Drug treatment

Eye (Lond). 2017 May 26. [Epub ahead of print]

Aflibercept in age-related macular degeneration: evaluating its role as a primary therapeutic option.

Ashraf M, Souka AAR.

Abstract: The recent VIEW studies have demonstrated the non-inferiority of monthly and bi-monthly aflibercept in the management of wet age related macular degeneration (AMD) compared with ranibizumab. However, the current data are limited mainly to fixed dosing regimens with few studies looking at flexible dosing regimens of aflibercept in wet AMD. In addition, recent data from the VIEW 96 week extension has shown that patients being shifted from fixed dosing regimens to PRN have shown a drop in visual acuity and increase in central macular thickness. This is an indication that fixed dosing, a non-sustainable option, is only effective as long as it is continued. Regimens such as treat and extend (TAE) and pro re nata (PRN) have been studied extensively in ranibizumab and bevacizumab and have shown to be effective options. With the presence of effective, established and less costly drugs such as ranibizumab and bevacizumab, the role of aflibercept as a primary treatment modality has yet to be clearly defined. The current review provides an analysis of the VIEW studies, as well as the extension phases. It also looks at post hoc analysis of predictors of response and outcomes. We have also conducted a search on studies comparing between PRN regimens using aflibercept and other anti-VEGF agents. This review also explores cheaper off label aflibercept; ziv-aflibercept in the treatment of wet AMD. The main purpose of the review is to delineate the role of aflibercept as a primary therapeutic option and if there are any significant advantages that would advocate its use over alternative anti-VEGF drugs. Finally, we propose a treatment algorithm for patients being started on aflibercept during the first year and thereafter.

PMID: 28548650


Switch to aflibercept or ranibizumab after initial treatment with bevacizumab in eyes with neovascular AMD.

Waizel M, Todorova MG, Masyk M, Wolf K, Rickmann A, Helaia K, Blanke BR, Szurman P.

BACKGROUND: To evaluate changes in central macular thickness (CMT) and visual outcome in patients with neovascular age-related macular degeneration (AMD) treated initially with bevacizumab and subsequently switched to either aflibercept or ranibizumab.
METHODS: Observational clinical study was performed. We measured the structural outcome (CMT on SD-OCT; μm) and the visual outcome (best corrected visual acuity (BCVA); logMAR), as follows: before treatment (at baseline), following bevacizumab treatment (switch follow-up) and after switching from bevacizumab to aflibercept- or ranibizumab treatment (final follow-up, AG/, RG).

RESULTS: From a total of 96 eyes treated with intravitreal injections of bevacizumab (10.5 ± 7.6 (mean ± SD)), 58 eyes switched to aflibercept (6.5 ± 3.9; AG) and 38 eyes switched to ranibizumab (7.1 ± 5.3; RG) (≥ 3 injections, each). In addition, these eyes were compared to 37 eyes under bevacizumab monotherapy.

PRIMARY OUTCOME: In the AG, the CMT decreased slightly from 430 ± 220 μm at baseline to 419 ± 212 μm at switch follow-up (p = 0.86), but decreased significantly to 318 ± 202 μm at final follow-up, AG (p < 0.0001). In the ranibizumab group (RG), the CMT increased from 396 ± 174 μm at baseline to 499 ± 333 μm at switch follow-up (p = 0.012), but decreased significantly to 394 ± 202 μm at final follow-up, RG (p = 0.007). Secondary outcome: In the AG, the mean BCVA worsened from logMAR 0.57 ± 0.33 at baseline to 0.63 ± 0.30 at switch follow-up and improved slightly to 0.53 ± 0.71 at final follow-up, AG (p = 0.46). In the RG, mean BCVA worsened from 0.57 ± 0.28 at baseline to 0.64 ± 0.31 at switch follow-up and improved slightly to 0.60 ± 0.36 at final follow-up, RG (p = 0.64).

CONCLUSION: Switching from bevacizumab to either aflibercept, or ranibizumab, has a strong anatomical effect in eyes with neovascular AMD. Nevertheless, even if the switch to aflibercept shows a minimal functional benefit over that to ranibizumab, visual prognosis remains limited.

PMID: 28535756 PMCID: PMC5442868


Relationship Between Visual Acuity and Retinal Thickness During Anti-Vascular Endothelial Growth Factor Therapy for Retinal Diseases.

Ou WC, Brown DM, Payne JF, Wykoff CC.

PURPOSE: Investigate the relationship between best-corrected visual acuity (BCVA) and central retinal thickness (CRT) in eyes receiving ranibizumab for three common retinal diseases.

DESIGN: Retrospective analysis of clinical trial data

METHODS: Early Treatment Diabetic Retinopathy Study BCVA and spectral-domain optical coherence tomography measured CRT of 387 eyes of 345 patients enrolled in six prospective clinical trials for management of neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusion (RVO) were evaluated by Pearson correlation and linear regression.

RESULTS: At baseline, there was a small correlation between BCVA and CRT in pooled AMD trial data (r = -0.24). A medium correlation was identified in pooled DME trial data (r = -0.42). No correlation was found in pooled RVO trial data. At M12, no correlation was found between changes from baseline in BCVA and CRT in data from pooled AMD trial data. Medium correlations were identified in both pooled DME (r = -0.45) and pooled RVO (r = -0.35) trial data at M12. Changes in BCVA and CRT associated with edema recurrence upon transition from monthly to pro re nata (PRN) dosing were correlated in AMD (r = -0.27) and RVO (r = -0.72) trials, but not in DME trial data.

CONCLUSION: DME demonstrated a convincing relationship between BCVA and CRT. Correlations appear to be more complex in AMD and RVO. At the inflection point between monthly and PRN dosing, when recurrence of edema is anticipated in many patients, CRT appears strongly correlated with loss of BCVA in RVO.

PMID: 28549848
Safety and Effectiveness of Cataract Surgery with Simultaneous Intravitreal Anti-VEGF in Patients with Previously Treated Exudative Age-Related Macular Degeneration.


INTRODUCTION: To evaluate the safety and impact on visual acuity, retinal and choroidal morphology of simultaneous cataract surgery and intravitreal anti-vascular endothelial growth factor on patients with visually significant cataracts and previously treated exudative age-related macular degeneration.

MATERIAL AND METHODS: Prospective study, which included 21 eyes of 20 patients with exudative age-related macular degeneration submitted to simultaneous phacoemulsification and intravitreal ranibizumab or bevacizumab. The patients were followed for 12 months after surgery using a pro re nata strategy. Visual acuity, foveal and choroidal thickness changes were evaluated 1, 6 and 12 months post-operatively.

RESULTS: There was a statistically significant increase in mean visual acuity at one (13.4 letters, p < 0.05), six (11.5 letters, p < 0.05) and twelve months (11.3 letters, p < 0.05) without significant changes in retinal or choroidal morphology. At 12 months, 86% of eyes were able to maintain visual acuity improvement. There were no significant differences between the two anti-vascular endothelial growth factor drugs and no complications developed during follow-up.

DISCUSSION: Simultaneous phacoemulsification and intravitreal anti-vascular endothelial growth factor is safe and allows improvement in visual acuity in patients with visually significant cataracts and exudative age-related macular degeneration. Visual acuity gains were maintained with a pro re nata strategy showing that in this subset of patients, phacoemulsification may be beneficial.

CONCLUSION: Cataract surgery and simultaneous anti-vascular endothelial growth factor therapy improves visual acuity in patients with exudative age-related macular degeneration.

Foveal thickness reduction after anti-vascular endothelial growth factor treatment in chronic diabetic macular edema.

Willmann G, Nepomuceno AB, Messias K, Barroso L, Scott IU, Messias A, Jorge R.

AIM: To report foveal thickness reduction in eyes with resolution of macular edema and recovery of a foveal depression after one-year of anti-vascular endothelial growth factor (anti-VEGF) therapy for center-involving diabetic macular edema (DME).

METHODS: Foveal thickness was assessed with optical coherence tomography to determine the central subfield foveal thickness (CSFT) and macular volume in 42 eyes with DME (CSFT>275 µm). Evaluations also included measurement of best-corrected visual acuity (BCVA), and were performed at baseline, and upon foveal depression recovery achieved after 12 monthly intravitreal injections of either 1.5 mg/0.06 mL bevacizumab (n=21) or 0.5 mg/0.05 mL ranibizumab (n=21). Data was compared to 42 eyes of normally sighted, non-diabetic, healthy individuals with similar age, gender and race distributions.

RESULTS: Mean baseline BCVA was 0.59±0.04 and 0.32± 0.03 logMAR (P<0.001) after treatment and resolution of DME, with all, but 3 eyes, showing BCVA improvement. Mean CSFT before treatment was 422.0±20.0 µm, and after treatment, decreased to 241.6±4.6 µm (P<0.001), which is significantly thinner than CSFT found in control subjects (272.0±3.4 µm; P<0.001). Moreover, in 33/42 DM eyes (79%), CSTF was thinner than the matched control eye. Macular volume showed comparable results, but with lower
differences between groups (control: 8.5±0.4 mm³; DME: 8.2±1.0 mm³; P=0.0267).

CONCLUSION: DME eyes show significantly lower foveal thickness than matched controls after DME resolution achieved with one-year anti-VEGF therapy. Further investigation into the reasons for this presumable retinal atrophy using fluorescein angiography and functional parameters as well as establishing possible predictors is warranted. This finding should be considered during the treatment of DME.

PMID: 28546934 PMCID: PMC5437465

**Medicine (Baltimore). 2017 May;96(21):e6965.**

**Maculopapular rash after intravitreal injection of an antivascular endothelial growth factor, aflibercept, for treating age-related macular degeneration: A case report.**

Nagai N, Ibuki M, Shinoda H, Kameyama K, Tsubota K, Ozawa Y.

RATIONALE: Aflibercept, an anti-vascular endothelial growth factor (VEGF) drug, is used for treatment of colon cancer as well as retinal diseases, including wet age-related macular degeneration (AMD). It is injected into the vitreous cavity of eyes for treatment of AMD. Although vascular suppression-including cardiovascular events and local infection related to the injection procedure are well-known potential adverse events, pathological immune responses after intravitreal aflibercept (IVA) injection have not been described.

PATIENT CONCERNS: A 60-year-old Japanese man diagnosed with polypoidal choroidal vasculopathy (PCV), a subtype of wet AMD, was treated by anti-VEGF injection. Ten hours after the last IVA injection, he presented with systemic erythema with itching.

DIAGNOSES: On the basis of the palpable erythema and papules observed on the trunk and extremities, along with redness of the pharynx, the patient was diagnosed with maculopapular-type drug eruption. The findings of biopsy of erythematous skin on the back revealed lymphocyte infiltration and telangiectasia in the upper dermis, thus confirming the diagnosis.

INTERVENTIONS: The patient was administered 30 mg prednisolone to resolve the immunoreaction.

OUTCOMES: With this treatment, the eruption turned brown, and the pharyngeal lesion and itching were resolved, and the maculopapular rash after intravitreal IVA was resolved.

LESSONS: This case illustrates the importance of medical staff being aware of aflibercept-a widely used anti-VEGF drug in various fields, including retinal diseases-as a potential cause of drug allergy.

PMID: 28538392

**Retina. 2017 May 18. [Epub ahead of print]**

**BETTER PROGNOSIS FOR EYES WITH PRESERVED FOVEAL DEPRESSION AFTER INTRAVITREAL RANIBIZUMAB INJECTION FOR MACULAR EDEMA SECONDARY TO CENTRAL RETINAL VEIN OCCLUSION.**

Kitagawa S, Yasuda S, Ito Y, Ueno S, Iwase T, Terasaki H.

PURPOSE: To determine the prognosis of eyes with central retinal vein occlusion that had a preserved foveal depression at the baseline and were treated by intravitreal ranibizumab injections (IRIs).

METHODS: The authors reviewed the medical records of 23 eyes of 23 consecutive treatment-naive patients who received IRIs to treat the macular edema due to central retinal vein occlusion. Eyes were classified by the pre-IRI presence or absence of a foveal depression. A foveal depression was defined as a
central foveal thickness that was <50 μm thinner than the average thickness at 200 μm temporal and nasal to the central fovea. The characteristics of the two groups were compared.

RESULTS: Seven of 23 eyes had a preserved foveal depression before the IRI. The mean number of injections within 12 months after the initial IRI was significantly fewer (P < 0.001) in eyes with foveal depression (1.6 ± 0.5) than in eyes without foveal depression (4.3 ± 1.3). The mean best-corrected visual acuity at 12 months after the initial IRI was significantly better (P = 0.003) in eyes with foveal depression (0.10 ± 0.17 logarithm of the minimum angle of resolution [logMAR] units; 20/25 Snellen units) than in eyes without foveal depression (0.77 ± 0.54 logMAR units; 20/118 Snellen units).

CONCLUSION: These results indicate that the prognosis is better for eyes with a foveal depression before the IRI treatment for a macular edema secondary to central retinal vein occlusion.

PMID: 28538263


Prognostic factors of short-term outcomes of intravitreal ranibizumab in diabetic macular edema.

Lai IA, Hsu WC, Yang CM, Hsieh YT.

AIM: To evaluate the prognostic factors for short-term visual and anatomical improvement of intravitreal ranibizumab (IVR) for diabetic macular edema (DME).

METHODS: Fifty-one eyes from 35 patients that received three consecutive monthly IVR for DME with moderate visual loss were retrospectively recruited; all cases had their baseline best-corrected visual acuity (BCVA) between 20/400 and 20/40. BCVA and central subfield thickness (CST) at baseline and month 3 were collected. Linear mixed models were used to evaluate the prognostic factors for visual and anatomical improvement at month 3.

RESULTS: Younger age, poorer baseline BCVA and proliferative diabetic retinopathy (PDR) were correlated with better visual improvement at month 3 (P=0.002, 0.0001 and 0.007, respectively). Thicker CST and the presence of subretinal fluid at baseline were correlated with a greater reduction in CST (P<0.0001 and P=0.018, respectively). The presence of epiretinal membrane or previous posterior subtenon injection of triamcinolone acetonide (PSTA) were associated with a smaller reduction in CST (P=0.029 and 0.018, respectively), but had no significant effects in visual improvement at month 3 (P>0.05 for both).

CONCLUSION: For eyes with DME and moderate visual loss, those with younger age, poorer baseline BCVA or PDR tend to have better visual improvement after three consecutive monthly IVR. Epiretinal membrane or previous PSTA result in less resolution of CST, but do not significantly affect visual improvement.

PMID: 28546935 PMCID: PMC5437466

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

Comparison of Intravitreal Ranibizumab, Aflibercept, and Dexamethasone Implant after Bevacizumab Failure in Macular Edema Secondary to Retinal Vascular Occlusions.

Hanhart J, Rozenman Y.

PURPOSE: To compare the visual and anatomic outcomes of macular edema secondary to retinal vein occlusion after switching from bevacizumab to ranibizumab, aflibercept, or dexamethasone implant.
METHODS: Fifteen eyes were switched to ranibizumab, 12 to aflibercept, and 10 to dexamethasone. At 3, 6, 9, and 12 months, the outcome measures were visual acuity (VA) and central macular thickness (CMT).

RESULTS: One year after the switch, CMT decreased from 430.11 ± 91.21 to 291.86 ± 43.87 µm (p < 0.001). VA increased in 59.5% of the eyes. No difference between the groups was found in those outcomes at 1 year, but the number of injections varied: 3.30 ± 0.95 for dexamethasone, 6.50 ± 2.11 for aflibercept, and 8.27 ± 2.37 for ranibizumab (p < 0.001).

CONCLUSIONS: Most of the eyes that failed initial bevacizumab therapy benefit from switching to another modality. The number of required injections during the first year after the switch varies.

PMID: 28535531

Other treatment & diagnosis


Correlation of neutrophil/lymphocyte and platelet/lymphocyte ratio with visual acuity and macular thickness in age-related macular degeneration.


AIM: To investigate the place of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in the diagnosis of and prognosis for neovascular age-related macular degeneration (AMD).

METHODS: One hundred AMD patients and 100 healthy controls were included in the study. Blood samples were obtained from the venous blood, which is used for routine analysis, and these samples were subjected to complete blood count. NLR was defined as the neutrophil count divided by the number of lymphocytes, and PLR was defined as the platelet count divided by the number of lymphocytes.

RESULTS: No statistically significant difference was observed between the two groups under consideration in terms of demographic features (P>0.05). The average NLR in the patient group was found to be significantly higher than that in the healthy control group (P<0.05). The average PLR was significantly higher in the patient group as compared to the control group (P<0.05). As best corrected visual acuity (BCVA) increased, both NLR and PLR decreased (significant negative correlations at 49.8% and 63.0%, respectively), whereas as central macular thickness (CMT) increased, both NLR and PLR increased (significant positive correlations at 59.3% and 70.0%, respectively).

CONCLUSION: NLR and PLR levels are higher among neovascular AMD patients as compared to healthy control group. NLR and PLR levels were found to be inversely proportional to BCVA and directly proportional to CMT.

PMID: 28546933 PMCID: PMC5437464


Magnetic nanoparticles conjugated with "RPE cell -MCP-1 antibody -VEGF antibody" compounds for the targeted therapy of age-related macular degeneration: a hypothesis.

Du ZJ, Li P, Wang L.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in the elderly throughout the world. Treatment of AMD utilizing retinal pigment epithelium (RPE) transplantation represents a promising therapy. However, simplex RPE transplantation can only replace the diseased RPE cells, but has no abilities to stop the development of AMD. It has been indicated that oxidization triggers the
Macular Disease Foundation Australia
Suite 902, 447 Kent Street, Sydney, NSW, 2000, Australia.
Tel: +61 2 9261 8900 | Fax: +61 2 9261 8912 | E: research@mdfoundation.com.au | W: www.mdfoundation.com.au

development of AMD by inducing the dysfunction and degeneration of RPE cells, which results in the upregulation of local monocyte chemotactic protein-1 (MCP-1) expression. MCP-1 induces macrophage recruitment which triggers local inflammation. As a result, the expression of vascular endothelial growth factor (VEGF) is upregulated by MCP-1 mediated inflammation and results in the formation of choroidal neovascularization (CNV). We accordingly propose a targeted therapy of AMD by subretinal transplanting the compound of RPE cell, MCP-1 antibody, and VEGF antibody and using a magnetic system to guide RPE cell compounds conjugated with superparamagnetic iron oxide nanoparticles (SPIONs). Furthermore, SPION-labelled RPE cells can be tracked and detected in vivo by non-invasive magnetic resonance imaging (MRI). This novel RPE cell transplantation methodology seems very promising to provide a new therapeutic approach for the treatment of AMD.

PMID: 28546942 PMCID: PMC5437473


Long-term results after limited macular translocation surgery for wet age-related macular degeneration.

Oshima H, Iwase T, Ishikawa K, Yamamoto K, Terasaki H.

PURPOSE: To evaluate the long-term results of limited macular translocation (LMT) surgery with radial choriocapillary outfolding in patients with wet age-related macular degeneration (AMD) and subfoveal choroidal neovascularization (CNV). In addition, to identify the factors associated with the final best-corrected visual acuity (BCVA).

METHODS: The medical records of 20 eyes of 20 consecutive patients (65.2±9.8 years) who had undergone LMT for the treatment of wet AMD and were followed for at least 5 years, were reviewed. The surgical outcomes including the BCVA, degree of foveal displacement, and complications were recorded.

RESULTS: The mean foveal displacement was 1332 ± 393 μm after the LMT. The CNV was removed in 16 eyes and photocoagulated in 4 eyes. The mean preoperative VA was 0.83 ± 0.33 logMAR units which significantly improved to 0.59 ± 0.37 logMAR units at 1 year after the surgery (P = 0.015). This BCVA was maintained at 0.59 ± 0.41 logMAR units on the final examination. The final BCVA was significantly correlated with that at 1 year after the surgery (r = 0.83, P<0.001). Multiple linear regression analysis showed that the final BCVA was significantly correlated with the BCVA at 1 year after the surgery (P<0.001), a recurrence of a CNV (P = 0.001), and the age (P = 0.022).

CONCLUSIONS: LMT improves the BCVA significantly at 1 year, and the improved BCVA lasted for at least 5 years. These results indicate that the impaired function of the sensory retina at the fovea can recover on the new RPE after the displacement for at least 5 years. The ability to maintain good retinal function on the new RPE for a long period is important for future treatments of CNVs such as the transplantation of RPE cells and stem cells.

PMID: 28542257

Biomedicines. 2017 Mar 27;5(2).


Guedri H, Ben Abdallah M, Echouchene F, Belmabrouk H.

Abstract: Several clinical studies reveal the relationship between alterations in the topologies of the human retinal blood vessel, the outcrop and the disease evolution, such as diabetic retinopathy, hypertensive retinopathy, and macular degeneration. Indeed, the detection of these vascular changes always has gaps.
In addition, the manual steps are slow, which may be subjected to a bias of the perceiver. However, we can overcome these troubles using computer algorithms that are quicker and more accurate. This paper presents and investigates a novel method for measuring the blood vessel diameter in the retinal image. The proposed method is based on a thresholding segmentation and thinning step, followed by the characteristic point determination step by the Douglas-Peucker algorithm. Thereafter, it uses the active contours to detect vessel contour. Finally, Heron's Formula is applied to assure the calculation of vessel diameter. The obtained results for six sample images showed that the proposed method generated less errors compared to other techniques, which confirms the high performance of the proposed method.

PMID: 28536355


Polypoidal Choroidal Vasculopathy with Feeder Vessels: Characteristics, Fellow Eye Findings, and Long-term Treatment Outcomes.


PURPOSE: To evaluate the long-term outcomes of anti-vascular endothelial growth factor (VEGF) therapy for polypoidal choroidal vasculopathy (PCV) with feeder vessels and to investigate fellow-eye findings.

METHODS: This retrospective observational study included 14 eyes with treatment-naïve PCV accompanied by feeder vessels that were treated with anti-VEGF monotherapy. The best-corrected visual acuity (BCVA) at baseline was compared with that at the last follow-up. The fellow-eye indocyanine green angiography findings were also analyzed.

RESULTS: The mean follow-up period was 28.1 ± 19.2 months (range, 12 to 60 months). During the follow-up period, 5.9 ± 2.5 anti-VEGF injections were administered. The logarithm of the minimal angle of resolution (logMAR) BCVAs at the time of diagnosis, at 3 months, and at the last follow-up were 0.81 ± 0.49, 0.55 ± 0.44, and 0.71 ± 0.54, respectively. Although the BCVA at the last follow-up was not different from the baseline value (p=0.809), an improvement of ≥0.2 logMAR BCVA was observed in seven eyes (50.0%). In 11 eyes that underwent bilateral indocyanine green angiography at diagnosis, PCV, branching vascular networks, and late geographic hyperfluorescence were noted in two (18.2%), five (45.4%), and three (27.3%) fellow eyes, respectively. During the follow-up period, the development of polypoidal lesions in the fellow eye was observed in three patients.

CONCLUSIONS: In this study, long-term improvement in BCVA was noted in 50% of the included patients who received anti-VEGF monotherapy. A relatively high incidence of pathological findings in the fellow eye and bilateral involvement suggest the need for bilateral examinations.

PMID: 28534339


Proposal of a simple optical coherence tomography-based scoring system for progression of age-related macular degeneration.

Lei J, Balasubramanian S, Abdelfattah NS, Nittala MG, Sadda SR.

PURPOSE: To develop a simple, clinically practical, optical coherence tomography (OCT)-based scoring system for early age-related macular degeneration (AMD) to prognosticate risk for progression to late AMD.

METHODS: We retrospectively reviewed OCT images (512 × 128 macular cube, Cirrus) from 138 patients diagnosed of early AMD in at least one eye and follow-up of at least 12 months. For patients with early AMD in both eyes, only the right eye was chosen as the study eye for longitudinal assessment. Scans were
graded on four SD-OCT criteria associated with disease progression in previous studies: drusen volume within a central 3-mm circle ≥0.03 mm³, intraretinal hyperreflective foci (HRF), hyporeflective foci (hRF) within a drusenoid lesion (DL), and subretinal drusenoid deposits (SDD). Each criterion was assigned one point. For risk assessment of the study eye, the baseline status of the fellow eye was also considered, and thus these four features were also assessed in the fellow eye. The number of risk factors were summed for both eyes, yielding a total score (TS) of 0 to 8 for each patient. A fellow eye with evident choroidal neovascularization (CNV) or atrophy automatically received 4 points. Scores were then grouped into four categories to facilitate comparative analysis: I. (TS of 0, 1, 2), II. (TS of 3, 4), III. (TS of 5, 6) and IV. (TS of 7, 8). Correlation of baseline category assignment with progression to late AMD (defined as the presence of atrophy or CNV on OCT) by the last follow-up visit was evaluated with logistic regression analysis.

RESULTS: The rate of progression to late AMD was 39.9% (55/138). Progression rates by category (I to IV) were 0, 14.3, 47.5, and 73.3%, respectively. Logistic regression analysis showed risk of progression to late AMD was 3.0 times (95% CI: 1.2-7.9) higher for an eye assigned to category IV than for an eye in category III and 16.4 (95% CI: 4.7-58.8) times higher than for an eye in category II.

CONCLUSIONS: A simple scoring system relevant to prognosis for early AMD, and practical for use in a busy clinic, can be developed using SD-OCT criteria alone.

PMID: 28534244


Recent advances in the management of dry age-related macular degeneration: A review.
Bandello F, Sacconi R, Querques L, Corbelli E, Cicinelli MV, Querques G.

Abstract: Age-related macular degeneration (AMD), the most important cause of vision loss in elderly people, is a degenerative disorder of the central retina with a multifactorial etiopathology. AMD is classified in dry AMD (d-AMD) or neovascular AMD depending on the presence of choroidal neovascularization. Currently, no therapy is approved for geographic atrophy, the late form of d-AMD, because no treatment can restore the damage of retinal pigment epithelium (RPE) or photoreceptors. For this reason, all treatment approaches in d-AMD are only likely to prevent and slow down the progression of existing atrophy. This review focuses on the management of d-AMD and especially on current data about potential targets for therapies evaluated in clinical trials. Numerous examinations are available in clinics to monitor morphological changes in the retina, RPE and choroid of d-AMD patients. Fundus autofluorescence and optical coherence tomography (OCT) are considered the most useful tools in the diagnosis and follow-up of d-AMD alterations, including the monitoring of atrophy area progression. Instead, OCT-angiography is a novel imaging tool that may add further information in patients affected by d-AMD. Several pathways, including oxidative stress, deposits of lipofuscin, chronic inflammation and choroidal blood flow insufficiency, seem to play an important role in the pathogenesis of d-AMD and represent possible targets for new therapies. A great number of treatments for d-AMD are under investigation with promising results in preliminary studies. However, only few of these drugs will enter the market, offering a therapeutic chance to patients affected by the dry form of AMD and help them to preserve a good visual acuity. Further studies with a long-term follow-up would be important to test the real safety and efficacy of drugs under investigation.

PMID: 28529701 PMCID: PMC5428517


Hypocrellin B and nano silver loaded polymeric nanoparticles: Enhanced generation of singlet oxygen for improved photodynamic therapy.
Natesan S, Krishnaswami V, Ponnnusamy C, Madiyalakan M, Woo T, Palanisamy R.

Abstract: A nanoparticulate photodynamic approach was employed with an objective to achieve enhanced production of singlet oxygen (1O2), for the management of posterior segment eye diseases like age related macular degeneration. The hypocrellin B (HB) loaded poly lactide-co-glycolide nanoparticle formulations were incorporated with nano silver (HBS-NPs). The optimized HBS-NPs contained 2.60±0.06mg/mL of HB and showed (i) 135.6 to 828.2nm size range, and (ii) negative zeta potential with a narrow polydispersity index. The DSC thermograms suggested the amorphous nature of HB inside the HBS-NPs. With the average encapsulation efficiency of 92.9±1.79%, the drug release from the HBS-NPs followed a biphasic pattern with an initial burst of 3.50% during first 8h followed by a sustained release of 47.82% within 3days. The interaction between nano silver and HB as assessed by the increase in spectral intensity of Raman spectrum demonstrates that HB may be attached over the nano silver. Generation of reactive oxygen species (ROS) by HBS-NPs was significantly higher than that of HB/HB-NPs. The singlet oxygen generating efficiency assessed using EPR spectrometer follows the order of nano silver>HB-NPs>pure HB drug solution>HBS-NPs. The HBS-NPs had a concentration and time dependent phototoxicity on A549 (human adeno lung carcinoma) cells in the presence of light providing a superior phototoxic effect (82.2% at 50μM) at 2h irradiation. The CAM treated with HBS-NPs showed a significant anti-angiogenic effect compared to a blank formulation. In vivo biodistribution studies revealed that intravenous administration of HBS-NPs lead into significant exposure to the posterior segment of the eye. This proof of principle study demonstrates that HB based nanoparticles may be a valuable new tool for application in ocular photodynamic therapy for the treatment of AMD in future.

PMID: 28532114

**Pathogenesis**

**Exp Eye Res. 2017 May 23. [Epub ahead of print]**

**Four decades of ocular renin-angiotensin and kallikrein-kinin systems (1977-2017).**

Igić R.

This review offers a contemporary history of the renin-angiotensin (RAS) and kallikrein-kinin (KKS) systems with emphasis on how these complex systems affect the eye. It describes the types of communication (cross-talk) between the two systems and evaluates their potential role in the development of diabetic retinopathy, diabetic macular edema, age-related macular degeneration, glaucoma, and uveitis. In addition to detailing the important physiological actions of components of the RAS and KKS, possibilities are suggested for new therapeutic avenues in the treatment of common ocular diseases. Historical notes indicate the major events in this research area, marking four decades from the first publication on the discovery of renin and angiotensin converting enzyme in the eye to the present time.

PMID: 28549900

**Br J Pharmacol. 2017 May 26. [Epub ahead of print]**

**Vitamin D Receptor Agonists Regulate Ocular Developmental Angiogenesis and Modulate Expression of dre-miR-21 and VEGF.**

Merrigan SL, Kennedy BN.

BACKGROUND AND PURPOSE: Pathological growth of ocular vasculature networks can underpin visual impairment in neovascular age-related macular degeneration, proliferative diabetic retinopathy and retinopathy of prematurity. Our aim was to uncover novel pharmacological regulators of ocular angiogenesis by phenotype-based screening in zebrafish.
EXPERIMENTAL APPROACH: A bioactive chemical library of 465 drugs was screened to identify small molecule inhibitors of ocular hyaloid vasculature (HV) angiogenesis in zebrafish larvae. Selectivity was assessed by evaluation of non-ocular intersegmental vasculature development. Safety pharmacology examined visual behaviour and retinal histology in larvae. Molecular mechanisms of action were interrogated using expression profiling of target mRNAs and miRNAs in larval eyes.

KEY RESULTS: Library screening identified 10 compounds which significantly inhibited HV developmental angiogenesis. Validated hit calcitriol selectively demonstrated dose-dependent attenuation of HV development. In agreement, vitamin D receptor (VDR) agonists paricalcitol, doxercalciferol, maxacalcitol, calcipotriol, seocalcitol, calcifediol and tacalcitol significantly and selectively attenuated HV development. VDR agonists induced minor ocular morphology abnormalities and affected normal visual function. Calcitriol induced a 3-7-fold increase in ocular dre-miR-21 expression. Consistently, all-trans-retinoic acid attenuated HV development and increased ocular dre-miR-21 expression. Interestingly, zebrafish ocular vegfaa and vegfab expression was significantly increased while, vegfl, flt1 and kdrl expression was unchanged by calcitriol.

CONCLUSION AND IMPLICATIONS: These studies identify VDR agonists as significant and selective anti-angiogenics in the developing vertebrate eye and miR21 as a key downstream regulated miRNA. These targets should be further evaluated as molecular hallmarks of, and therapeutic targets for pathological ocular neovascularisation.

PMID: 28547797


Homocysteine mediates transcriptional changes of the inflammatory pathway signature genes in human retinal pigment epithelial cells.

Singh M, Tyagi SC.

AIM: To test whether homocysteine (Hcy) can influence the transcriptional profile, we hypothesized that Hcy can lead to the induction of proinflammatory molecules in the retinal cells of aging people.

METHODS: An unbiased in vitro inflammatory pathway focused study was designed employing retinal pigment epithelial (RPE) cell line, ARPE-19. Cells were cultured in the presence or absence of Hcy to capture target genes' expression profile. Three different concentrations of Hcy were added in the culture medium of confluent monolayers. cRNAs were made from the isolated total RNAs and the labeled cRNA probes were hybridized to microarrays specific for human disease pathway inflammatory cytokines, chemokines and their receptor gene micro-array panels as per manufacture's recommendations. Two Hcy up-regulated molecules: IL6 and CEBPB were further validated via Western blot analysis. Hcy's effect on ARPE-19 cellular morphology and genomic DNA integrity were also evaluated.

RESULTS: Gene microarray analyses of RPE cells in response to Hcy treatment revealed alterations in the expressions of several inflammatory gene transcripts such as CCL5, CEBPB, IL13RA2, IL15RA, IL6, IL8 and CXCL3 that were up-regulated. The transcripts for C3, CCL2, IL11RA and IL18 genes exhibited down-regulation. The IL6 and CEBPB expressions were subsequently validated at the protein levels. Treatment of the retinal cells with increasing Hcy concentration influenced their density in culture however their morphology and DNA integrity remained unaffected.

CONCLUSION: These findings suggest that Hcy can potentially mediate the expression of chemokines, cytokines and interleukins receptors in the retinal cells without having any debilitating effects on their morphology and the genomic DNA integrity.

PMID: 28546923 PMCID: PMC5437454
Survival Improvement in Human Retinal Pigment Epithelial cells via Fas Receptor Targeting by miR-374a.

Tasharrofi N, Kouhkan F, Soleimani M, Soheili ZS, Kabiri M, Saber MM, Dorkoosh FA.

Abstract: Oxidative conditions of the eye could contribute to retinal cells loss through activating the Fas-L/Fas pathway. This phenomenon is one of the leading causes of some ocular diseases like age-related macular degeneration (AMD). By targeting proteins at their mRNA level, microRNAs (miRNAs) can regulate gene expression and cell function. The aim of the present study is to investigate Fas targeting by miR-374a and find whether it can inhibit Fas-mediated apoptosis in primary human retinal pigment epithelial (RPE) cells under oxidative stress. So, the primary human RPE cells were transfected with pre-miR-374a pLEX construct using polymeric carrier and were exposed to H2 O2 (200 µM) as an oxidant agent for induction of Fas expression. Fas expression at mRNA and protein level was evaluated by quantitative real-time PCR and western blot analysis, respectively. These results revealed that miR-374a could prevent Fas upregulation under oxidative conditions. Moreover, Luciferase activity assay confirmed that Fas could be a direct target of miR-374a. The cell viability studies demonstrated that caspase-3 activity was negligible in miR-374a treated cells compared to the controls. Our data suggest miR-374a is a negative regulator of Fas death receptor which is able to enhance the cell survival and protect RPE cells against oxidative conditions.

PMID: 28543858

Human plasma metabolomics in age-related macular degeneration (AMD) using nuclear magnetic resonance spectroscopy.


PURPOSE: To differentiate the plasma metabolomic profile of patients with age related macular degeneration (AMD) from that of controls, by Nuclear Magnetic Resonance (NMR) spectroscopy.

METHODS: Two cohorts (total of 396 subjects) representative of central Portugal and Boston, USA phenotypes were studied. For each cohort, subjects were grouped according to AMD stage (early, intermediate and late). Multivariate analysis of plasma NMR spectra was performed, followed by signal integration and univariate analysis.

RESULTS: Small changes were detected in the levels of some amino acids, organic acids, dimethyl sulfone and specific lipid moieties, thus providing some biochemical information on the disease. The possible confounding effects of gender, smoking history and age were assessed in each cohort and found to be minimal when compared to that of the disease. A similar observation was noted in relation to age-related comorbidities. Furthermore, partially distinct putative AMD metabolite fingerprints were noted for the two cohorts studied, reflecting the importance of nutritional and other lifestyle habits in determining AMD metabolic response and potential biomarker fingerprints. Notably, some of the metabolite changes detected were noted as potentially differentiating controls from patients diagnosed with early AMD.

CONCLUSION: For the first time, this study showed metabolite changes in the plasma of patients with AMD as compared to controls, using NMR. Geographical origins were seen to affect AMD patients’ metabolic profile and some metabolites were found to be valuable in potentially differentiating controls from early stage AMD patients. Metabolomics has the potential of identifying biomarkers for AMD, and further work in this area is warranted.

PMID: 28542375 PMCID: PMC5436712
An enhanced bioluminescence-based Annexin V probe for apoptosis detection in vitro and in vivo.

Head T, Dau P, Duffort S, Daftarian P, Joshi PM, Vazquez-Padron R, Deo SK, Daunert S.

Abstract: The process of controlled cellular death known as apoptosis has an important central role not only in normal homeostatic maintenance of tissues, but also in numerous diseases such as cancer, neurodegenerative, autoimmune, and cardiovascular diseases. As a result, new technologies with the capability to selectively detect apoptotic cells represent a central focus of research for the study of these conditions. We have developed a new biosensor for the detection of apoptotic cells, incorporating the targeted selectivity for apoptotic cells from Annexin V with the sensitivity of bioluminescence signal generation from a serum-stable mutant of Renilla luciferase (RLuc8). Our data presents a complete characterization of the structural and biochemical properties of this new Annexin-Renilla fusion protein (ArFP) construct, as well as a validation of its ability to detect apoptosis in vitro. Moreover, this work represents the first report of a bioluminescent Annexin V apoptosis sensor utilized in vivo. With this new construct, we examine apoptosis within disease-relevant animal models of surgery-induced ischemia/reperfusion, corneal injury, and retinal cell death as a model of age-related macular degeneration. In each of these experiments, we demonstrate successful application of the ArFP construct for detection and bioluminescence imaging of apoptosis within each disease or treatment model. ArFP represents an important new tool in the continuously growing kit of technologies for apoptosis detection, and our results from both in vitro and in vivo experiments suggest a diverse range of potential clinically relevant applications including cancer therapeutic screening and efficacy analysis, atherosclerosis and cardiovascular disease detection, and the monitoring of any number of other conditions in which apoptosis has a central role.

PMID: 28542141

Mitochondrial disorders and the eye.

Van Bergen NJ, Chakrabarti R, O'Neill EC, Crowston JG, Trounce IA.

Abstract: The clinical significance of disturbed mitochondrial function in the eye has emerged since mitochondrial DNA (mtDNA) mutation was described in Leber's hereditary optic neuropathy. The spectrum of mitochondrial dysfunction has become apparent through increased understanding of the contribution of nuclear and somatic mtDNA mutations to mitochondrial dynamics and function. Common ophthalmic manifestations of mitochondrial dysfunction include optic atrophy, pigmentary retinopathy, and ophthalmoplegia. The majority of patients with ocular manifestations of mitochondrial disease also have variable central and peripheral nervous system involvement. Mitochondrial dysfunction has recently been associated with age-related retinal disease including macular degeneration and glaucoma. Therefore, therapeutic targets directed at promoting mitochondrial biogenesis and function offer a potential to both preserve retinal function and attenuate neurodegenerative processes.

PMID: 28539774 PMCID: PMC5436186

Atorvastatin Promotes Phagocytosis and Attenuates Pro-Inflammatory Response in Human Retinal Pigment Epithelial Cells.

Abstract: Phagocytosis of daily shed photoreceptor outer segments is an important function of the retinal pigment epithelium (RPE) and it is essential for retinal homeostasis. RPE dysfunction, especially impairment of its phagocytic ability, plays an essential role in the pathogenesis of age-related macular degeneration (AMD). Statins, or HMG CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibitors, are drugs with multiple properties that have been extensively used to treat hyperlipidemia. However, their effect on RPE cells has not been fully elucidated. Here we report that high dose atorvastatin increased the phagocytic function of ARPE-19 cells, as well as rescue the cells from the phagocytic dysfunction induced by cholesterol crystals and oxidized low-density lipoproteins (ox-LDL), potentially by increasing the cellular membrane fluidity. Similar effects were observed when evaluating two other hydrophobic statins, lovastatin and simvastatin. Furthermore, atorvastatin was able to block the induction of interleukins IL-6 and IL-8 triggered by pathologic stimuli relevant to AMD, such as cholesterol crystals and ox-LDL. Our study shows that statins, a well-tolerated class of drugs with rare serious adverse effects, help preserve the phagocytic function of the RPE while also exhibiting anti-inflammatory properties. Both characteristics make statins a potential effective medication for the prevention and treatment of AMD.

PMID: 28539592 PMCID: PMC5443823


FHR-1 Binds to C-Reactive Protein and Enhances Rather than Inhibits Complement Activation.


Abstract: Factor H-related protein (FHR) 1 is one of the five human FHRs that share sequence and structural homology with the alternative pathway complement inhibitor FH. Genetic studies on disease associations and functional analyses indicate that FHR-1 enhances complement activation by competitive inhibition of FH binding to some surfaces and immune proteins. We have recently shown that FHR-1 binds to pentraxin 3. In this study, our aim was to investigate whether FHR-1 binds to another pentraxin, C-reactive protein (CRP), analyze the functional relevance of this interaction, and study the role of FHR-1 in complement activation and regulation. FHR-1 did not bind to native, pentameric CRP, but it bound strongly to monomeric CRP via its C-terminal domains. FHR-1 at high concentration competed with FH for CRP binding, indicating possible complement deregulation also on this ligand. FHR-1 did not inhibit regulation of solid-phase C3 convertase by FH and did not inhibit terminal complement complex formation induced by zymosan. On the contrary, by binding C3b, FHR-1 allowed C3 convertase formation and thereby enhanced complement activation. FHR-1/CRP interactions increased complement activation via the classical and alternative pathways on surfaces such as the extracellular matrix and necrotic cells. Altogether, these results identify CRP as a ligand for FHR-1 and suggest that FHR-1 enhances, rather than inhibits, complement activation, which may explain the protective effect of FHR-1 deficiency in age-related macular degeneration.

PMID: 28533443


Angiogenesis and Eye Disease.

Usui Y, Westenskow PD, Murinello S, Dorrell MI, Scheppke L, Bucher F, Sakimoto S, Paris LP, Aguilar E, Friedlander M.

Abstract: The retina consists of organized layers of photoreceptors, interneurons, glia, epithelial cells, and endothelial cells. The economic model of supply and demand used to appropriately determine cost is highly applicable to the retina, in which the extreme metabolic demands of phototransduction are met by precisely
localized and designed vascular networks. Proper development and maintenance of these networks is critical to normal visual function; dysregulation is characteristic of several devastating human diseases, including but not limited to age-related macular degeneration and diabetic retinopathy. In this article, we focus on the lessons learned from the study of retinal vascular development and how these lessons can be used to better maintain adult vascular networks and prevent retinal diseases. We then outline the vasculotrophic contributions from neurons, retinal pigment epithelium (RPE) cells, and glia (specifically microglia) before we shift our focus to pathology to provide molecular contexts for neovascular retinal diseases. Finally, we conclude with a discussion that applies what we have learned about how retinal cells interact with the vasculature to identify and validate therapeutic approaches for neurovascular disease of the retina.

PMID: 28532369

**Nat Rev Drug Discov. 2017 May 19. [Epub ahead of print]**

**Therapeutic targeting of the angiopoietin-TIE pathway.**

Saharinen P, Eklund L, Alitalo K.

Abstract: The endothelial angiopoietin (ANG)-TIE growth factor receptor pathway regulates vascular permeability and pathological vascular remodelling during inflammation, tumour angiogenesis and metastasis. Drugs that target the ANG-TIE pathway are in clinical development for oncological and ophthalmological applications. The aim is to complement current vascular endothelial growth factor (VEGF)-based anti-angiogenic therapies in cancer, wet age-related macular degeneration and macular oedema. The unique function of the ANG-TIE pathway in vascular stabilization also renders this pathway an attractive target in sepsis, organ transplantation, atherosclerosis and vascular complications of diabetes. This Review covers key aspects of the function of the ANG-TIE pathway in vascular disease and describes the recent development of novel therapeutics that target this pathway.

PMID: 28529319

**Epidemiology**

**Eye (Lond). 2017 May 26. [Epub ahead of print]**

**Prevalence and the risk factors for visual impairment in age-related macular degeneration.**


Purpose: To characterize the type, and the causes of visual impairment (VI) in various stages of early and late age-related macular degeneration (AMD) and the factors associated with visual impairment in subjects with AMD.

Methods: 6617 subjects ≥60 years were enumerated; 5495 (83.04%) participated in eye examination. Of which, 4791 subjects had gradable fundus images. AMD was graded per International ARM Epidemiological Study Group. Subjects underwent detailed ophthalmic exam. VI was defined per the WHO classification. Mild VI was defined as VA less than 6/12 to 6/18, moderate VI-VA less than 6/18 but up to 6/60, severe VI-VA less than 6/60 but up to 3/60 and legal blindness-VA worse than 3/60. Factors associated with VI in AMD was analyzed with univariate and logistic regression analysis.

Results: Nine hundred and eighty-eight subjects were identified as having AMD (893 with early AMD and 95 with late AMD); 85% of the subjects (95% CI: 82.7-87.1) had no VI, 13.1% had mild VI (95% CI: 11.1-15.3), 0.8% had severe VI (95% CI: 0.4-1.6), 1.1% had legal blindness (95% CI: 0.6-1.9). Prevalence of any VI was 13.7% in early AMD and 27.4% in late AMD, P=0.0004; age group 65-70 years (OR=1.89, 95% CI:
1.16-3.08, P=0.011), and those ≥75 years (OR=3.67, 95% CI: 1.95-6.91, P=0.0001) had greater odds of VI compared with age group 60-64 years. Male gender was a protective factor for VI (OR=0.57, CI: 0.36-0.90, P=0.016). Cataract (31.8%) and refractive error (28.4%) accounted for a majority of the VI.

Conclusions: Cataract and refractive error account for a significant proportion of VI in the south Indian population with AMD. Early AMD is the third leading cause of VI. Greater age and female gender are associated with VI in subjects with AMD.

PMID: 28548646

Genetics


What Does Genetics Tell Us About Age-Related Macular Degeneration?

Grassmann F, Ach T, Brandl C, Heid IM, Weber BHF.

Abstract: Age-related macular degeneration (AMD) is a chronic degenerative disease of the central retina and a major cause of vision impairment and blindness with millions of people affected in the elderly population. In recent years, considerable efforts have been made to understand disease pathology with the long-term goal of designing novel and effective treatment options for this devastating disease. Although striking advances in treating the neovascular stage of late AMD have occurred, no therapy is available for almost half of all AMD patients, specifically those who are affected by the atrophic form of the disease. This review highlights current knowledge on the genetic factors associated with early- and late-stage forms of the disease. It also summarizes the findings regarding the extent to which these factors may play a role in the transition from one disease stage to another, and it emphasizes the need to explore further the underlying mechanisms for both development and progression of this disease as a starting point for designing innovative therapies for it.

PMID: 28532374

Diet, lifestyle & low vision


Ramírez Estudillo JA, León Higuera MI, Rojas Juárez S, Ordaz Vera ML, Pablo Santana Y, Celis Suazo B.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of blindness in the western world. As a consequence of AMD, patients develop structural damage that comprises the fovea and subsequently present loss of central vision, low visual acuity and unstable fixation. Contrary to what happens with anti-angiogenic treatment in neovascular AMD, there is currently no definitive treatment to reverse geographic atrophy progression. The aim of this study was to determine the effectiveness of the visual rehabilitation treatment via microperimetry in patients with geographic atrophy.

METHODS: Longitudinal and prospective study, 18 patients with areas of geographic atrophy in their eye of better visual acuity were included. Macular integrity assessment (Maia) microperimeter (CentreVue, Padova, Italy) was used to diagnose retinal fixation and sensitivity in these patients. Based on these data and using the training module available in the equipment, the patients underwent visual rehabilitation sessions intended to allow the patient to establish the best possible fixation in the best area of retinal sensitivity. To determine the training effectiveness, the following variables were compared before and after: visual acuity in LogMAR scale with ETDRS charts, reading speed with Minnesota Low-Vision Reading Test.
(MN Read), average sensitivity threshold in microperimetry; P1 and 95% Bivariate Contour Ellipse Area (BCEA) values were used for fixation stability measurement.

RESULTS: Mean age was 77 years old (65-92). Visual acuity of the trained eye was on average 0.7 versus 0.6 LogMAR (p = 0.006) before and one week after training. Reading speed, using both eyes, was 47 words per minute (wpm) before training and 69 wpm after training (p = 0.04). Average retinal sensitivity was 14.1 versus 14.6 db (p = 0.4). Fixation stability improved with P1 values of 45% versus 51% (p = 0.05) and 95% BCEA values of 43 versus 25 (p = 0.02) before and after training, respectively.

CONCLUSIONS: Visual training via microperimetry in patients with age-related macular degeneration is effective in improving fixation stability, reading speed, and visual acuity, measured one week after training is completed.

PMID: 28536656 PMCID: PMC5439132


Physical Activity and Age-related Macular Degeneration: A systematic literature review and meta-analysis.


PURPOSE: Age-related macular degeneration (AMD) is the main cause of irreversible severe vision loss in developed countries. It has been suggested that a healthy lifestyle may assist in delaying the onset and progression of AMD, however evidence for an association between physical activity and age-related macular degeneration (AMD) remains inconclusive.

DESIGN: Systematic review and meta-analysis

METHODS: Medline, EMBASE and Google Scholar were systematically searched for studies up to May 2015. Reference lists of published articles were hand searched and study authors were contacted to provide additional data. Those in the lowest category of activity in each study were compared with all other participants to assess the association between physical activity and both early and late AMD using random effects meta-analysis.

RESULTS: Nine studies (age range 30-97 years) were included in the meta-analysis. Physical activity was found to have a protective association with both early AMD (8 studies, n = 38,112, odds ratio (OR) 0.92 95% confidence interval (CI) 0.86-0.98) and late AMD (7 studies, n = 28,854, OR 0.59 95% CI 0.49-0.72).

CONCLUSIONS: Physical activity is associated with lower odds of early and late AMD in Caucasian populations. These findings have important implications, reinforcing the public health message of staying active throughout life. However, further longitudinal studies are required to confirm and further characterize a protective effect of physical activity on the onset and/or progression of AMD.

PMID: 28549846

Eye (Lond). 2017 May 26. [Epub ahead of print]

Electronic retinal implants and artificial vision: journey and present.

Mills JO, Jalil A, Stanga PE.

Abstract: Retinitis pigmentosa and age-related macular degeneration are two significant causes of severe visual dysfunction. In both, the retinal photoreceptors degenerate, preventing successful conversion of light
into electrical energy that is interpreted in the visual cortex as visual function. Artificial vision or visual function began over two centuries ago with the idea of creating artificial light pulses, or phosphenes, through cortical stimulation. The pursuit is now on to improve artificial visual function. Two retinal implants appear the most likely to succeed in the future having undergone multicentre human trials: the Argus II electronic epiretinal device (Second Sight Medical Products, CA, USA) and Alpha-IMS electronic subretinal device (Retina Implant AG, Germany). The trial results to date are encouraging with visual improvement and acceptable safety profiles reported for both devices. At present, the visual function generated by either device does not offer high enough resolution or acuity for a patient to regain a fully functional life. Despite this, both devices not only have the potential, but have actually improved the vision-related quality of life in a significant number of patients implanted. With this in mind, the economic argument is clear. Provided device-life is long enough, its cost should be acceptable for the obtained improvement in the quality of life. The aim of this Review Article is to assist those readers that may be considering offering any of these devices as a treatment for blindness in Retinitis Pigmentosa.

PMID: 28548648


Dietary analysis and nutritional behaviour in people with and without age-related macular disease.

Stevens R, Bartlett H, Cooke R.

BACKGROUND AND AIMS: Consumption of antioxidant nutrients can reduce the risk of progression of age-related macular degeneration (AMD) - the leading cause of visual impairment in adults over the age of 50 years in the UK. Lutein and zeaxanthin (L&Z) are of particular interest because they are selectively absorbed by the central retina. The objectives of this study were to analyse the dietary intake of a group of AMD patients, assess their ability to prepare and cook healthy food, and to make comparisons with people not affected by AMD.

METHODS: 158 participants with AMD were recruited via the UK charity The Macular Society, and fifty participants without AMD were recruited from optometric practice. A telephone interview was conducted by trained workers where participants completed a 24 h food diary, and answered questions about cooking and shopping capabilities.

RESULTS: In the AMD group, the average L&Z intake was low in for both males and females. Those able to cook a hot meal consumed significantly more L&Z than those who were not able. Most participants were not consuming the recommended dietary allowance of fibre, calcium, vitamin D and E, and calorific intake was also lower than recommendations for their age-group. The non-AMD group consumed more kilocalories and more nutrients than the AMD group, but the L&Z intake was similar to those with AMD. The main factor that influenced participant's food choices was personal preference.

CONCLUSION: For an 'informed' population, many AMD participants were under-consuming nutrients considered to be useful for their condition. Participants without AMD were more likely to reach recommended daily allowance values for energy and a range of nutrients. It is therefore essential to design more effective dietary education and dissemination methods for people with, and at risk of, AMD.

PMID: 28531385


Intrinsically Photosensitive Retinal Ganglion Cell Function, Sleep Efficiency and Depression in Advanced Age-Related Macular Degeneration.

Maynard ML, J Zele A, S Kwan A, Feigl B.
PURPOSE: Melanopsin expressing intrinsically photosensitive retinal ganglion cells (ipRGC) input to multiple brain regions including those for pupil control, circadian rhythms, sleep and mood regulation. Here we measured ipRGC function and its relationship to sleep quality and depression in patients with advanced AMD.

METHODS: The melanopsin-mediated post-illumination pupil response (PIPR) was measured in 53 patients with advanced AMD (age 78.8 ± 8.8 years) and in 20 healthy controls (age 72.5 ± 3.3 years). Sleep quality and efficiency was assessed using the Pittsburgh Sleep Quality Index (PSQI). Risk of depression was determined using the Center for Epidemiologic Studies Depression questionnaire.

RESULTS: The group with AMD showed significantly reduced pupil constrictions (P = 0.039); PIPR amplitudes (P = 0.003); global sleep scores (P = 0.01); and higher levels of depression (P < 0.001) than the control group. There was a significant correlation between the PIPR amplitude and global sleep score in the AMD group (P = 0.01). The amplitude of PIPR significantly correlated with sleep efficiency (P = 0.008; regression, P = 0.01, R2 = 0.13), but not sleep quality (P = 0.23) in the AMD group. There was no correlation between PIPR and depression scores.

CONCLUSIONS: Intrinsically photosensitive RGC dysfunction in advanced AMD contributes to the observed reduction in sleep efficiency. The correlation between the melanopsin-mediated PIPR and sleep may indicate reduced photic input to the suprachiasmatic nucleus and ventrolateral preoptic area due to ipRGC dysfunction in AMD.

PMID: 28535270


Aiding the Eye, Watching the Brain: James Weiland, IEEE Fellow, explores the unique challenges of retinal prostheses.

Grifantini K.

Abstract: The retina is a sophisticated neural network that provides humans with high-resolution vision. And for those who suffer from retinal disease or deterioration, particularly age-related macular degeneration (the leading cause of blindness among people over the age of 50 in the United States), a better understanding of how to stimulate the retina or completely override its path to the area of the brain that processes vision may offer hope to restore sight.

PMID: 28534762


Organization of the Central Visual Pathways Following Field Defects Arising from Congenital, Inherited, and Acquired Eye Disease.

Morland AB.

Abstract: Visual field defects that arise from eye disease are increasing as human life spans lengthen. The consequences of visual field defects on the central visual pathways are important to assess, particularly in light of potential treatments of eye disease that restore function to the retina. For individuals with field defects arising from congenital eye disease, primary visual cortex (V1) appears to remap, whereas this form of reorganization is not present in individuals with field defects that arise later in life as a result of inherited or acquired eye disease. However, research has revealed that the areas of V1 that normally map the visual field defect are active under specific circumstances. This review attempts to resolve whether or not this activity reflects reorganization of the central visual pathways. Alongside the measures of function
are measures of anatomical properties of the human visual pathway, which demonstrate transneuronal degeneration in individuals with eye disease. These results are concerning because degeneration of the central visual pathways may ultimately limit the success of sight-restoring treatments of eye disease.

PMID: 28532373


**Electrical Stimulation of the Retina to Produce Artificial Vision.**

Weiland JD, Walston ST, Humayun MS.

Abstract: Retinal prostheses aim to restore vision to blind individuals suffering from retinal diseases such as retinitis pigmentosa and age-related macular degeneration. These devices function by electrically stimulating surviving retinal neurons, whose activation is interpreted by the brain as a visual percept. Many prostheses are currently under development. They are categorized as epiretinal, subretinal, and suprachoroidal prostheses on the basis of the placement of the stimulating microelectrode array. Each can activate ganglion cells through direct or indirect stimulation. The response of retinal neurons to these modes of stimulation are discussed in detail and are placed in context of the visual percept they are likely to evoke. This article further reviews challenges faced by retinal prosthesis and discusses potential solutions to address them.

PMID: 28532361