are highlighted herein. This review article provides a framework for future development of tissue-engineered retina as a preclinical model and possible treatments for AMD.

PMID: 29453223

J Vis Exp. 2018 Jan 22;(131).

Subretinal Transplantation of Human Embryonic Stem Cell Derived-retinal Pigment Epithelial Cells Into a Large-eyed Model of Geographic Atrophy.

Petrus-Reurer S, Bartuma H, Aronsson M, Westman S, Lanner F, Kvanta A.

Abstract: Geographic atrophy (GA), the late stage of dry age-related macular degeneration is characterized by loss of the retinal pigment epithelial (RPE) layer, which leads to subsequent degeneration of vital retinal structures (e.g., photoreceptors) causing severe vision impairment. Similarly, RPE-loss and decrease in visual acuity is seen in long-term follow up of patients with advanced wet age-related macular degeneration (AMD) receiving intravitreal anti-vascular endothelial growth factor (VEGF) treatment. Therefore, on the one hand, it is fundamental to efficiently derive RPE cells from an unlimited source that could serve as replacement therapy. On the other hand, it is important to assess the behavior and integration of the derived cells in a model of the disease entailing surgical and imaging methods as close as possible to those applied in humans. Here, we provide a detailed protocol based on our previous publications that describes the generation of a preclinical model of GA using the albino rabbit eye, for evaluation of the human embryonic stem cell derived retinal pigment epithelial cells (hESC-RPE) in a clinically relevant setting. Differentiated hESC-RPE are transplanted into naive eyes or eyes with NaIO3-induced GA-like retinal degeneration using a 25 G transvitreal pars plana technique. Evaluation of degenerated and transplanted areas is performed by multimodal high-resolution non-invasive real-time imaging.

PMID: 29443034


Subretinal Human Umbilical Tissue-Derived Cell Transplantation Preserves Retinal Synaptic Connectivity and Attenuates Müller Glial Reactivity.


Abstract: Human umbilical tissue-derived cells (hUTC or palucorcel) are currently under clinical investigation for the treatment of geographic atrophy, a late stage of macular degeneration, but how hUTC transplantation mediates vision recovery is not fully elucidated. Subretinal administration of hUTC preserves visual function in the Royal College of Surgeons (RCS) rat, a genetic model of retinal degeneration caused by Mertk loss-of-function. hUTC secrete synaptogenic and neurotrophic factors that improve the health and connectivity of the neural retina. Therefore, we investigated the progression of synapse and photoreceptor loss and whether hUTC treatment preserves photoreceptors and synaptic connectivity in the RCS rats of both sexes. We found that RCS retinas display significant deficits in synaptic development already by postnatal day 21 (P21), prior to the onset of photoreceptor degeneration. Subretinal transplantation of hUTC at P21 is necessary to rescue visual function in RCS rats, and the therapeutic effect is enhanced with repeated injections. Synaptic development defects occurred concurrently with morphological changes in Müller glia, the major perisynaptic glia in the retina. hUTC transplantation strongly diminished Müller glia reactivity and specifically protected the α2δ-1-containing retinal synapses, which are responsive to Thrombospondin (TSP) family synaptogenic proteins secreted by Müller glia. Müller glial reactivity and reduced synaptogenesis observed in RCS retinas could be
recapitulated by CRISPR/Cas9-mediated loss-of-Mertk in Müller glia in wildtype rats. Taken together, our results show that hUTC-transplantation supports the health of retina at least in part by preserving the functions of Müller glial cells, revealing a previously unknown aspect of hUTC transplantation-based therapy.

SIGNIFICANCE STATEMENT: Despite the promising effects observed in clinical trials and preclinical studies, how subretinal hUTC transplantation mediates vision improvements is not fully known. Using a rat model of retinal degeneration, the RCS rat (lacking Mertk), here we provide evidence that hUTC transplantation protects visual function and health by protecting photoreceptors and preserving retinal synaptic connectivity. Furthermore, we find that loss of Mertk function only in Müller glia is sufficient to impair synaptic development and cause activation of Müller glia. hUTC transplantation strongly attenuates the reactivity of Müller glia in RCS rats. These findings highlight novel cellular and molecular mechanisms within the neural retina which underlie disease mechanisms and pinpoint Müller glia as a novel cellular target for hUTC transplantation.

PMID: 29431645

Diet, lifestyle & low vision

Gut Microbes. 2018 Feb 12:0. [Epub ahead of print]

Gut microbiota modify risk for dietary glycemia-induced age-related macular degeneration.

Rowan S, Taylor A.

Abstract: Age-related macular degeneration (AMD) is a leading cause of blindness world-wide. Although the etiology of AMD is multifactorial, diet and nutrition have strong epidemiologic associations with disease onset and progression. Recent studies indicate a role for gut microbiota in development of AMD in mouse models and in some forms of human AMD. We previously found that consuming lower glycemia diets is associated with protection against AMD in humans and switching from higher to lower glycemia diets arrests AMD phenotypes in mice. Gut microbiota populations and circulating microbial cometabolites were altered in response to dietary carbohydrates, indicating a gut-retina axis. Here we explore additional gut microbiota-AMD interactions that point toward pathogenic roles for some gut microbiota families, including Ruminococcaceae and Lachnospiraceae, and individual members of Turicibacteraceae, Clostridiaceae, and Mogibacteriaceae. We also speculate on potential mechanisms by which gut microbiota influence AMD, with the objective of devising new AMD diagnoses and treatments.

PMID: 29431583