Drug treatment

Ophthalmology. 2017 May 24. [Epub ahead of print]

Brolucizumab Versus Aflibercept in Participants with Neovascular Age-Related Macular Degeneration: A Randomized Trial.


PURPOSE: To compare the efficacy and safety of brolucizumab with aflibercept to treat neovascular age-related macular degeneration (AMD).

DESIGN: Prospective, randomized, double-masked, multicenter, 2-arm, phase 2 study.

PARTICIPANTS: Eighty-nine treatment-naïve participants, aged ≥50 years, with active choroidal neovascularization secondary to AMD.

METHODS: Eligible participants were randomized 1:1 to intravitreal brolucizumab (6 mg/50 μl) or aflibercept (2 mg/50 μl). Both groups received 3 monthly loading doses and were then treated every 8 weeks (q8) with assessment up to week 40. In the brolucizumab group, the final q8 cycle was extended to enable 2 cycles of treatment every 12 weeks (q12; to week 56); participants on aflibercept continued on q8. Unscheduled treatments were allowed at the investigator's discretion.

MAIN OUTCOME MEASURES: The primary and secondary hypotheses were noninferiority (margin: 5 letters at a 1-sided alpha level 0.1) in best-corrected visual acuity (BCVA) change from baseline of brolucizumab versus aflibercept at weeks 12 and 16, respectively. BCVA, central subfield thickness (CSFT), and morphologic features were assessed throughout the study.

RESULTS: The mean BCVA change from baseline (letters) with brolucizumab was noninferior to aflibercept at week 12 (5.75 and 6.89, respectively [80% confidence interval for treatment difference, -4.19 to 1.93]) and week 16 (6.04 and 6.62 [-3.72 to 2.56]), with no notable differences up to week 40. Outcomes exploring disease activity during the q8 treatment cycles suggest greater stability of the brolucizumab participants, supported by receipt of fewer unscheduled treatments versus aflibercept (6 vs. 15) and more stable CSFT reductions. In addition, from post hoc analysis, a greater proportion of brolucizumab-treated eyes had resolved intraretinal and subretinal fluid compared with aflibercept-treated eyes. Approximately 50% of brolucizumab-treated eyes had stable BCVA during the q12 cycles. Brolucizumab and aflibercept adverse events were comparable.

CONCLUSIONS: During the matched q8 phase, the BCVA in brolucizumab-treated eyes appeared comparable to aflibercept-treated eyes, with more stable CSFT reductions, receipt of fewer unscheduled treatments, and higher rates of fluid resolution. The brolucizumab safety profile was similar to aflibercept over 56 weeks of treatment. A 12-week treatment cycle for brolucizumab may be viable in a relevant proportion of eyes.

PMID: 28551167
Klin Monbl Augenheilkd. 2017 Jun 2. [Epub ahead of print]

[Results of Re-switch from Intravitreal Aflibercept to Ranibizumab in Patients with Exudative Age-related Macular Degeneration]. [Article in German]

Waibel S, Matthé E, Sandner D.

Background: The purpose of this study was to investigate the effectiveness of re-switch from intravitreal aflibercept to ranibizumab in patients with exudative age-related macular degeneration.

Materials and Methods: This retrospective case series included 17 eyes of 17 patients who had previously switched from ranibizumab to aflibercept and finally back to ranibizumab. Main outcomes were change of visual acuity (VA) and assessment of central macular thickness (CMT). Secondary outcomes included predictive factors which had a beneficial effect as VA and CMT before re-switch, number of previous injections and gender.

Results: The mean VA was 0.64 ± 0.36 logMAR before the switch, and 0.87 ± 0.40 logMAR before the re-switch, and gained with a slight but not significantly improvement up to 0.85 ± 0.58 logMAR after the re-switch (p = 0.896). The average CMT before the switch was 448.6 µm ± 181.5. This decreased to 343.8 µm ± 161.3 after the switch (p = 0.614) to 299.1 µm ± 155.8 at switchback (p = 0.133). Overall, 8 patients (47%) had an improvement of vision, whereas in 5 patients (30%) VA deteriorated. Further analysis of predictive factors revealed a mean improvement of VA in male patients after re-switch, while female patients lost VA, with statistical significance between after the switch and after the re-switch to the benefit of male patients (p = 0.016).

Conclusions: A re-switch from aflibercept to ranibizumab may enable improvement in morphological parameters and stabilization of VA in patients with exudative age-related macular degeneration who achieved no more benefit from the initial switch.

PMID: 28575913

Retina. 2016 Oct 25. [Epub ahead of print]

EFFECT OF INTRAVITREAL RANIBIZUMAB ON GANGLION CELL COMPLEX AND PERIPAPILLARY RETINAL NERVE FIBER LAYER IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION USING SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Zucchiatti I, Cicinelli MV, Parodi MB, Pierro L, Gagliardi M, Accardo A, Bandello F.

PURPOSE: To analyze the changes in ganglion cell complex and peripapillary retinal nerve fiber layer thickness, in central macular thickness and choroidal thickness on spectral domain optical coherence tomography in patients with neovascular age-related macular degeneration treated with intravitreal ranibizumab injections.

METHODS: All consecutive patients with untreated neovascular age-related macular degeneration received loading phase of three monthly intravitreal ranibizumab, followed by retreatments on a pro re nata protocol for 12 months.

PRIMARY OUTCOME: changes in ganglion cell complex and retinal nerve fiber layer at the end of follow-up. Secondary outcome: changes in best-corrected visual acuity, central macular thickness, and choroidal thickness at the end of follow-up. Choroidal thickness was measured at 500 µm, 1000 µm, and 1,500 µm intervals nasally, temporally, superiorly, and inferiorly to the fovea, respectively, on horizontal and vertical line scans centered on the fovea.

RESULTS: Twenty-four eyes were included. Ganglion cell complex and peripapillary retinal nerve fiber layer thickness did not show statistically significant changes through 12 months (55.6 ± 18.5 and 81.9 ± 9.9 µm at baseline, 52.7 ± 19.3 and 84.6 ± 15.5 µm at month 12, P > 0.05). Central macular thickness showed progressive decrease from baseline to month 12, with maximum reduction at month 3 (P < 0.001).
Statistically significant reduction in choroidal thickness was registered in the nasal 500, 1000, and 1,500 μm from the fovea, corresponding to the papillomacular region (from 169.6 ± 45.3 to 153.9 ± 46.9, P < 0.001).

CONCLUSION: Intravitreal ranibizumab injections did not affect retinal nerve fiber layer and ganglion cell complex thickness in 1-year follow-up. Choroidal thickness in papillomacular area and central macular thickness was significantly reduced at the end of treatment. Further studies, with larger sample, longer follow-up, and greater number of injections, are warranted.

PMID: 28574419


Simultaneous dexamethasone intravitreal implant and anti-VEGF therapy for neovascular age-related macular degeneration resistant to anti-VEGF monotherapy.


PURPOSE: To evaluate the efficacy of a dexamethasone intravitreal implant in combination with intravitreal anti-VEGF agents for treatment resistant neovascular age-related macular degeneration (nvAMD).

METHODS: This study was designed as a single-center, retrospective interventional case series. Consecutive patients with treatment-resistant nvAMD underwent simultaneous combined injection of anti-VEGF agent and dexamethasone intravitreal implant. Eighteen patients with mean age of 81.5 years were included. Patients received average of 26.3 anti-VEGF injections before dual therapy, with mean follow up of 8.2 months after dual therapy.

RESULTS: Dual therapy produced a significant mean decrease in CFT (126.3 μm), compared to a mean increase of 29.9 μm when treated with anti-VEGF monotherapy (p=0.0017). Patients also had mean decrease in MCV of -0.85 mm3 with dual therapy compared with anti-VEGF monotherapy (p=0.0014). There was a moderate correlation between the number of prior anti-VEGF injections and the magnitude of anatomic response, suggesting that shorter disease duration may positively influence response to combined treatment. Although there was a slight trend towards improved mean visual acuity after dual therapy, these differences did not reach statistical significance. Nevertheless, with combination treatment, 33% of patients gained one or more lines of vision. Dual therapy resulted in a significantly lower number of required anti-VEGF injections (4.25 vs 5.33) and an increase of the anti-VEGF injection-free interval to 1.41 months from 1.12 months during the 6 months following dual therapy compared to the same interval before dual therapy. Dual therapy was well tolerated; two eyes developed mild IOP elevation effectively managed with topical therapy and one patient developed worsening cataract.

CONCLUSIONS: Combined treatment of anti-VEGF with the dexamethasone intravitreal implant is a viable alternative for treatment-resistant nvAMD, and may reduce treatment burden. Earlier treatment with dual therapy may be beneficial to maximize anatomic and visual outcomes in these patients.

PMID: 28553669 PMCID: PMC5444334


Real-Life Experience with Aflibercept and Ranibizumab in the Treatment of Newly Diagnosed Neovascular Age-Related Macular Degeneration over 24 Months.

Garweg JG, Gerhardt C, Kodjikian L, Pfister IB.

PURPOSE: Comparative data appertaining to the long-term effects of Aflibercept or Ranibizumab in newly diagnosed cases of neovascular age-related macular degeneration (nAMD) over follow-up periods exceeding 12 months in clinical routine are scarce.
METHODS: In this retrospective comparative analysis, a case series of patients with treatment-naïve nAMD and requiring anti-vascular endothelial growth factor (VEGF) therapy in a routine clinical setting were treated with either Aflibercept [Afl (n = 106)] or Ranibizumab [Ran (n = 47)]. During the drug-loading phase, 3 monthly injections were administered. Thereafter, a treat-and-extend protocol was pursued for a maximum of 24 months. Ran was administered predominantly in eyes with classical lesions; Afl was administered in all others. The primary outcome parameters included anatomical and functional stability after 24 months.

RESULTS: Patients were comparable regarding age, gender distribution, and lens status. Fewer patients presented with intraretinal fluid in the Afl than in the Ran group at diagnosis (46.2% vs. 67.4%; P = 0.02), but not after the drug-loading phase. After the drug-loading phase, visual acuity [-4.2 letters (Afl) vs. -4.5 letters (Ran); P = 0.78] and the central foveal thickness remained stable. Linked to the lesion type, the number of scheduled clinical visits during the course of 24 months was higher for the Ran- than for the Afl group [11.9 ± 4.7 visits (Ran) vs. 8.4 ± 3.1 visits (Afl); P = 0.0005]. However, the total number of injections was similar [10.5 ± 2.8 (Ran) vs. 11.7 ± 3.6 (Afl); P = 0.06].

CONCLUSIONS: Based on tailoring according to the lesion type in cases of nAMD, the anatomical and the functional outcomes of treatment with either Afl or Ran were comparable for a maximum of 2 years.

PMID: 28557667


Two-year functional and anatomical results after converting treatment resistant eyes with exudative age-related macular degeneration to aflibercept in accordance with a treat and extend protocol.

Jørstad ØK, Faber RT, Moe MC.

PURPOSE: To study the effects of converting to aflibercept in accordance with a treat and extend (T&E) strategy in eyes with treatment resistant exudative age-related macular degeneration (AMD).

METHODS: Two-year prospective study of eyes with exudative AMD and persistent macular fluid despite monthly treatment with ranibizumab or bevacizumab. Eyes were converted to 2.0 mg aflibercept in accordance with a T&E protocol.

RESULTS: Fifty eyes from 47 patients were included. At baseline, the mean central retinal thickness (CRT) was 273 μm and mean best-corrected visual acuity (BCVA) 0.25 logarithm of the minimal angle of resolution (logMAR). The mean number of aflibercept injections the first year was 9.2. After 1 year, there was a reduction in mean CRT to 228 μm (p < 0.001); 22 eyes (44%) had a dry macula; and the mean BCVA was 0.24 logMAR (p = 0.531). The mean number of aflibercept injections the second year was 8.0 (p = 0.013 compared to first year). After 2 years, 24 eyes (48%) received treatment more frequently than every eighth week. The mean CRT was 225 μm (p < 0.001 compared to baseline); 31 eyes (62%) had a dry macula; and mean BCVA was 0.32 logMAR (p = 0.005 compared to baseline). Five eyes did not complete 2 years of aflibercept treatment after failing to improve.

CONCLUSION: A majority of eyes showed improved anatomic outcomes. There was a small decrease in mean BCVA after the second year of treatment. About half of the eyes required treatment more frequently than the recommended aflibercept label of an 8-week interval.

PMID: 28556485

JAMA Ophthalmol. 2017 Jun 1. [Epub ahead of print]

Oral Tyrosine Kinase Inhibitor for Neovascular Age-Related Macular Degeneration: A Phase 1 Dose-Escalation Study.
Jackson TL, Boyer D, Brown DM, Chaudhry N, Elman M, Liang C, O'Shaughnessy D, Parsons EC, Patel S, Slakter JS, Rosenfeld PJ.

IMPORTANCE: An oral treatment for neovascular age-related macular degeneration would be less burdensome than repeated intravitreous injections. X-82 is an oral tyrosine kinase inhibitor active against vascular endothelial growth factor (VEGF) and platelet-derived growth factor.

OBJECTIVE: To undertake safety testing of oral X-82 administered for the treatment of neovascular AMD.

DESIGN, SETTING, AND PARTICIPANTS: Phase 1, open-label, uncontrolled, dose-escalation study at 5 US retinal clinics between November 2012 and March 2015 (Retina-Vitreous Associates Medical Group, Beverly Hills, California; Blanton Eye Institute, Houston Methodist Hospital, Retina Consultants of Houston, Houston, Texas; New England Retina Associates, Guilford, Connecticut; Elman Retina Group, Baltimore, Maryland; and Retina Research Institute of Texas, Abilene). Thirty-five participants with neovascular age-related macular degeneration, 7 of whom were treatment naive.

INTERVENTIONS: Participants received oral X-82 for 24 weeks at 50 mg alternate days (n = 3), 50 mg daily (n = 8), 100 mg alternate days (n = 4), 100 mg daily (n = 10), 200 mg daily (n = 7), and 300 mg daily (n = 3), with intravitreous anti-VEGF therapy using predefined retreatment criteria. Every 4 weeks, participants underwent best-corrected visual acuity measurement, fundus examination, and spectral-domain optical coherence tomography.

MAIN OUTCOMES AND MEASURES: The main outcome was adverse events. Other outcomes included visual acuity, central subfield retinal thickness, and number of anti-VEGF injections.

RESULTS: Of the 35 participants, the mean age was 76.8 years, 16 were men and 19 were women, and 33 were white and 2 were nonwhite. Of 25 participants (71%) who completed the 24 weeks of X-82 treatment, all except 1 maintained or improved their visual acuity (mean [SD], +3.8 [9.6] letters). Fifteen participants (60%) required no anti-VEGF injections (mean, 0.68). Mean [SD] central subfield thickness reduced by -50 [97] μm, with 8 participants (all receiving at least 100 mg daily) demonstrating sustained reductions despite no anti-VEGF injections. The most common adverse events attributed to X-82 were diarrhea (n = 6), nausea (n = 5), fatigue (n = 5), and transaminase elevation (n = 4). A dose relationship to the transaminase elevations was not identified; all normalized when X-82 was discontinued. All but 1 were asymptomatic. Ten participants withdrew consent or discontinued prematurely, 6 owing to adverse events attributed to X-82 including leg cramps (n = 2), elevated alanine aminotransferase (n = 2), diarrhea (n = 1), and nausea/anorexia (n = 1).

CONCLUSIONS AND RELEVANCE: X-82 can be associated with reversible, elevated liver enzymes; hence, liver function testing is needed to identify those unsuited to treatment. Although 17% of participants discontinued X-82 owing to AEs, those who completed the study had lower than expected anti-VEGF injection rates. Further studies appear justified, with a phase 2 randomized clinical study under way.

PMID: 28570723


Topical versus subconjunctival anti-vascular endothelial growth factor therapy (Bevacizumab, Ranibizumab and Aflibercept) for treatment of corneal neovascularization.

Al-Debasi T, Al-Bekairy A, Al-Katheri A, Al Harbi S, Mansour M.

Abstract: In order to evaluate the effect of topical and subconjunctival anti-vascular endothelial growth factor (anti-VEGF) therapy, Ranibizumab, Bevacizumab and Aflibercept as a therapy for corneal neovascularization (NV) treatment, the aim of this study was to review all data related to some of anti-VEGF as a promising therapies for corneal NV treatment. Corneal NV is a dangerous condition leading to a marked reduction in vision due to angiogenesis of abnormal vessels that block light. During the recent years, we have recognized new drug proliferation for corneal NV treatment. Recently, anti-VEGF therapies
are one of the most important drugs used for corneal NV treatment. Several growth factors are involved in angiogenesis. The most important growth factor in corneal angiogenesis is VEGF. VEGF can be considered as key mediators in corneal angiogenesis. It is upregulated during corneal NV. In fact, anti-VEGF therapies have shown efficacy in attenuation of corneal NV in both animal models and clinical trials. A promising therapeutic success has been achieved using antibodies directed against VEGF. Bevacizumab has demonstrated efficacy and efficiency in the treatment of different neo-vascular ocular diseases and it has partially reduced corneal NV through different routes of administrations: topical, subconjunctival, and intraocular application. A similar efficacy to bevacizumab profiles in the treatment of neo-vascular age-related macular degeneration was induced by ranibizumab. Moreover, at worse levels of initial visual acuity of diabetic macular edema, aflibercept was more effective at improving vision. Anti-VEGF agents (Bevacizumab, Ranibizumab and Aflibercept) seem to have a higher efficiency and efficacy for corneal NV treatment. Both subconjunctival therapy and topical therapy of bevacizumab prohibit corneal NV, while early treatment with subconjunctival administration of ranibizumab may successfully reduce corneal NV. Therefore, establishment of safe doses is highly important before these drugs can be involved in the clinical setting. Further investigations and studies are highly warranted to adjust the dose and route of administration for the antibodies directed against VEGF to be the key therapeutic agents in the corneal NV treatment.

PMID: 28559722 PMCID: PMC5436388

Ophthalmology. 2017 May 24. [Epub ahead of print]

Therapies for Macular Edema Associated with Branch Retinal Vein Occlusion: A Report by the American Academy of Ophthalmology.

Ehlers JP, Kim SJ, Yeh S, Thorne JE, Mruthyunjaya P, Schoenberger SD, Bakri SJ.

PURPOSE: To evaluate the available evidence on the ocular safety and efficacy of current therapeutic alternatives for the management of macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

METHODS: Literature searches were last conducted on January 31, 2017, in PubMed with no date restrictions and limited to articles published in English, and in the Cochrane Database without language limitations. The searches yielded 321 citations, of which 109 were reviewed in full text and 27 were deemed appropriate for inclusion in this assessment. The panel methodologist assigned ratings to the selected studies according to the level of evidence.

RESULTS: Level I evidence was identified in 10 articles that addressed anti-vascular endothelial growth factor (VEGF) pharmacotherapies for ME, including intravitreal bevacizumab (5), aflibercept (2), and ranibizumab (4). Level I evidence was identified in 6 studies that examined intravitreal corticosteroids, including triamcinolone (4) and the dexamethasone implant (2). Level I evidence also was available for the role of macular grid laser photocoagulation (7) and scatter peripheral laser surgery (1). The inclusion of level II and level III studies was limited given the preponderance of level I studies. The number of studies on combination therapy is limited.

CONCLUSIONS: Current level I evidence suggests that intravitreal pharmacotherapy with anti-VEGF agents is effective and safe for ME secondary to BRVO. Prolonged delay in treatment is associated with less improvement in visual acuity (VA). Level I evidence also indicates that intravitreal corticosteroids are effective and safe for the management of ME associated with BRVO; however, corticosteroids are associated with increased potential ocular side effects (e.g., elevated intraocular pressure, cataracts). Laser photocoagulation remains a safe and effective therapy, but VA results lag behind the results for anti-VEGF therapies.

PMID: 28551163
CD36 gene is associated with intraocular pressure elevation after intravitreal application of anti-VEGF agents in patients with age-related macular degeneration: Implications for the safety of the therapy.


BACKGROUND: The wet form of age-related macular degeneration (AMD) is characterized by pathological vascularization of the outer retinal layers. The condition responds to treatment with antibodies against vascular endothelial growth factor (VEGF), but the patients receiving such anti-VEGF therapy sometimes show undesirable acute short-term increases in the intraocular pressure (IOP). The cause of this adverse effect is unknown, and here, we are testing a hypothesis that it is related to CD36 gene polymorphisms.

MATERIALS AND METHODS: A group of 134 patients with AMD were given three therapeutic doses of anti-VEGF antibody (ranibizumab) at monthly intervals. Their IOP was measured immediately before and 30 min after each injection. Patients’ DNA was analyzed, and the changes in IOP were matched against seven polymorphisms of the CD36 gene.

RESULTS: Three polymorphisms were found to be associated with increases in IOP: rs1049673 (p = 0.006), rs3211931 (p = 0.01), and rs1761667 (p = 0.043) at the time of the third injection only. Pronounced elevations (IOP > 25 mmHg) were associated with rs1049673 polymorphism: GC genotype (p < 0.01) and CC genotype (p < 0.05); both increasing the risk 2.6-fold, the presence of C-allele conferring a 1.5-fold greater risk and with rs3211931 polymorphism: AG genotype (p < 0.01) and GG genotype (p < 0.05); increasing the risk 2.6-fold (AG) and 2.7-fold (GG).

CONCLUSIONS: CD36 receptor may be involved in mediating the effects of VEGF on IOP. The findings will help to identify the patients at risk of acutely elevated IOP following the anti-VEGF therapy.

PMID: 28557591

JAMA Ophthalmol. 2017 Jun 1. [Epub ahead of print]

Tyrosine Kinase Inhibitors in Age-Related Macular Degeneration.

Apte RS.

PMID: 28570729


An Update on Intravitreal Aflibercept in Treating Macular Diseases.

Lai TYY.

PMID: 28558181

Other treatment & diagnosis

Retina. 2017 May 26. [Epub ahead of print]

IMPROVING THE AGE-RELATED MACULAR DEGENERATION CONSTRUCT: A New Classification System.

Spaide RF.
Abstract: Previous models of disease in age-related macular degeneration (AMD) were incomplete in that they did not encompass subretinal drusenoid deposits (pseudodrusen), subtypes of neovascularization, and polypoidal choroidal vasculopathy. In addition, Type 3 neovascularization starts in the retina and may not necessarily involve the choroid. As such, the term choroidal neovascularization is not appropriate for these eyes. The new aspects in the AMD construct are to include specific lipoprotein extracellular accumulations, namely drusen and subretinal drusenoid deposits, as early AMD. The deposition of specific types of deposit seems to be highly correlated with choroidal thickness and topographical location in the macula. Late AMD includes macular neovascularization or atrophy. The particular type of extracellular deposit is predictive of the future course of the patient. For example, eyes with subretinal drusenoid deposits have a propensity to develop outer retinal atrophy, complete outer retinal and retinal pigment epithelial atrophy, or Type 3 neovascularization as specific forms of late AMD. Given Type 3 neovascularization may never involve the choroid, the term macular neovascularization is suggested for the entire spectrum of neovascular disease in AMD. In contrast to older classification systems, the proposed system encompasses the relevant presentations of disease and more precisely predicts the future course of the patient. In doing so, the concept was developed that there may be genetic risk alleles, which are not necessarily the same alleles that influence disease expression.

PMID: 28557901


Evaluating ocular blood flow.

Maram J, Srinivas S, Sadda SR.

Abstract: Studies have shown that vascular impairment plays an important role in the etiology and pathogenesis of various ocular diseases including glaucoma, age-related macular degeneration, diabetic retinopathy, and retinal venous occlusive disease. Thus, qualitative and quantitative assessment of ocular blood flow (BF) is a topic of interest for early disease detection, diagnosis, and management. Owing to the rapid improvement in technology, there are several invasive and noninvasive techniques available for evaluating ocular BF, with each of these techniques having their own limitations and advantages. This article reviews these important techniques, with a particular focus on Doppler Fourier domain optical coherence tomography (OCT) and OCT-angiography.

PMID: 28573987


Nanoparticle-loaded biodegradable light-responsive in situ forming injectable implants for effective peptide delivery to the posterior segment of the eye.

Bisht R, Jaiswal JK, Rupenthal ID.

Abstract: Diseases affecting the posterior segment the eye, such as age-related macular degeneration (AMD), are the leading cause of blindness worldwide. Conventional dosage forms, such as eye drops, have to surmount several elimination mechanisms and complex barriers to achieve therapeutic concentrations at the target site often resulting in low anterior segment bioavailability (ca. 2-5%) with generally none of the drug reaching posterior segment tissues. Thus, frequent intravitreal injections are currently required to treat retinal conditions which have been associated with poor patient compliance due to pain, risk of infection, hemorrhages, retinal detachment and high treatment related costs. To partially overcome these issues, ocular implants have been developed for some posterior segment indications; however, the majority require surgical implantation and removal at the end of the intended treatment period. The transparent nature of the cornea and lens render light-responsive systems an attractive strategy for the management of diseases affecting the back of the eye. Light-responsive in situ forming injectable implants (ISFIs) offer various benefits such as ease of application in a minimally invasive manner and more site specific control over drug
release. Moreover, the biodegradable nature of such implants avoids the need for surgical removal after release of the payload. Incorporating drug-loaded polymeric nanoparticles (NPs) into these implants may reduce the high initial burst release from the polymeric matrix and further sustain drug release thus avoiding the need for frequent injections as well as minimizing associated side effects. However, light-responsive systems for ophthalmic application are still in their early stages of development with limited reports on their safety and effectiveness. We hypothesize that the innovative design and properties of NP-containing light-responsive ISFIs can serve as a platform for effective management of ocular diseases requiring long term treatment.

PMID: 28571808


Ultra-widefield fundus autofluorescence in age-related macular degeneration.


BACKGROUND: Establish accuracy and reproducibility of subjective grading in ultra-widefield fundus autofluorescence (FAF) imaging in patients with age-related macular degeneration (AMD), and determine if an association exists between peripheral FAF abnormalities and AMD.

METHODS: This was a prospective, single-blinded case-control study. Patients were consecutively recruited for the study. Patients were excluded if there was a history of prior or active ocular pathology other than AMD or image quality was insufficient for analysis as determined by two independent graders. Control patients were those without any evidence of AMD or other ophthalmic disease apart from cataract. Using the Optos 200Tx (Optos, Marlborough, MA, USA), a ResMax central macula and an ultra-widefield peripheral retina image was taken for each eye in both normal color and short wavelength FAF. Ultra-widefield photographs were modified to mask the macula. Each ResMax and ultra-widefield image was independently graded by two blinded investigators.

RESULTS: There were 28 AMD patients and 11 controls. There was a significant difference in the average age between AMD patients and control groups (80 versus 64, respectively P<0.001). There was moderate, statistically significant agreement between observers regarding image interpretation (78.4%, K = 0.524, P<0.001), and 69.0% (K = 0.49, P<0.001) agreement between graders for FAF abnormality patterns. Patients with AMD were at greater risk for peripheral FAF abnormalities (OR: 3.43, P = 0.019) and patients with FAF abnormalities on central macular ResMax images were at greater risk of peripheral FAF findings (OR: 5.19, P = 0.017).

CONCLUSION: Subjective interpretation of FAF images has moderate reproducibility and validity in assessment of peripheral FAF abnormalities. Peripheral FAF abnormalities are seen in both AMD and control patients. Those with AMD, poor visual acuity, and macular FAF abnormalities are at greater risk.

PMID: 28570556


Associations Between β-Peripapillary Atrophy and Reticular Pseudodrusen in Early Age-Related Macular Degeneration.

Garg A, Blumberg DM, Al-Aswad LA, Oll M, Yzer S, Forbes M, Allikmets RL, Bearelly S.

PURPOSE: Choroidal thinning has been associated with reticular pseudodrusen (RPD) and β-peripapillary atrophy (β-PPA), which have been linked to normal-tension glaucoma (NTG). This analysis sought to determine whether RPD are independently associated with β-PPA in early AMD patients. Secondary outcomes included the association of RPD and preexisting diagnosis of glaucoma, cup-to-disc ratio (CDR), subfoveal choroidal thickness (SFCT), and IOP.
METHODS: This prospective cross-sectional study examined 78 age- and sex-matched early AMD patients: 43 RPD patients (63 eyes) and 35 non-RPD patients (64 eyes). Exclusion criteria included advanced AMD, high myopia, and vitreoretinal conditions/surgery. RPD and non-RPD groups were identified by confocal scanning laser ophthalmoscopy. β-PPA as well as CDR were graded on digital, nonstereoscopic fundus photos. SFCT was measured on spectral-domain optical coherence tomography for 69 patients (35 RPD and 34 non-RPD). IOP and glaucoma diagnosis were extracted from charts.

RESULTS: β-PPA had a greater prevalence in RPD than non-RPD (44% vs. 19%, P = 0.002); however, this relationship was not significant when SFCT was added to the model (P = 0.150). A preexisting diagnosis of glaucoma (P = 0.156), CDR (P = 0.176), and IOP (P = 0.98) was not different between groups.

CONCLUSIONS: RPD in early AMD are associated with presence of β-PPA, but choroidal thickness is a confounder in this relationship. Because β-PPA is a common finding in NTG, focusing on a potential shared pathway between RPD and NTG could improve the understanding of pathophysiology and expand therapies for each condition.

PMID: 28564702 PMCID: PMC5455172


Ten-Year Follow-Up after Bilateral Submacular Neovascular Membrane Removal in a Case of Autosomal Recessive Bestrophinopathy.

Moreira CA Jr, Moreira-Neto CA, Junqueira Nobrega M, Cunha de Souza E.

Abstract: Herein, we report the case of an 8-year-old girl who presented in December 2000 with a submacular neovascular membrane in the right eye, with a clinical diagnosis of Best disease. At that time, she underwent pars plana vitrectomy (PPV) with removal of the subretinal choroidal neovascularization (CNV). Her vision improved from 20/200 to 20/25. Four years later, a new CNV developed in the other eye. Initially, she underwent unsuccessful photodynamic therapy. As her vision worsened, she underwent a second, this time successful, PPV with membrane removal in the left eye, with vision improving to 20/30. Ten years later, she returned complaining of vision loss over the last year. Her vision was 20/200 OU, and optical coherence tomography demonstrated very large intraretinal cystoid spaces resembling bilateral macular schisis. Four ranibizumab injections as well as dorzolamide eye drops were tried, both without success. Finally, she underwent PPV with internal limiting membrane peeling and gas-fluid exchange in the left eye. One month later, the macula appeared flat and vision had improved to 20/60. The same procedure was performed 1 year later for the right eye, with vision improving to 20/80. One year later, mild cystic spaces developed again in both eyes, although much smaller than previously observed. Her vision remained stable.

PMID: 28559838 PMCID: PMC5437425


Esmaeili M, Dehnavi AM, Rabbani H, Hajizadeh F.

Abstract: The process of interpretation of high-speed optical coherence tomography (OCT) images is restricted due to the large speckle noise. To address this problem, this paper proposes a new method using two-dimensional (2D) curvelet-based K-SVD algorithm for speckle noise reduction and contrast enhancement of intra-retinal layers of 2D spectral-domain OCT images. For this purpose, we take curvelet transform of the noisy image. In the next step, noisy sub-bands of different scales and rotations are separately thresholded with an adaptive data-driven thresholding method, then, each thresholded sub-band is denoised based on K-SVD dictionary learning with a variable size initial dictionary dependent on the size
of curvelet coefficients' matrix in each sub-band. We also modify each coefficient matrix to enhance intra-retinal layers, with noise suppression at the same time. We demonstrate the ability of the proposed algorithm in speckle noise reduction of 100 publically available OCT B-scans with and without non-neovascular age-related macular degeneration (AMD), and improvement of contrast-to-noise ratio from 1.27 to 5.12 and mean-to-standard deviation ratio from 3.20 to 14.41 are obtained.

PMID: 28553581 PMCID: PMC5437767


Targeted Delivery of FLT-Morpholino Using Cyclic RGD Peptide.


PURPOSE: We previously showed that intravitreal injection of the sFLT morpholino-oligomer (FLT-MO) suppresses laser-induced choroidal neovascularization (CNV) in mice by decreasing the membrane bound form of Flt-1 while increasing the soluble form of Flt-1 via alternative splicing shift. In this study, we examined whether cyclic RGD peptide (cRGD) can promote morpholino-oligomer accumulation in CNV following tail vein injection, and whether systemic cRGD conjugated FLT-MO (cRGD-FLT-MO) suppresses CNV growth.

METHODS: cRGD conjugated fluorescent morpholino-oligomer (cRGD-F-MO) was injected via tail vein into mice with previous retinal laser photocoagulation and examined for cRGD-F-MO accumulation in CNV. To examine whether cRGD-FLT-MO suppresses CNV growth, mice were tail-vein injected with cRGD-FLT-MO, cRGD conjugated standard morpholino-oligomer (cRGD-STD-MO), or Dulbecco's Phosphate-Buffered Saline (DPBS) 1 and 4 days postlaser photocoagulation. Seven days postlaser photocoagulation, eyes were harvested and laser CNV was stained with isolectin GS-IB4, allowing quantification of CNV size by confocal microscopy.

RESULTS: cRGD-F-MO accumulation in CNV commenced immediately after tail vein injection and could be observed even 1 day after injection. cRGD-FLT-MO tail vein injection significantly suppressed CNV size (2.7 × 105 ± 0.3 × 105 μm3, P < 0.05 by Student's t-test) compared with controls (DPBS: 5.1 × 105 ± 0.6 × 105 μm3 and cRGD-STD-MO: 5.5 × 105 ± 0.8 × 105 μm3).

CONCLUSIONS: cRGD peptide facilitates morpholino-oligomer accumulation in CNV following systemic delivery. cRGD-FLT-MO suppressed CNV growth after tail-vein injection, demonstrating the potential utility of cRGD peptide for morpholino-oligomer delivery to CNV.

TRANSLATIONAL RELEVANCE:

Current therapy for neovascular age-related macular degeneration involves intravitreal injection of anti-vascular endothelial growth factor drugs. Our results indicate that CNV can be treated systemically, thus eliminating risks and hazards associated with intravitreal injection.

PMID: 28553563 PMCID: PMC5444505


Antiangiogenic activity of PLGA-Lupeol implants for potential intravitreal applications.

Soares DCF, de Paula Oliveira DC, Barcelos LS, Barbosa AS, Vieira LC, Townsend DM, Rubello D, de Barros ALB, Duarte LP, Silva-Cunha A.

Abstract: Uncontrolled angiogenesis is directly associated with ocular diseases such as macular degeneration and diabetic retinopathy. Implantable polymeric drug delivery systems have been proposed
for intravitreal applications and in the present work, we evaluated the antiangiogenic potential of PLGA ocular implants loaded with the triterpene lupeol using in vitro and in vivo models. The drug/polymer physiochemical properties of the lupeol-loaded PLGA were validated as functionally similar using differential scanning calorimetry, Fourier transform infrared spectroscopy, and scanning electron microscopy. Interestingly, in an in vitro culture system, lupeol (100\(\mu\)g/mL and 250\(\mu\)g/mL) was capable to inhibited the proliferation as well as the migration of Human Umbilical Vein Endothelial Cells (HUVEC), without interfering in cell viability, promoting a significant reduction in the percentage of vessels (39.41% and 44.12%, respectively), compared with the control group. In vivo test, by using the chorioallantoic membrane (CAM) model, lupeol-loaded PLGA ocular implants showed antiangiogenic activity comparable to the FDA-approved anti-VEGF antibody Bevacizumab. Overall, our results suggest lupeol-loaded PLGA ocular implants were able to inhibit the angiogenic process by impairing both proliferation and migration of endothelial cells.

PMID: 28558353


[PHACOEMULSIFICATION IN EYES WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION (AMD)]. [Article in Hebrew]

Rappoport D, Goldberg M, Bukelman A, Katz H, Goldberg L, Pollack A.

INTRODUCTION: Age-related macular degeneration (AMD) is the leading cause of blindness in the western world. The debate continues over the safety of cataract surgery in the setting of neovascular (wet) AMD. This retrospective review aims to describe our experience in treating patients with wet AMD, who underwent cataract surgery by phacoemulsification.

METHODS: We prepared a retrospective chart review of patients treated in our clinic between the years 2006 - 2013.

RESULTS: Forty-two eyes of 38 patients were included. Visual acuity (VA) improved significantly 1 month after cataract removal, without a significant change in retinal thickness. Twenty-six patients (62%) needed anti-VEGF injections during follow-up after surgery within an average period of 6 months. In eyes that were dry preoperatively, the re-injection rate was lower than those that were still wet (56 % vs. 80%) and the time from surgery to the first injection was longer in dry eyes (7 months and 3 months, respectively). Eyes that were injected with anti-VEGF up to one week before surgery had greater improvement in VA immediately after surgery but the proportion of those receiving injections (78%) was greater and the time to first injection post-surgery was earlier (3 months) compared to eyes that received the last injection 6 months or more prior to surgery ( 53 % and - 7 months).

CONCLUSIONS: Cataract removal improves vision in wet AMD patients. It is of great importance to treat these patients and try to reach dry retina prior to surgery and a close followup is needed after surgery. In eyes that were more stable within 6 months before surgery and their retina was dry, the re-injection rate post surgery was lower and the time to first injection was longer.

PMID: 28551897


In Vivo Efficacy of an Injectable Microsphere-Hydrogel Ocular Drug Delivery System.


PURPOSE: Demonstrate in vivo that controlled and extended release of a low dose of anti-vascular endothelial growth factor (anti-VEGF) from a microsphere-hydrogel drug delivery system (DDS) has a therapeutic effect in a laser-induced rat model of choroidal neovascularization (CNV).
METHODS: Anti-VEGF (ranibizumab or aflibercept) was loaded into poly(lactic-co-glycolic acid) microspheres that were then suspended within an injectable poly(N-isopropylacrylamide)-based thermo-responsive hydrogel DDS. The DDS was shown previously to release bioactive anti-VEGF for ~200 days. CNV was induced using an Ar-green laser. The four experimental groups were as follows: (i) non-treated, (ii) drug-free DDS, (iii) anti-VEGF-loaded DDS, and (iv) bolus injection of anti-VEGF. CNV lesion areas were measured based on fluorescein angiograms and quantified using a multi-Otsu thresholding technique. Intraocular pressure (IOP) and dark-adapted electroretinogram (ERG) were also obtained pre- and post-treatment (1, 2, 4, 8, and 12 weeks).

RESULTS: The anti-VEGF-loaded DDS group had significantly smaller (60%) CNV lesion areas than non-treated animals throughout the study. A small transient increase in IOP was seen immediately after injection; however, all IOP measurements at all time points were within the normal range. There were no significant changes in ERG maximal response compared to pre-treatment measurements for the drug-loaded DDS, which suggests no adverse effects on retinal cellular function.

CONCLUSIONS: The current study demonstrates that the DDS can effectively decrease laser-induced CNV lesions in a murine model. Controlled and extended release from our DDS achieved greater treatment efficacy using an order of magnitude less drug than what is required with bolus administration. This suggests that our DDS may provide a significant advantage in the treatment of posterior segment eye diseases.

PMID: 28557571

Adv Healthc Mater. 2017 May 29. [Epub ahead of print]
Wet-AMD on a Chip: Modeling Outer Blood-Retinal Barrier In Vitro.
Chung M, Lee S, Lee BJ, Son K, Jeon NL, Kim JH.

Abstract: Choroidal neovascularization (CNV) in the retinal pigment epithelium (RPE)-choroid complex constituting outer blood retinal barrier (oBRB) is a critical pathological step in various ophthalmic diseases, which results in blindness, such as wet type age-related macula degeneration. Current in vitro experimental models using petri dishes or transwell are unable to study CNV morphogenesis. Here, a unique organotypic eye-on-a-chip model is described that mimics the RPE-choroid complex in vitro. This model consists of an RPE monolayer and adjacent perfusable blood vessel network, which is supporting barrier function of oBRB. The intact barrier function of the RPE-choroid complex is reconstituted while maintaining important structural features. Further, this model can successfully mimic the pathogenesis of CNV especially in terms of morphogenesis, which is penetrating angiogenic sprouts from pre-existing choroidal vessels that result in breakdown of RPE monolayer. The alleviation of the pathological angiogenesis can be modeled with bevacizumab, a clinical drug for CNV treatment. It is believed that this model can be used to aid in the development of advanced in vitro eye drug evaluation in conjunction with animal models.

PMID: 28557377

Pathogenesis

Methods Mol Biol. 2017 May 31. [Epub ahead of print]
Immunohistochemical Detection of Sphingosine-1-Phosphate and Sphingosine Kinase-1 in Human Tissue Samples and Cell Lines.
Reynolds GM, Visentin B, Sabbadini R.

Abstract: Sphingosine-1-phosphate (S1P) and the enzyme primarily responsible for its production, sphingosine kinase-1 (SphK-1), are dysregulated in multiple human diseases including cancer, multiple sclerosis (MS), diabetes, neurological diseases, fibrosis, and certain pathologies associated with impaired
angiogenesis such as age-related macular degeneration (AMD). Antibody-based techniques to identify and localize S1P and SphK-1 within cells and tissue specimens represent a powerful tool, not only to understand biological role of these molecules but also to validate these unique in-class targets in multiple state diseases. Consequently, the potential applications of these molecules for therapy and diagnostic purposes are currently under investigation. Here, we describe a new improved technique, Agitated Low Temperature Epitope Retrieval (ALTER) for staining procedures, to identify expression of S1P and SphK-1 in human frozen tissue samples. The challenges encountered in the process of localization in tissue samples of lipid molecules such as S1P are discussed.

PMID: 28560513


["Protein of senility" CCL11, "protein of juvenility" GDF11 and their role in age-related pathology]. [Article in Russian]

Khavinson VK, Kuznik BI, Ryzhak GA, Linkova NS, Kozina LS, Sall TS.

Abstract: The paper presents the latest literature data on the structure and functions of «protein of juvenility» - CCL11 and «protein of senility» - GDF11. Chemokine CCL11 injected to young animals has been shown to lead to degenerative changes in the central nervous system (CNS), disturb cognitive functions and impede tissue regeneration. CCL11 concentration increases dramatically in schizophrenia, Alzheimer's disease, neuro-inflammatory disorders, cerebral malaria, drug addiction, as well as in atherosclerosis, periodontal disease, macular degeneration, cancer and other pathologies. In contrast to CCL11, differentiation growth factor 11 (GDF11), being administered to old mice, eliminates age-associated hypertrophy of the heart, improves muscle tone and prevents degenerative changes in the CNS, improves cognitive functions and enhances tissue regeneration. Its concentration decreases in cardiovascular disease, osteoporosis, and other «diseases of old age». At the same time, the higher the GDF11 level in the blood, the milder myocardial infarction, stroke and other age-related diseases of the cardiovascular system.

PMID: 28556640


The inhibition of NOTCH2 reduces UVB-induced damage in retinal pigment epithelium cells.


Abstract: Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly. The pathogenesis of dry AMD remains indistinct and the mechanism of retinal pigment epithelium (RPE) cells death in dry AMD is controversial. The aim of the present study was to investigate the functions of Notch signaling in ultraviolet B (UVB)-induced damage of RPE cells. It was identified that, in RPE cells, UVB increased intracellular reactive oxygen species (ROS) and induced cell apoptosis. In addition, UVB activated Notch signaling in a dose dependent manner. Surprisingly, NOTCH2, but not NOTCH1, was demonstrated to be the major Notch receptor in RPE cells. Under normal conditions, the inhibition of NOTCH2 reduced cell growth and cell migration, but had no impact on intracellular ROS and cell apoptosis. However, in the presence of UVB, the inhibition of NOTCH2, but not NOTCH1, attenuated intracellular ROS and cell apoptosis. The function of Notch signaling involved in UVB damage of RPE cells may not only be significant to understanding the pathogenesis of AMD (especially dry AMD), but also useful for designing effective therapeutic agents for dry AMD.

PMID: 28560393

The complexities underlying age-related macular degeneration: could amyloid beta play an important role?


Abstract: Age-related macular degeneration (AMD) causes irreversible loss of central vision for which there is no effective treatment. Incipient pathology is thought to occur in the retina for many years before AMD manifests from midlife onwards to affect a large proportion of the elderly. Although genetic as well as non-genetic/environmental risks are recognized, its complex aetiology makes it difficult to identify susceptibility, or indeed what type of AMD develops or how quickly it progresses in different individuals. Here we summarize the literature describing how the Alzheimer's-linked amyloid beta (Aβ) group of misfolding proteins accumulate in the retina. The discovery of this key driver of Alzheimer's disease in the senescent retina was unexpected and surprising, enabling an altogether different perspective of AMD. We argue that Aβ fundamentally differs from other substances which accumulate in the ageing retina, and discuss our latest findings from a mouse model in which physiological amounts of Aβ were subretinally-injected to recapitulate salient features of early AMD within a short period. Our discoveries as well as those of others suggest the pattern of Aβ accumulation and pathology in donor aged/AMD tissues are closely reproduced in mice, including late-stage AMD phenotypes, which makes them highly attractive to study dynamic aspects of Aβ-mediated retinopathy. Furthermore, we discuss our findings revealing how Aβ behaves at single-cell resolution, and consider the long-term implications for neuroretinal function. We propose Aβ as a key element in switching to a diseased retinal phenotype, which is now being used as a biomarker for late-stage AMD.

PMID: 28553324 PMCID: PMC5436342

Neurotherapeutics. 2017 May 30. [Epub ahead of print]

Tonabersat Prevents Inflammatory Damage in the Central Nervous System by Blocking Connexin43 Hemichannels.

Kim Y, Griffin JM, Nor MNM, Zhang J, Freestone PS, Danesh-Meyer HV, Rupenthal ID, Acosta M, Nicholson LFB, O'Carroll SJ, Green CR.

Abstract: The cis benzopyran compound tonabersat (SB-220453) has previously been reported to inhibit connexin26 expression in the brain by attenuating the p38-mitogen-activated protein kinase pathway. We show here that tonabersat directly inhibits connexin43 hemichannel opening. Connexin43 hemichannels have been called "pathological pores" based upon their role in secondary lesion spread, edema, inflammation, and neuronal loss following central nervous system injuries, as well as in chronic inflammatory disease. Both connexin43 hemichannels and pannexin channels released adenosine triphosphate (ATP) during ischemia in an in vitro ischemia model, but only connexin43 hemichannels contributed to ATP release during reperfusion. Tonabersat inhibited connexin43 hemichannel-mediated ATP release during both ischemia and reperfusion phases, with direct channel block confirmed using electrophysiology. Tonabersat also reduced connexin43 gap junction coupling in vitro, but only at higher concentrations, with junctional plaques internalized and degraded via the lysosomal pathway. Systemic delivery of tonabersat in a rat bright-light retinal damage model (a model for dry age-related macular degeneration) resulted in significantly improved functional outcomes assessed using electroretinography. Tonabersat also prevented thinning of the retina, especially the outer nuclear layer and choroid, assessed using optical coherence tomography. We conclude that tonabersat, already given orally to over 1000 humans in clinical trials (as a potential treatment for, and prophylactic treatment of, migraine because it was thought to inhibit cortical spreading depression), is a connexin hemichannel inhibitor and may have the potential to be a novel treatment of central nervous system injury and chronic neuroinflammatory disease.

PMID: 28560708
Genetics


Recent advances and future directions for the pharmacogenetic basis of anti-VEGF treatment response in neovascular age-related macular degeneration.

Riaz M, Baird PN.

PMID: 28553337 PMCID: PMC5436355

Ophthalmologica. 2017 May 31. [Epub ahead of print]

Genetic Polymorphisms and the Phenotypic Characterization of Individuals with Early Age-Related Macular Degeneration.

Oeverhaus M, Meyer Zu Westrup V, Dietzel M, Hense HW, Pauleikhoff D.

PURPOSE: While the importance of risk polymorphisms for the pathogenesis of age-related macular degeneration (AMD) is well established, their impact on morphological and functional phenotypes is largely unclear. We aimed to characterize individual phenotypes in patients who were either homozygous for a risk allele in the CFH gene, ARMS2 gene, or both as compared to non-carriers.

METHODS: Patients with early AMD (n = 85) were assessed during a follow-up examination of a prospective study (MARS) with multimodal diagnostics including SD-OCT and microperimetry.

RESULTS: Compared to non-carriers, OCT scans revealed lower retinal thickness in patients homozygous for CFH or ARMS2, which was caused by a significantly reduced photoreceptor layer. The number and ultrastructure of drusen were also significantly different.

CONCLUSIONS: These findings indicate that patients with risk alleles demonstrate distinct phenotypic differences of morphology and function as compared to non-carriers. In particular in the CFH group, a loss of photoreceptors occurred concomitantly with reduced retinal sensitivity. Further studies might help to better understand the pathophysiology.

PMID: 28558370

Stem cells


Stem cell-derived retinal pigment epithelium transplantation for treatment of retinal disease.

Nommiste B, Fynes K, Tovell VE, Ramsden C, da Cruz L, Coffey P.

Abstract: Age-related macular degeneration remains the most common cause of blindness in the western world, severely comprising patients' and carers' quality of life and presenting a great cost to the healthcare system. As the disease progresses, the retinal pigmented epithelium (RPE) layer at the back of the eye degenerates, contributing to a series of events resulting in visual impairment. The easy accessibility of the eye has allowed for in-depth study of disease progression in patients, while in vivo studies have facilitated investigations into healthy and diseased RPE. Consequently, a number of research groups are examining different approaches for the replacement of RPE cells in age-related macular degeneration (AMD) patients. This chapter examines some of these initial proof-of-principle studies and goes on to review the use of pluripotent stem cells as a source for RPE replacement in a number of current AMD clinical trials. Finally, we consider just some of the regulatory and manufacturing challenges presented in taking a promising AMD treatment from the research bench into clinical trials in patients, and how to mitigate potential risks.
early in process development.

PMID: 28554398

**Prog Brain Res. 2017;231:191-223. Epub 2017 Mar 21.**

**Pluripotent stem cells and their utility in treating photoreceptor degenerations.**

Aghaizu ND, Kruczek K, Gonzalez-Cordero A, Ali RR, Pearson RA.

Abstract: Age-related macular degeneration and inherited retinal degenerations represent the leading causes of blindness in industrialized countries. Despite different initiating causes, they share a common final pathophysiology, the loss of the light sensitive photoreceptors. Replacement by transplantation may offer a potential treatment strategy for both patient populations. The last decade has seen remarkable progress in our ability to generate retinal cell types, including photoreceptors, from a variety of murine and human pluripotent stem cell sources. Driven in large part by the requirement for renewable cell sources, stem cells have emerged not only as a promising source of replacement photoreceptors but also to provide in vitro systems with which to study retinal development and disease processes and to test therapeutic agents.

PMID: 28554397

**Diet, lifestyle & low vision**


**Neuroprotective effect of bilberry extract in a murine model of photo-stressed retina.**


Abstract: Excessive exposure to light promotes degenerative and blinding retinal diseases such as age-related macular degeneration and retinitis pigmentosa. However, the underlying mechanisms of photo-induced retinal degeneration are not fully understood, and a generalizable preventive intervention has not been proposed. Bilberry extract is an antioxidant-rich supplement that ameliorates ocular symptoms. However, its effects on photo-stressed retinas have not been clarified. In this study, we examined the neuroprotective effects of bilberry extract against photo-stress in murine retinas. Light-induced visual function impairment recorded by scotopic and photopic electroretinograms showing respective rod and cone photoreceptor function was attenuated by oral administration of bilberry extract through a stomach tube in Balb/c mice (750 mg/kg body weight). Bilberry extract also suppressed photo-induced apoptosis in the photoreceptor cell layer and shortening of the outer segments of rod and cone photoreceptors. Levels of photo-induced reactive oxygen species (ROS), oxidative and endoplasmic reticulum (ER) stress markers, as measured by real-time reverse transcriptase polymerase chain reaction, were reduced by bilberry extract treatment. Reduction of ROS by N-acetyl-L-cysteine, a well-known antioxidant also suppressed ER stress. Immunohistochemical analysis of activating transcription factor 4 expression showed the presence of ER stress in the retina, and at least in part, in Müller glial cells. The photo-induced disruption of tight junctions in the retinal pigment epithelium was also attenuated by bilberry extract, repressing an oxidative stress marker, although ER stress markers were not repressed. Our results suggest that bilberry extract attenuates photo-induced apoptosis and visual dysfunction most likely, and at least in part, through ROS reduction, and subsequent ER stress attenuation in the retina. This study can help understand the mechanisms of photo-stress and contribute to developing a new, potentially useful therapeutic approach using bilberry extract for preventing retinal photo-damage.

PMID: 28570634
Cutan Ocul Toxicol. 2017 May 29:1-27.[Epub ahead of print]

Lutein improves cell viability and reduces Alu RNA accumulation in hydrogen peroxide challenged retinal pigment epithelial cells.

Chong YS, Mai CW, Leong CO, Wong LC.

PURPOSE: Dysfunction of the microRNA (miRNA)-processing enzyme DICER1 and Alu RNA accumulation are linked to the pathogenesis of age-related macular degeneration (AMD). This study determined the optimal dose of lutein (LUT) and zeaxanthin (ZEA) to protect human retinal pigment epithelium (RPE) cells against hydrogen peroxide (H2O2). The effect of the optimal dose of LUT and ZEA as DICER1 and Alu RNA modulators in cultured human RPE cells challenged with H2O2 was investigated.

MATERIALS AND METHODS: ARPE-19 cells were pre-treated with LUT, ZEA or both for 24 hours before 200 µM H2O2 challenge. Cell viability was measured by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. DICER1 and Alu RNA were quantified by western blotting and real-time polymerase chain reaction, respectively.

RESULTS: H2O2 increased cell Alu RNA expression and decreased cell viability of ARPE-19, but had no significant impact on the DICER1 protein level. LUT, alone and in combination with ZEA pre-treatment, prior to H2O2 challenge significantly improved cell viability of ARPE-19 and reduced the level of Alu RNA compared to the negative control.

CONCLUSION: These results support the use of LUT alone, and in combination with ZEA, in AMD prevention and treatment. This study is also the first to report LUT modulating effects on Alu RNA.

PMID: 28554225

Disclaimer: This newsletter is provided as a free service to eye care professionals by the Macular Disease Foundation Australia. The Macular Disease Foundation cannot be liable for any error or omission in this publication and makes no warranty of any kind, either expressed or implied in relation to this publication.