Drug treatment


Introduction of a nurse-led intravitreal injection service in ophthalmology.

Gallagher MJ.

Abstract

Anti-VEGF (anti-vascular endothelial growth factor) agents are useful for a variety of previously untreatable eye conditions; indications for their use are increasing. As this treatment evolved from cutting-edge to mainstream NHS practice, it resulted in a significant increase in appointments for intravitreal (IVT) injections, clinical assessment and follow-up, and hence an increasing challenge to ensure its timely availability to all who needed it. In addressing that challenge, NHS Lothian successfully initiated an advanced nurse practitioner IVT service in addition to its medical IVT service, which has increased its capacity to provide the requisite high-quality care to this patient group.

PMID: 28745964


Treatment of age-related neovascular macular degeneration: the patient’s perspective.


OBJECTIVES: The aim of this study was to assess patients’ views and expectations with regard to neovascular age-related macular degeneration (nAMD) and intravitreal anti-VEGF therapy (IVT).

METHODS: We conducted a multicenter, non-interventional, prospective cohort study including nAMD patients treated with IVT in Germany. Patients with at least one IVT before study enrollment and aged ≥50 years were included. Three telephone interviews were conducted during a 12-month observational period. Here, patient’s beliefs/expectations with regard to the nAMD disease and the IVT treatment were discussed. Only patients who completed all three phone interviews were included in the analyses. We used a two-step cluster analysis to identify patient clusters regarding specific patient attitudes towards nAMD and its treatment.

RESULTS: Three hundred and thirty-two patients completed all interviews (mean age of 76.4 ± 7.2 years, 59.0% women). Out of these, 57.8% acknowledged that they needed general assistance in daily life, while 77.4% stated being able to attend general medical appointments on their own. However, 64.7% needed a driver or an accompanying person to attend their IVT appointments. In addition, 3.9% of the patients were afraid of IVT side effects. Also, 87.3% and 43.1% of the patients could name their disease or the anti-VEGF drug administered, respectively. More than three-quarters of the patients (83.1%) were aware of possible
consequences of nAMD by stating vision loss or blindness, but only 16.6% knew that nAMD is a chronic disease. Generally, patients were optimistic: 70.2%, 5.1% and 13.0% of them expected stable visual acuity (VA), a significant improvement or expected worsening of VA in the next year, respectively. Almost two thirds of patients who provided their therapy expectations (47.0%) anticipated fewer injections/discontinuation of IVT. We identified five patient clusters differing significantly from each other with regard to four variables: being afraid of IVT, nAMD disease awareness, optimism with regard to effectiveness of IVT, and nAMD disease and treatment knowledge.

CONCLUSIONS: Only a minority of patients is aware of the chronic nature of nAMD. To motivate patients to accept a life-long IVT treatment, physicians and caregivers must know that there exist different patient types with significant differences in communication needs.

PMID: 28776095


Emerging vascular endothelial growth factor antagonists to treat neovascular age-related macular degeneration.

Hussain RM, Ciulla TA.

INTRODUCTION: Evolving anti-vascular endothelial growth factor (VEGF) treatments for neovascular age-related macular degeneration (nAMD) include long acting agents, combination strategies involving new pathways, topical agents, sustained-release, and genetic therapy strategies. Areas covered: Brolucizumab and abicipar pegol have smaller molecular size, facilitating higher concentrations and potentially longer duration than current anti-VEGF agents. Agents being combined with anti-VEGFs include OPT-302 (to inhibit VEGF-C and VEGF-D); pegpleranib and rinucumab (to inhibit platelet derived growth factor, PDGF - but both failed to show consistently improved visual outcomes compared to anti-VEGF monotherapy); and RG7716, ARP-1536 and nesvacumab (to activate the Tie-2 tyrosine kinase receptor, which reduces permeability). X-82 is an oral anti-VEGF and anti-PDGF being tested in phase 2 studies. Topical anti-VEGF ± anti-PDGF drugs under study include pazopanib, PAN-90806, squalamine lactate, regorafenib, and LHA510. Sustained-release anti-VEGF delivery treatments, such as the ranibizumab Port Delivery System, GB-102, NT-503, hydrogel depot, Duraser, and ENV1305 aim to reduce the burden of frequent injections. Gene therapies with new viral vectors hold the potential to induce sustained expression of anti-angiogenic proteins via the retina's cellular apparatus, and include AVA-101/201, ADVM-202/302, AAV2-sFLT01, RGX314, and Retinostat. Expert opinion: There are many emerging anti-VEGF treatments that aim to improve visual outcomes and reduce the treatment burden of nAMD.

PMID: 28756707


Neovascular age-related macular degeneration management in the third year: final results from the TREX-AMD randomised trial.


BACKGROUND/AIMS: Prospectively evaluate outcomes in the third year of neovascular age-related macular degeneration (AMD) management using ranibizumab with continued treat and extend (TREX) dosing compared with monthly visits with retreatment upon evidence of exudative disease activity (PRN, pro re nata).

METHODS: Subjects with treatment-naïve neovascular AMD were randomised 1:2 to Monthly or TREX and
managed through 2 years. In the third year, subjects randomised to Monthly were managed PRN while subjects randomised to TREX were continued on TREX dosing or transitioned to PRN after achieving an interval of 12 weeks between visits.

RESULTS: Sixty subjects enrolled and 46 (77%) completed month 36 (M36). Transition from Monthly to PRN was associated with a decline in best corrected visual acuity (BCVA) (+10.5 letters (month 24) to +5.4 (M36, p=0.09)); three (15%) subjects required no dosing during year 3, and 47% (114/243) of possible PRN injections were delivered, yielding a mean of 6.1 injections during year 3. Among the 9 (23%) TREX subjects transitioned to PRN, the need for ongoing anti-vascular endothelial growth factor retreatments was small, with 4 (4%) intravitreal injections being delivered among 106 PRN visits; this subgroup displayed an inferior BCVA trajectory compared with the remainder of subjects. Outcomes among subjects continued on TREX were more favourable, with a mean gain of +5.0 letters at M36.

CONCLUSIONS: Upon transition to PRN, subjects randomised to monthly dosing experienced a decline in BCVA. Among subjects initially randomised to TREX who transitioned to PRN after achieving a 12-week interval between visits, the overall need for additional treatment was low.

PMID: 28779006


Structural and functional assessment after intravitreal injection of ranibizumab in diabetic macular edema.


PURPOSE: To evaluate structure and function improvement in central retina by optical coherence tomography (OCT) and multifocal electroretinography (mf-ERG) in diabetic macular edema (DME) patients after intravitreal injection of ranibizumab (IVR) treatment.

METHODS: Twenty-seven eyes in 27 patients with DME received three consecutive monthly injections of IVR (0.05 ml, 10 mg/ml) and as needed thereafter. The clinical parameters of best-corrected visual acuity (BCVA), central foveal thickness (CFT) and mf-ERG were monitored for 6 months before and after IVR. The findings at baseline, 1, 3 and 6 months were analyzed. Correlation and regression analyses were performed on BCVA, CFT, mf-ERG amplitude and implicit time of the N1 and P1 waves.

RESULTS: IVR significantly improved visual acuity from the beginning of the treatment (P < 0.05). There were significant decreases in the CFT compared with the baseline after IVR (P < 0.05). The mean amplitude of P1 and N1 in the central ring at all examinations increased significantly compared with the baseline (P < 0.05). The mean P1 and N1 implicit times in the central ring were shortened, but not significantly (P > 0.05). There were significant correlations of BCVA with CFT, P1 and N1 amplitudes in the central retina (P < 0.05).

CONCLUSION: In addition to the improvement in BCVA and the reduction in CFT, IVR improved macular retinal function, as assessed by mf-ERG, in diabetic eyes. The combination of OCT and mf-ERG for macular evaluation may better assess DME.

PMID: 28756595

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Baseline Optical Coherence Tomography Findings as Outcome Predictors after Switching from Ranibizumab to Aflibercept in Neovascular Age-Related Macular Degeneration following a Treat-and-Extend Regimen.
Türksever C, Prünte C, Hatz K.

PURPOSE: To evaluate outcome predictors of aflibercept in neovascular age-related macular degeneration pretreated with ranibizumab based on a treat-and-extend regimen (TER).

METHODS: We performed a retrospective evaluation of 18-month follow-up of 45 consecutive patients with limited response to ranibizumab.

RESULTS: At month 18, mean central retinal thickness and intraretinal fluid (IRF) height were significantly reduced. The recurrence-free treatment interval (RFTI) increased from 7.0 ± 1.8 to 8.5 ± 2.4 weeks (p = 0.01); visual acuity remained stable. At month 18, 58.1% of patients showed a longer RFTI. At month 12, eyes with baseline subretinal fluid (SRF) had a shorter RFTI than those without SRF (p = 0.032). Eyes with baseline IRF showed a longer RFTI than those without IRF (p = 0.037). Baseline hyperreflective foci (HRF) presence indicated improvement in SRF (p = 0.024) and IRF at month 12 (p = 0.049).

CONCLUSION: Baseline HRF presence predicted better morphological outcome, while SRF predicted a shorter RFTI and IRF a longer RFTI after switching from ranibizumab to aflibercept within a TER.

PMID: 28772268

Doc OphthalmoL. 2017 Aug 4. [Epub ahead of print]
Multifocal electroretinography changes at the 1-year follow-up in a cohort of diabetic macular edema patients treated with ranibizumab.

Baget-Bernaldiz M, Romero-Aroca P, Bautista-Perez A, Mercado J.

PURPOSE: To determine the changes in the multifocal electroretinogram (mfERG) at 1 year in a clinical series of diabetic macular edema (DME) patients treated with ranibizumab (RNBZ) using a pro re nata protocol.

METHODS: We analyzed a clinical series of 35 eyes of 35 patients with DME at baseline and after treating them with RNBZ over 1 year, in order to determine the change in the macular function, which was assessed by means of the response density and the implicit time of the first-order kernel (FOK) P1 wave of the mfERG at the foveola (R1), fovea (R2) and parafovea (R3). These electrophysiological parameters were studied taking into account different independent variables, such as DME type, degree of diabetic retinopathy (DR), level of preservation of both the ellipsoid zone (IS/OS) and the external limiting membrane (ELM) and changes in central retinal thickness (CRT) and total macular volume (TMV). We also studied the relationship between the response density and the best-corrected visual acuity (BCVA).

RESULTS: Eyes with cystic and spongiform DME showed better response density with respect to the serous type (p < 0.001) at baseline. Similarly, eyes with high IS/OS and ELM preservation rates showed higher initial response density compared to the others (p < 0.001). Eyes with moderate DR had better response density compared to those with severe and proliferative DR (p = 0.001). At the beginning of the study, those eyes with proliferative and severe DR showed longer implicit times with respect to those with moderate DR (p = 0.04). The response density significantly increased in eyes that anatomically restored the IS/OS and the ELM after being treated with RNBZ (both p < 0.001). Similarly, eyes with spongiform DME further improved the response density with respect to those with cystic and serous DME (p < 0.001). On the contrary, eyes with hard exudates showed less improvement in their response density at the end of the study (p < 0.001). We observed a significant relationship between BCVA and the response density achieved at the end of the study (p = 0.012). Eyes with severe and proliferative DR significantly shortened implicit time compared to those with moderate DR (p = 0.04).

CONCLUSIONS: The multifocal electroretinogram allowed us to differentiate groups of eyes with DME according to their electrophysiological profile, both initially and after being treated with RNBZ. Ranibizumab increased the response density in all DME types included in the study, with a maximum response in those
eyes with spongiform type. Once treated with RNBZ, the macular electrophysiological activity improved in eyes that had a well-preserved ellipsoid zone and ELM. The presence of hard exudates was a limitation to the response density achieved at the foveola.

PMID: 28779336


Menassa N, Burgula S, Empeslidis T, Tsaousis KT.

Abstract: A 45-year-old man had developed a choroidal neovascular membrane (CNVM) in his left eye at the age of 38 years and had received six intravitreal ranibizumab injections with resulting visual acuities of 6/60 in the affected eye and 6/4 in the unaffected right eye (Snellen charts). Family history and genetic testing revealed tissue inhibitor of metalloproteinase-3 (TIMP3) gene positive Sorsby fundus dystrophy (SFD). The patient has been under regular follow-up since. At the age of 45 years, he presented with subretinal fluid accumulation in his right eye suggestive of CNVM and received six intravitreal ranibizumab injections, which maintained visual acuity of 6/7.5 in his right eye. Although SFD is a rare condition, it should be suspected and ruled out in young patients presenting with suspicious fundoscopic findings and subretinal fluid on optical coherence tomography. Early intervention can possibly delay macular fibrosis and loss of vision secondary to SFD associated with CNVM.

PMID: 28775088


Comparison of Clinical Trial and Systematic Review Outcomes for the 4 Most Prevalent Eye Diseases.

Saldanha IJ, Lindsley K, Do DV, Chuck RS, Meyerle C, Jones LS, Coleman AL, Jampel HD, Dickersin K, Virgili G.

IMPORTANCE: Suboptimal overlap in outcomes reported in clinical trials and systematic reviews compromises efforts to compare and summarize results across these studies.

OBJECTIVES: To examine the most frequent outcomes used in trials and reviews of the 4 most prevalent eye diseases (age-related macular degeneration [AMD], cataract, diabetic retinopathy [DR], and glaucoma) and the overlap between outcomes in the reviews and the trials included in the reviews.

DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional study examined all Cochrane reviews that addressed AMD, cataract, DR, and glaucoma; were published as of July 20, 2016; and included at least 1 trial and the trials included in the reviews. For each disease, a pair of clinical experts independently classified all outcomes and resolved discrepancies. Outcomes (outcome domains) were then compared separately for each disease.

MAIN OUTCOMES AND MEASURES: Proportion of review outcomes also reported in trials and vice versa.

RESULTS: This study included 56 reviews that comprised 414 trials. Although the median number of outcomes per trial and per review was the same (n = 5) for each disease, the trials included a greater number of outcomes overall than did the reviews, ranging from 2.9 times greater (89 vs 30 outcomes for glaucoma) to 4.9 times greater (107 vs 22 outcomes for AMD). Most review outcomes, ranging from 14 of 19 outcomes (73.7%) (for DR) to 27 of 29 outcomes (93.1%) (for cataract), were also reported in the trials. For trial outcomes, however, the proportion also named in reviews was low, ranging from 19 of 107
outcomes (17.8%) (for AMD) to 24 of 89 outcomes (27.0%) (for glaucoma). Only 1 outcome (visual acuity) was consistently reported in greater than half the trials and greater than half the reviews.

CONCLUSIONS AND RELEVANCE: Although most review outcomes were reported in the trials, most trial outcomes were not reported in the reviews. The current analysis focused on outcome domains, which might underestimate the problem of inconsistent outcomes. Other important elements of an outcome (ie, specific measurement, specific metric, method of aggregation, and time points) might have differed even though the domains overlapped. Inconsistency in trial outcomes may impede research synthesis and indicates the need for disease-specific core outcome sets in ophthalmology.

PMID: 28772305


Changes in multiple cytokine concentrations in the aqueous humour of neovascular age-related macular degeneration after 2 months of ranibizumab therapy.


PURPOSE: To determine changes in multiple cytokine concentrations in the anterior chamber during the induction phase of ranibizumab treatment in patients with neovascular age-related macular degeneration (AMD).

METHODS: This prospective study included 48 treatment-naïve neovascular AMD eyes of 48 patients who received three consecutive monthly injections of ranibizumab at the Japan Community Health Care Organization Tokyo Shinjuku Medical Center between November 2010 and August 2012. We collected ~0.2 mL aqueous humour before the first and third (2 months later) injections. Controls were 80 eyes with cataracts without retinal disease. The cytokines C-X-C motif chemokine ligand 1 (CXCL1), interferon-γ-induced protein 10 (IP-10), C-X-C motif chemokine ligand 12 (CXCL12), C-X-C motif chemokine ligand 13 (CXCL13), monocyte chemotactic protein 1 (MCP-1), CCL11, C-C motif chemokine ligand 11 (CCL11), interleukin-6 (IL-6), interleukin-10 (IL-10) and matrix metalloproteinase 9 (MMP-9) were analysed using multiplex cytokine assays.

RESULTS: Mean ages of the patients with AMD and controls were 73 and 75 years, respectively, and 31 (65%) and 37 (46%) subjects were men, respectively. Polypoidal choroidal vasculopathy was found in 27 eyes (56%). Mean concentrations of cytokines in aqueous humour in patients with neovascular AMD before the first and third ranibizumab injections were as follows (in pg/mL): CXCL1, 8.4 and 3.3; IP-10, 110 and 55; CXCL12, 480 and 240; CXCL13, 9.2 and 2.6; MCP-1, 620 and 220; CCL11, 7.1 and 2.8; IL-6, 5.9 and 1.6; IL-10, 0.15 and 0.015 (all p<0.0001), and MMP-9, 0.92 and 1.5 (p=0.0216), respectively. Concentrations of all cytokines decreased significantly after two consecutive ranibizumab injections, except for MMP-9, which increased significantly.

CONCLUSIONS: After two monthly consecutive antivascular endothelial growth factor injections, inflammatory cytokine levels in the aqueous humour of the eyes with AMD were strongly suppressed, while MMP-9 levels increased.

PMID: 28765149

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Baseline Factors Affecting Changes in Diabetic Retinopathy Severity Scale Score After Intravitreal Aflibercept or Laser for Diabetic Macular Edema: Post Hoc Analyses from VISTA and VIVID.

PURPOSE: To evaluate whether select baseline systemic and ocular factors influence ≥2-step improvement in the Diabetic Retinopathy Severity Scale (DRSS) score at week 100 in VISTA and VIVID.

DESIGN: Post hoc analysis of 2 similarly designed phase 3 trials, VISTA and VIVID.

PARTICIPANTS: Total of 456 patients with center-involved diabetic macular edema (DME).

METHODS: VISTA and VIVID randomized 872 DME patients to receive intravitreal aflibercept injection (IAI) 2 mg every 4 weeks (2q4), IAI 2 mg every 8 weeks after 5 monthly doses (2q8), or macular laser photocoagulation. This post hoc analysis evaluated the influence of select baseline factors on ≥2-step DRSS score improvement by logistic regression in an integrated VISTA and VIVID dataset using observed cases (n = 456) with patients in each treatment group divided into tertiles based on each characteristic.

MAIN OUTCOME MEASURES: Proportion of patients with ≥2-step improvement in DRSS score from baseline at week 100 by age, duration of diabetes, hemoglobin A1c (HbA1c), body mass index (BMI), best-corrected visual acuity (BCVA), central subfield thickness (CST), and DRSS score.

RESULTS: At week 100, 10.1%, 34.3%, and 37.6% of patients in the laser, 2q4, and 2q8 groups experienced a ≥2-step DRSS score improvement, respectively. Age, duration of diabetes, HbA1c, BMI, BCVA, and CST had no impact on the ability to achieve ≥2-step improvement in DRSS score. Initial DRSS score was the only factor significantly associated with ≥2-step DRSS score improvement in all treatment groups at weeks 24, 52, 76, and 100. Relatively higher proportions of IAI-treated patients with worse BCVA or thicker CST experienced ≥2-step DRSS score improvement compared with those with better BCVA or thinner CST, respectively, but these associations were not statistically significant.

CONCLUSION: A strong association was present between baseline DRSS score and ≥2-step DRSS score improvement at week 100 for DME patients in VISTA and VIVID.

PMID: 28764888


ARMS2 A69S polymorphism is associated with the number of ranibizumab injections needed for exudative age-related macular degeneration in a pro re nata regimen during 4 years of follow-up.


PURPOSE: To investigate whether single-nucleotide polymorphisms (SNPs) known to be strongly associated with the development of age-related macular degeneration (AMD) have an influence on recurrence rate of choroidal neovascularization (CNV) activity during 4-year ranibizumab treatment for exudative AMD.

METHODS: This prospective study included 103 treatment-naïve patients (103 eyes) that received initially a loading dose of 3 monthly ranibizumab injections and thereafter, were treated according to an as-needed regimen for a 4-year follow-up period. Baseline values, visual outcome, and recurrence rate were examined. CFH Y402H and ARMS2 A69S polymorphisms were determined and their association with lesion recurrence and visual outcome was analyzed using a one-way analysis of variance (ANOVA) with post hoc comparison tested by Fisher's LSD method. Multivariate linear regression analysis was then used to identify factors associated with recurrence rate.

RESULTS: The cumulative total mean number of ranibizumab injections at the end of each year of the follow-up was 5.3 ± 1.8, 9.2 ± 2.9, 12.6 ± 4.6, and 15.7 ± 6.1. There was great inter-patient variability. Nineteen eyes (18.5%) did not experience recurrence during the first year, and five (4.8%) still displayed inactive CNV after 4 years of follow-up. No significant association was found between the number of injections and mean best corrected visual acuity (BCVA) change or final BCVA at the end of the study.
period. Genotypes had no influence on baseline characteristics or visual outcome but a significant association was found between the A69S polymorphism and the number of injections needed by the patients. Homozygous for the T risk allele required more retreatments over the 48-month follow-up.

CONCLUSIONS: The ARMS2 A69S polymorphism was associated with CNV recurrence rate in our patient cohort. Prediction of a greater risk of recurrence could help to design more appropriate follow-up treatment strategies for patients with neovascular AMD.

PMID: 28744656

C5512051

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EFFICACY AND FREQUENCY OF INTRAVITREAL AFLIBERCEPT VERSUS BEVACIZUMAB FOR MACULAR EDEMA SECONDARY TO CENTRAL RETINAL VEIN OCCLUSION.

Lotfy A, Solaiman KAM, Abdelrahman A, Samir A.

PURPOSE: To compare the safety, efficacy, and frequency of intravitreal injection of aflibercept and bevacizumab for treatment of macular edema secondary to central retinal vein occlusion.

DESIGN: Prospective, comparative, randomized, interventional study.

PATIENTS AND METHODS: Eyes with macular edema secondary to central retinal vein occlusion were randomized between two groups according to the intravitreal injection used. Group A included eyes treated with intravitreal aflibercept, and Group B included eyes treated with intravitreal bevacizumab injections. The inclusion criteria were macular edema secondary to central retinal vein occlusion and follow-up duration of at least 12 months after the first injection. Exclusion criteria were macular ischemia, associated diabetes, hypertensive or renal retinopathy, other retinal disease, and previous anti-vascular endothelial growth factor injection. The main outcome measures are central foveal thickness, best-corrected visual acuity, time intervals between injections, improved retinal nonperfusion, and any reported complication.

RESULTS: Group A included 39 patients with a mean age of 57.4 ± 8.2 years. Group B included 40 eyes with a mean age of 56.5 ± 9.1 years. Twelve months after the first injection, central foveal thickness significantly improved from 475.45 ± 71.05 m to 259.11 ± 20.67 m in Group A and from 460.22 ± 89.38 m to 264.29 ± 32.05 m in Group B; best-corrected visual acuity significantly improved from 0.81 ± 0.16 logarithm of the minimum angle of resolution (20/125) to 0.34 ± 0.14 logarithm of the minimum angle of resolution (20/40) in Group A and from 0.73 ± 0.15 logarithm of the minimum angle of resolution (20/100) to 0.33 ± 0.17 logarithm of the minimum angle of resolution (20/40) in Group B; the mean number of injections was 3.72 ± 2.93 in Group A and was 5.44 ± 2.85 in Group B (P < 0.05); and the mean interval between injections was 54.23 ± 8.47 days in Group A and was 35.12 ± 7.76 days in Group B (P < 0.05). Retinal nonperfusion improved in 9/12 eyes in Group A and in 3/8 eyes in Group B (P < 0.05).

CONCLUSION: Both aflibercept and bevacizumab are comparably effective for treatment of macular edema secondary to central retinal vein occlusion without significant complications. However, the burden of frequent intravitreal injections could be significantly reduced when using aflibercept.

PMID: 28767552

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IMPACT OF LONG-TERM INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR ON PREEXISTING MICROSTRUCTURAL ALTERATIONS IN DIABETIC MACULAR EDEMA.
Wirth MA, Wons J, Freiberg FJ, Becker MD, Michels S.

PURPOSE: Evaluation of the influence of long-term intravitreal anti-vascular endothelial growth factor treatment on preexisting retinal microstructural alterations in patients with diabetic macular edema.

METHODS: Eyes with diabetic macular edema and a history of ≥ 20 intravitreal anti-vascular endothelial growth factor (aflibercept and/or ranibizumab) injections were included in this retrospective study. Primary outcome was the extent of disorganization of retinal inner layers, alterations at the outer plexiform layer/ Henle fiber layer junction, disruption of external limiting membrane/ellipsoid zone, disruption of retinal pigment epithelium/Bruch complex, and retinal atrophy at baseline versus after ≥ 20 intravitreal injections as visualized by spectral-domain optical coherence tomography images.

RESULTS: Of 383 eyes screened, 37 eyes were included in the current study. With the exception of outer plexiform layer/Henle fiber layer junction restoration, no significant changes regarding microstructural alterations between baseline and end of study were encountered after long-term anti-vascular endothelial growth factor (disorganization of retinal inner layers P = 0.381, outer plexiform layer/Henle fiber layer junction P = 0.001, external limiting membrane/ellipsoid zone P = 0.524, retinal pigment epithelium/Bruch complex P = 0.122, retinal atrophy P = 0.317). Best-corrected visual acuity significantly increased over the course of the study, corresponding to central retinal thickness and intraretinal fluid reduction (all P < 0.0001). The extent of microstructural alterations was negatively correlated with best-corrected visual acuity (P < 0.05).

CONCLUSION: Apart from outer plexiform layer/Henle fiber layer junction layer restoration, no effect on preexisting retinal alterations was encountered after long-term intravitreal injections. Thus, intravitreal ranibizumab or aflibercept did not have a major effect (neither positive nor negative) on microstructural alterations.

PMID: 28767550


Comparisons of Efficacy of Intravitreal Aflibercept and Ranibizumab in Eyes with Diabetic Macular Edema.

Shimizu N, Oshitari T, Tatsumi T, Takatsuna Y, Arai M, Sato E, Baba T, Yamamoto S.

Abstract: We compared the efficacy of intravitreal aflibercept (IVA) to intravitreal ranibizumab (IVR) injections in eyes with diabetic macular edema (DME). The medical records of 49 eyes of 36 patients who were diagnosed with DME and had received IVR and 46 eyes of 40 patients who had received IVA treatment were reviewed. The central macular thickness (CMT) and best-corrected visual acuity (BCVA) were measured at the baseline and at 1, 3, and 6 months after the IVR or IVA. The mean number of injections of IVR was 2.6 ± 1.1 and of IVA was 2.7 ± 1.4. At 6 months, the CMT was significantly thinner than the baseline after IVR and after IVA. The mean BCVA was significantly better than the baseline after IVR only at 1 and 3 months and after IVA at 1 and 6 months. The BCVA of eyes with serous retinal detachment (SRD) was significantly better at 1 month after the IVR and at 1 month and 6 months after the IVA. The BCVAs improved more significantly in the SRD+ group than in the SRD- group. The effects of IVA persist longer than that of IVR. The effectiveness of both IVR and IVA was not dependent on the presence of SRD (IRB#2107).

PMID: 28758110
Other treatment & diagnosis


Choriocapillaris’ alterations in the presence of reticular pseudodrusen compared to drusen: study based on OCTA findings.

Chatziralli I, Theodossiadis G, Panagiotidis D, Pousoulidi P, Theodossiadis P.

PURPOSE: To evaluate the qualitative changes of choriocapillaris in the presence of reticular pseudodrusen (RPD) and compare them with conventional small drusen due to dry age-related macular degeneration (AMD).

PROCEDURES: Participants in this study were 59 patients with non-neovascular AMD, presenting either RPD (23 patients) or drusen (36 patients) of similar size. All patients underwent best-corrected visual acuity, slit-lamp examination, spectral domain optical coherence tomography (SD-OCT) and optical coherence tomography angiography.

RESULTS: The morphology of RPD in SD-OCT was depicted either as conical or as amorphous in shape. The presence of RPD was associated with choriocapillaris’ reduced blood flow signal (non-perfusion), while the same but less intense choriocapillaris’ non-perfusion appearance was noticed in the presence of drusen of the same size. In 13% of patients with RPD, ghost-like vessels were observed in the non-perfusion area of choriocapillaris, while in none patients with drusen ghost vessels were present. In all 23 patients with RPD, the choriocapillaris non-perfusion was correspondent to the location of RPD. Additionally, in about 35% of them, choriocapillaris’ impairment was also observed, covering areas outside RPD.

CONCLUSIONS: Morphological impairment of choriocapillaris was more intense in patients with RPD than in those with conventional drusen of the same size. The existence of ghost vessels in the area of choriocapillaris’ density defect suggested that choriocapillaris’ alterations may occur in patients with RPD.

PMID: 28779271


ARMS2 variants may predict the 3-year outcome of photodynamic therapy for wet age-related macular degeneration.

Nakai S, Honda S, Matsumiya W, Miki A, Nakamura M.

PURPOSE: To determine the association of age-related maculopathy susceptibility2 (ARMS2) gene polymorphisms with the 3-year outcomes of photodynamic therapy (PDT) in wet age-related macular degeneration (wet AMD).

METHODS: The single nucleotide polymorphism (SNP) at rs10490924 in the ARMS2 gene of 65 patients with wet AMD who underwent PDT was genotyped using the TaqMan assay. The clinical characteristics and the outcomes of PDT were compared among the three genotypes at rs10490924. A multivariate regression analysis was performed to evaluate the influence of the clinical cofactors on the association of rs10490924 with the visual outcome at 36 months after the first PDT.

RESULTS: A significant difference was found among the genotypes in the age and the baseline lesion size. The patients with the GG genotype showed a significant improvement in vision, and the patients with the TT genotype showed a significant worsening of vision at all time points measured after the initial PDT. In the multivariate regression analysis, the number of the G allele at rs10490924 was associated with a significantly greater improvement in the baseline best-corrected visual acuity (BCVA) at 36 months after the first PDT.

PMID: 28792971
CONCLUSIONS: ARMS2 variants are likely associated with the 3-year outcomes of PDT in patients with wet AMD.

PMID: 28761324 PMCID: PMC5534487


Intraocular lenses in age-related macular degeneration.
Grzybowski A, Wasinska-Borowiec W, Alio JL, Amat-Peral P, Tabernero J.

PURPOSE: The aim of this work is to review the lenses, assessing their advantages and disadvantages. We describe a total of seven types of intraocular lenses (IOLs) recommended for age-related macular degeneration (AMD).

METHODS: We used the PubMed web platform to search for implantable devices in various stages of AMD. We searched for both prospective and retrospective studies and also case reports.

RESULTS: Clinical results in AMD patients have been described for a total of seven types of IOLs recommended for AMD: an implantable miniature telescope (IMT), IOL-VIP System, Lipshitz macular implant (LMI), sulcus-implanted Lipshitz macular implant, LMI-SI, Fresnel Prism Intraocular Lens, iolAMD and Scharioth Macula Lens.

CONCLUSIONS: We conclude that to objectively ascertain the effectiveness and safety of these lenses, further independent clinical studies with longer follow-up data are necessary prior to the general use of these optical devices.

PMID: 28741158


Reliability and Repeatability of Cone Density Measurements in Patients With Stargardt Disease and RPGR-Associated Retinopathy.

PURPOSE: To assess reliability and repeatability of cone density measurements by using confocal and (nonconfocal) split-detector adaptive optics scanning light ophthalmoscopy (AOSLO) imaging. It will be determined whether cone density values are significantly different between modalities in Stargardt disease (STGD) and retinitis pigmentosa GTPase regulator (RPGR)-associated retinopathy.

METHODS: Twelve patients with STGD (aged 9-52 years) and eight with RPGR-associated retinopathy (aged 11-31 years) were imaged using both confocal and split-detector AOSLO simultaneously. Four graders manually identified cone locations in each image that were used to calculate local densities. Each imaging modality was evaluated independently. The data set consisted of 1584 assessments of 99 STGD images (each image in two modalities and four graders who graded each image twice) and 928 RPGR assessments of 58 images (each image in two modalities and four graders who graded each image twice).

RESULTS: For STGD assessments the reliability for confocal and split-detector AOSLO was 67.9% and 95.9%, respectively, and the repeatability was 71.2% and 97.3%, respectively. The differences in the measured cone density values between modalities were statistically significant for one grader. For RPGR assessments the reliability for confocal and split-detector AOSLO was 22.1% and 88.5%, respectively, and repeatability was 63.2% and 94.5%, respectively. The differences in cone density between modalities were statistically significant for all graders.
CONCLUSIONS: Split-detector AOSLO greatly improved the reliability and repeatability of cone density measurements in both disorders and will be valuable for natural history studies and clinical trials using AOSLO. However, it appears that these indices may be disease dependent, implying the need for similar investigations in other conditions.

PMID: 28738413 PMCID: PMC5525557

Klin Monbl Augenheilkd. 2017 Jul 27. [Epub ahead of print]

[Cell Transplantation in Age-related Macular Degeneration]. [Article in German; Abstract available in German from the publisher]

Kirchhof B.

Abstract: Robert Machemer offers a surgical approach to age-related macular degeneration with his retinal rotation. There is already considerable experimental and clinical knowledge available in Europe and the US on transplantation techniques for age-related macular degeneration. On average, initial visual acuity can be preserved. When photodynamic therapy was standard for exudative AMD, transplantation was superior. Photodynamic therapy could not stop, but was instead able to slow down visual loss. Currently, VEGF-blocker therapy has priority, because the visual acuity can be improved. However, this advantage does not last much longer than two years. Therefore, in the future, transplantation with new cells and less surgical risk may be reconsidered. At present, homologous RPE stem cells show promising results. They may be delivered as "sheets" or as single cells. For dry AMD only, a prophylactic approach seems reasonable, because, thus far, we are unable to reverse the atrophy on the retinal side.

PMID: 28750435


Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications.


Abstract: OCT has revolutionized the practice of ophthalmology over the past 10-20 years. Advances in OCT technology have allowed for the creation of novel OCT-based methods. OCT-Angiography (OCTA) is one such method that has rapidly gained clinical acceptance since it was approved by the FDA in late 2016. OCTA images are based on the variable backscattering of light from the vascular and neurosensory tissue in the retina. Since the intensity and phase of backscattered light from retinal tissue varies based on the intrinsic movement of the tissue (e.g. red blood cells are moving, but neurosensory tissue is static), OCTA images are essentially motion-contrast images. This motion-contrast imaging provides reliable, high resolution, and non-invasive images of the retinal vasculature in an efficient manner. In many cases, these images are approaching histology level resolution. This unprecedented resolution coupled with the simple, fast and non-invasive imaging platform have allowed a host of basic and clinical research applications. OCTA has been shown to demonstrate many important clinical findings including areas of macular telangiectasia, impaired perfusion, microaneurysms, capillary remodeling, some types of intraretinal fluid, and neovascularization among many others. More importantly, OCTA provides depth-resolved information that has never before been available. Correspondingly, OCTA has been used to evaluate a spectrum of retinal vascular diseases including diabetic retinopathy (DR), retinal venous occlusion (RVO), uveitis, retinal arterial occlusion, and age-related macular degeneration among others. In this review, we will discuss the methods used to create OCTA images, the practical applications of OCTA in light of invasive dye-imaging studies (e.g. fluorescein angiography) and review clinical studies demonstrating the utility of OCTA for research and clinical practice.

PMID: 28760677
CONTINUOUS BEAM ARGON LASER IN EXTRA-FOVEAL CHOROIDAL NEOVASCULARISATION DUE TO AGE-RELATED MACULAR DEGENERATION (A Report on 3 Cases).

Verma L, Gurunadh VS, Tewari HK.

PMID: 28769489 PMCID: PMC5531034

Pathogenesis


Cigarette smoke induced autophagy-impairment regulates AMD pathogenesis mechanisms in ARPE-19 cells.

Govindaraju VK, Bodas M, Vij N.

Abstract: Age related macular degeneration (AMD) is one of the leading causes of blindness. Genetics, environmental insult, and age-related factors all play a key role in altering proteostasis, the homeostatic process regulating protein synthesis, degradation and processing. These factors also play a role in the pathogenesis of AMD and it has been well established that cigarette smoking (CS) initiates AMD pathogenic mechanisms. The primary goal of this study is to elucidate whether CS can induce proteostasis/autophagy-impairment in retinal pigment epithelial (RPE) cells. In our preliminary analysis, it was found that cigarette smoke extract (CSE) induces accumulation of ubiquitinated proteins in the insoluble protein fraction (p < 0.01), which was subsequently mitigated through cysteamine (p < 0.01) or fisetin (p < 0.05) treatment. Further, it was verified that these CSE induced ubiquitinated proteins accumulated in the perinuclear spaces (p<0.05) that were cleared off with cysteamine (p < 0.05) or fisetin (p < 0.05). Moreover, CSE-induced aggresome-formation (LC3B-GFP and Ub-RFP co-localization) and autophagy-flux impairment was significantly (p<0.01) mitigated by cysteamine (p<0.05) or fisetin (p<0.05) treatment, indicating the restoration of CSE-mediated autophagy-impairment. CSE treatment was also found to induce intracellular reactive oxygen species (ROS, p < 0.001) while impacting cell viability (p < 0.001), which was quantified using CMH2DCFDA-dye (ROS) and MTS (proliferation) or propodium iodide staining (cell viability) assays, respectively. Moreover, cysteamine and fisetin treatment ameliorated CS-mediated ROS production (p < 0.05) and diminished cell viability (p < 0.05). Lastly, CSE was found to induce cellular senescence (p < 0.001), which was significantly ameliorated by cysteamine (p < 0.001) or fisetin (p < 0.001). In conclusion, our study indicates that CS induced proteostasis/autophagy-impairment regulates mechanisms associated with AMD pathogenesis. Moreover, autophagy-inducing drugs such as cysteamine or fisetin can ameliorate AMD pathogenesis mechanisms that warrant further investigation in pre-clinical murine models.

PMID: 28767736


Altered activation state of circulating neutrophils in patients with neovascular age-related macular degeneration.

Krogh Nielsen M, Hector SM, Allen K, Subhi Y, Sørensen TL.

BACKGROUND: Neutrophil dysfunction plays a key role in the development of diseases characterized by inflammation and angiogenesis. Here, we studied the systemic expression of neutrophil markers reflecting activation, adhesion, and resolution of inflammation in patients with neovascular age-related macular degeneration (AMD).
RESULTS: This was a prospective case-control study of patients with neovascular AMD and age-matched healthy control individuals. Patients were recruited from an outpatient program, and control individuals were recruited amongst patients’ relatives. Current smokers and individuals with either active immune-disease or ongoing cancer were not included, as these factors are known to affect neutrophil function. Fresh-drawn venous blood was processed for flow cytometric analysis of neutrophil markers. We determined percentages of positive cells and compared expression levels using fluorescence intensity measures. We found conditional differences on marker expression between patients with neovascular AMD (n = 29) and controls (n = 28): no differences were found when looking broadly, but several differences emerged when focusing on non-smokers. Here, patients with neovascular AMD had increased expression of the activity marker cluster of differentiation (CD) 66b (P = 0.003; Mann-Whitney U test), decreased expression of adhesion marker CD162 (P = 0.044; Mann-Whitney U test), and lower expression of the resolution of inflammation marker C-X-C chemokine receptor 2 (P = 0.044; Mann-Whitney U test).

CONCLUSIONS: We present novel evidence suggesting that the activity of circulating neutrophils, sensitive to smoking, may differ in patients with neovascular AMD.

PMID: 28769990 PMCID: PMC5531023

Eur J Ophthalmol. 2017 Aug 2:0. [Epub ahead of print]

Increased levels of circulating CD34+ cells in neovascular age-related macular degeneration: relation with clinical and OCT features.

Kara C, Ç Özdal P, Beyazyıldız E, E Özcan N, Y Teke M, Vural G, Öztürk F.

PURPOSE: To investigate the levels of circulating CD34+ stem cells in patients with neovascular type age-related macular degeneration (AMD) and its relation with clinical and optical coherence tomography (OCT) findings.

METHODS: The study consisted of 55 patients: 28 patients (18 male and 10 female) with neovascular type AMD as a study group and 27 patients (12 male and 15 female) scheduled for cataract surgery as a control group. The level of CD34+ stem cells was measured by flow cytometry. Demographic and clinical data were recorded.

RESULTS: The mean ages of patients in the study and control groups were 71 ± 8 and 68 ± 6 years, respectively. There was no statistically significant difference in terms of age, sex, or systemic disease association between study and control groups. However, smoking status was significantly higher in the study group (67.9% vs 37.0%; p = 0.02). Stem cell levels were significantly higher in the study group (1.5 ± 0.9 vs 0.5 ± 0.3; p<0.001), but there was no relation between stem cell levels and clinical and OCT findings.

CONCLUSIONS: Increased circulating CD34+ stem cell levels were observed in patients with choroidal neovascular membrane associated with AMD, but no significant relation was found between cell levels and clinical and OCT findings.

PMID: 28777387


A computational study of VEGF production by patterned retinal epithelial cell colonies as a model for neovascular macular degeneration.

Baker QB, Podgorski GJ, Vargis E, Flann NS.

BACKGROUND: The configuration of necrotic areas within the retinal pigmented epithelium is an important element in the progression of age-related macular degeneration (AMD). In the exudative (wet) and non-
exudative (dry) forms of the disease, retinal pigment epithelial (RPE) cells respond to adjacent atrophied regions by secreting vascular endothelial growth factor (VEGF) that in turn recruits new blood vessels which lead to a further reduction in retinal function and vision. In vitro models exist for studying VEGF expression in wet AMD (Vargis et al., Biomaterials 35(13):3999-4004, 2014), but are limited in the patterns of necrotic and intact RPE epithelium they can produce and in their ability to finely resolve VEGF expression dynamics.

RESULTS: In this work, an in silico hybrid agent-based model was developed and validated using the results of this cell culture model of VEGF expression in AMD. The computational model was used to extend the cell culture investigation to explore the dynamics of VEGF expression in different sized patches of RPE cells and the role of negative feedback in VEGF expression. Results of the simulation and the cell culture studies were in excellent qualitative agreement, and close quantitative agreement.

CONCLUSIONS: The model indicated that the configuration of necrotic and RPE cell-containing regions have a major impact on VEGF expression dynamics and made precise predictions of VEGF expression dynamics by groups of RPE cells of various sizes and configurations. Coupled with biological studies, this model may give insights into key molecular mechanisms of AMD progression and open routes to more effective treatments.

PMID: 28775765 PMCID: PMC5540422


The Involvement of the Oxidative Stress in Murine Blue LED Light-Induced Retinal Damage Model.

Nakamura M, Kuse Y, Tsuruma K, Shimazawa M, Hara H.

Abstract: The aim of study was to establish a mouse model of blue light emitting diode (LED) light-induced retinal damage and to evaluate the effects of the antioxidant N-acetylcysteine (NAC). Mice were exposed to 400 or 800 lx blue LED light for 2 h, and were evaluated for retinal damage 5 d later by electroretinogram amplitude and outer nuclear layer (ONL) thickness. Additionally, we investigated the effect of blue LED light exposure on shorts-wave-sensitive opsin (S-opsin), and rhodopsin expression by immunohistochemistry. Blue LED light induced light intensity dependent retinal damage and led to collapse of S-opsin and altered rhodopsin localization from inner and outer segments to ONL. Conversely, NAC administered at 100 or 250 mg/kg intraperitoneally twice a day, before dark adaptation and before light exposure. NAC protected the blue LED light-induced retinal damage in a dose-dependent manner. Further, blue LED light-induced decreasing of S-opsin levels and altered rhodopsin localization, which were suppressed by NAC. We established a mouse model of blue LED light-induced retinal damage and these findings indicated that oxidative stress was partially involved in blue LED light-induced retinal damage.

PMID: 28769003


Kubo Y, Akanuma SI, Hosoya KI.

Abstract: The retina is a tissue essential for vision, and the blood-retina barrier (BRB) helps to maintain an optimal microenvironment for the neural system in the retina. Recent findings concerning the BRB showed the involvement of transporters at the inner and outer BRB in drug and nutrient transport, suggesting their utility in the development of novel drug delivery systems to the retina. An in vitro-in vivo relationship study of permeability suggested the influx transport of verapamil, a cationic drug, across the BRB, and further in
vivo and in vitro studies of cationic drugs, such as verapamil, propranolol and clonidine, revealed the involvement of carrier-mediated process in their influx transport at the BRB. Studies on substrate specificity in TR-iBRB2 cells, an in vitro model cell line of the inner BRB, suggests the involvement of novel organic cation transporter in the influx transport of cationic drugs at the inner BRB. Considering the neuroprotective effect previously reported for several cationic drugs, such as propranolol and clonidine, the study of cation transport at the BRB is widely expected to improve the treatment of retinal diseases, such as diabetic retinopathy and age-related macular degeneration.

PMID: 28768994 DOI: 10.1248/bpb.b17-00090


Exploring the cross talk between ER stress and inflammation in age-related macular degeneration.

Kheitan S, Minuchehr Z, Soheili ZS.

Abstract: Increasing evidence demonstrates that inflammation and endoplasmic reticulum (ER) stress is implicated in the development and progression of age-related macular degeneration (AMD), a multifactorial neurodegenerative disease. However the cross talk between these cellular mechanisms has not been clearly and fully understood. The present study investigates a possible intersection between ER stress and inflammation in AMD. In this study, we recruited two collections of involved protein markers to retrieve their interaction information from IMEx-curated databases, which are the most well-known protein-protein interaction collections, allowing us to design an intersection network for AMD that is unprecedented. In order to find expression activated subnetworks, we utilized AMD expression profiles in our network. In addition, we studied topological characteristics of the most expressed active subnetworks to identify the hubs. With regard to topological quantifications and expression activity, we reported a list of the most pivotal hubs which are potentially applicable as probable therapeutic targets. Furthermore, we introduced MAPK signaling pathway as a significantly involved pathway in the association between ER stress and inflammation, leading to promising new directions in discovering AMD formation mechanisms and possible treatments.

PMID: 28742151

FASEB J. 2017 Jul 24. [Epub ahead of print]

Animal models of ocular angiogenesis: from development to pathologies.

Liu CH, Wang Z, Sun Y, Chen J.

Abstract: Pathological angiogenesis in the eye is an important feature in the pathophysiology of many vision-threatening diseases, including retinopathy of prematurity, diabetic retinopathy, and age-related macular degeneration, as well as corneal diseases with abnormal angiogenesis. Development of reproducible and reliable animal models of ocular angiogenesis has advanced our understanding of both the normal development and the pathobiology of ocular neovascularization. These models have also proven to be valuable experimental tools with which to easily evaluate potential antiangiogenic therapies beyond eye research. This review summarizes the current available animal models of ocular angiogenesis. Models of retinal and choroidal angiogenesis, including oxygen-induce retinopathy, laser-induced choroidal neovascularization, and transgenic mouse models with deficient or spontaneous retinal/choroidal neovascularization, as well as models with induced corneal angiogenesis, are widely used to investigate the molecular and cellular basis of angiogenic mechanisms. Theoretical concepts and experimental protocols of these models are outlined, as well as their advantages and potential limitations, which may help researchers choose the most suitable models for their investigative work.-Liu, C.-H., Wang, Z., Sun, Y., Chen, J. Animal models of ocular angiogenesis: from development to pathologies.

PMID: 28739642

A pro-inflammatory function of toll-like receptor 2 in the retinal pigment epithelium as a novel target for reducing choroidal neovascularization in age-related macular degeneration.


Abstract: Current treatments for choroidal neovascularization, a major cause of blindness for patients with age-related macular degeneration, treat symptoms but not the underlying causes of the disease. Inflammation has been strongly implicated in the pathogenesis of choroidal neovascularization. We examined the inflammatory role of toll-like receptor 2 (TLR2) in age-related macular degeneration. TLR2 was robustly expressed by the retinal pigment epithelium in mouse and human eyes, both normal and with macular degeneration/choroidal neovascularization. Nuclear localization of NF-κB, a major downstream target of TLR2 signaling, was detected in the retinal pigment epithelium of human eyes, particularly in those with advanced stages of age-related macular degeneration. TLR2 antagonism effectively suppressed initiation and growth of spontaneous choroidal neovascularization in a mouse model, and the combination of anti-TLR2 and anti-vascular endothelial growth factor receptor 2 yielded an additive therapeutic effect on both area and number of spontaneous choroidal neovascularization lesions. Lastly, in primary human fetal retinal pigment epithelium cells, ligand binding to TLR2 induced robust expression of pro-inflammatory cytokines, and end products of lipid oxidation had a synergistic effect on TLR2 activation. Our data illustrate a functional role for TLR2 in the pathogenesis of choroidal neovascularization, likely by promoting inflammation of the retinal pigment epithelium, and validate TLR2 as a novel therapeutic target for reducing choroidal neovascularization.

PMID: 28739342


Neuroprotection by (endo)cannabinoids in glaucoma and retinal neurodegenerative diseases.

Rapino C, Tortolani D, Scipioni L, Maccarrone M.

Abstract: Emerging neuroprotective strategies are being explored to preserve the retina from degeneration, that occurs in eye pathologies like glaucoma, diabetic retinopathy, age-related macular degeneration, and retinitis pigmentosa. Incidentally, neuroprotection of retina is a defending mechanism designed to prevent or delay neuronal cell death, and to maintain neural function following an initial insult, thus avoiding loss of vision. Numerous studies have investigated potential neuroprotective properties of plant-derived phytocannabinoids, as well as of their endogenous counterparts collectively termed endocannabinoids (eCBs), in several degenerative diseases of the retina. eCBs are a group of neuromodulators that, mainly by activating G protein-coupled type-1 and type-2 cannabinoid (CB1 and CB2) receptors, trigger multiple signal transduction cascades that modulate central and peripheral cell functions. A fine balance between biosynthetic and degrading enzymes that control the right concentration of eCBs has been shown to provide neuroprotection in traumatic, ischemic, inflammatory and neurotoxic damage of the brain. Since the existence of eCBs and their binding receptors was documented in the retina of numerous species (from fishes to primates), their involvement in the visual processing has been demonstrated, more recently with a focus on retinal neurodegeneration and neuroprotection. The aim of this review is to present a modern view of the endocannabinoid system, in order to discuss in a better perspective available data from preclinical studies on the use of eCBs as new neuroprotective agents, potentially useful to prevent glaucoma and retinal neurodegenerative diseases.

PMID: 28738764

Anti-Vascular Endothelial Growth Factors Protect Retinal Pigment Epithelium Cells Against Oxidation by Modulating Nitric Oxide Release and Autophagy.


BACKGROUND/AIMS: The anti-vascular endothelial growth factors (VEGF), Aflibercept and Ranibizumab, are used for the treatment of macular degeneration. Here we examined the involvement of nitric oxide (NO), mitochondria function and of apoptosis/autophagy in their antioxidant effects in human retinal pigment epithelium cells (RPE).

METHODS: RPE were exposed to Ranibizumab/Aflibercept in the absence or presence of NO synthase (NOS) inhibitor and of autophagy activator/blocker, rapamicyn/3-methyladenine. Specific kits were used for cell viability, NO and reactive oxygen species detection and mitochondrial membrane potential measurement, whereas Western Blot was performed for apoptosis/autophagy markers and other kinases detection.

RESULTS: In RPE cultured in physiological conditions, Aflibercept/Ranibizumab increased NO release in a dose and time-dependent way. Opposite results were obtained in RPE pretreated with hydrogen peroxide. Moreover, both the anti-VEGF agents were able to prevent the fall of cell viability and of mitochondrial membrane potential. Those effects were reduced by the NOS inhibitor and 3-methyladenine and were potentiated by rapamycin. Finally, Aflibercept and Ranibizumab counteracted the changes of apoptosis/autophagy markers, NOS, Phosphatidylinositol-3-Kinase/Protein Kinase B and Extracellular signal-regulated kinases 1/2 caused by peroxidation.

CONCLUSION: Aflibercept and Ranibizumab protect RPE against peroxidation through the modulation of NO release, apoptosis and autophagy.

PMID: 28743128


Anti-angiogenic properties of artemisinin derivatives (Review).

Wei T, Liu J.

Abstract: Angiogenesis, the process involving the development of new blood vessels from existing capillaries, is critical for growth and wound healing. However, pathological angiogenesis contributes to the pathogenesis of numerous diseases, including cancer, rheumatoid arthritis, diabetic retinopathy and macular degeneration. Hence, the inhibition of angiogenesis is an effective therapeutic approach for these diseases. Apart from its anti-malarial properties, artemisinin and its derivatives also exhibit potent anti-angiogenic properties. The molecular mechanisms underlying their inhibitory effects on angiogenesis have been studied by several groups. These investigations have revealed that artemisinins inhibit angiogenesis via the perturbations of cellular signaling pathways involved in the regulation of angiogenesis. Along with a brief introduction to artemisinin derivatives, this review provides a detailed summary of the effects of artemisinins on the mitogen-activated protein kinase (MAPK) pathway, the nuclear factor-κB (NF-κB) pathway and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway. Due to the multiplicity of their actions on relevant signaling pathways, artemisinins are promising candidates with potential for use as anti-angiogenic agents for the treatment of related diseases or disorders.

PMID: 28765885
Intravitreal injection of docosahexaenoic acid attenuated photoreceptor cell injury in a NaIO3-induced age-related macular degeneration rat model.


Abstract: In most studies, the major supplement docosahexaenoic acid (DHA) is administered orally or intraperitoneally. In this study, we proposed to assess the safety and efficacy of the intravitreal injection of DHA in an age-related macular degeneration (AMD) rat model. Different concentrations of DHA were injected into the vitreous body. Histopathology and terminal deoxynucleotidyl transferase dUTP nick-end labeling (TUNEL) analysis showed that there was no difference in thickness, observable structure, or apoptosis among the untreated, normal saline, and DHA groups (0.2, 1.0, 5.0 and 10 μg). However, GFAP expression was increased in the 10 μg group. To investigate whether intravitreal injection of DHA could protect photoreceptors, we developed a NaIO3-induced retinal damage model in adult rats. Decreases in deformation and thickness were observed in the outer nuclear layer (ONL) after NaIO3 administration but were improved with DHA injection. The NaIO3 group showed a substantial reduction in the number of nuclei in ONL, whereas the DHA group showed an increase. Additionally, significant increases in SOD activity and Nrf2 expression were observed after DHA injection; GFAP and NF-κB expression levels were markedly decreased by DHA injection. Moreover, Western blotting showed that Bax, cleaved caspase-3 and CHOP were notably increased in the NaIO3 group but were significantly decreased by DHA injection. Collectively, intravitreal injection of DHA is safe and effective in select doses in a NaIO3-induced AMD rat model. The current results suggest that intravitreal injection of DHA may be a new avenue for the treatment of AMD.

PMID: 28751206

Taxifolin protects RPE cells against oxidative stress-induced apoptosis.


PURPOSE: Oxidative stress-induced damage to RPE cells has been suggested to be an important factor in the pathogenesis of age-related macular degeneration. Taxifolin, a flavonol, has been shown to exhibit significant antioxidant properties. The purpose of this study was to investigate the potential protective effects of taxifolin on RPE cells cultured under oxidative stress conditions and to elucidate the underlying mechanisms.

METHODS: Human RPE (ARPE-19) cells were treated with different concentrations of taxifolin and 0.4 mM of H2O2 for 24 h. Cell viability was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. Apoptosis was quantitatively measured by annexin V/propidium iodide double staining, and the expression levels of poly (ADP-ribose) polymerase (PARP) were evaluated by western blotting. Reactive oxygen species (ROS) were measured using a commercially available ROS detection system. The expressions of phase II enzymes, including NAD(P)H quinone oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), and glutamate-cysteine ligase modifier (GCLM) and catalytic (GCLC) subunits, were examined using real-time PCR and western blotting. The nuclear localization of the nuclear factor (erythroid-derived 2)-like 2 (NRF2) protein was detected by western blotting. Results: Taxifolin clearly inhibited the decrease in H2O2-induced cell viability, cell apoptosis, and intracellular ROS generation. In addition, taxifolin inhibited the H2O2-induced PARP cleavage. Moreover, treatment with taxifolin activated mRNA and the protein expression of NRF2 by inducing the translocation of NRF2 to the nucleus. Consequently, the mRNA and protein levels of the phase II enzymes NQO1, HO-1, GCLM, and GCLC increased. Conclusions: Taxifolin was shown to protect RPE cells against oxidative stress-induced apoptosis. The potential mechanism appears to involve the activation of NRF2 and the phase II antioxidant enzyme system.

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Epidemiology

JAMA Ophthalmol. 2017 Jul 27. [Epub ahead of print]

Association of C-Reactive Protein Genetic Polymorphisms With Late Age-Related Macular Degeneration.


IMPORTANCE: C-reactive protein (CRP) is a circulating inflammatory marker associated with late age-related macular degeneration (AMD). It remains uncertain whether the association between CRP concentrations and AMD is causal.

OBJECTIVE: To assess whether CRP (OMIM 123260) single-nucleotide polymorphisms that influence circulating CRP concentrations are associated with late AMD.

DESIGN, SETTING, AND PARTICIPANTS: Participants in 2 UK, hospital-based, case-control studies (Cambridge AMD study and Moorfields Eye Hospital AMD study) and 1 pan-European, cross-sectional, population-based study (the European Eye [EUREYE] Study) were recruited between November 6, 2000, and April 30, 2007. Participants underwent dilated stereo-digital fundus photography graded according to the International Classification of Age-related Maculopathy and Macular Degeneration. There were 1727 cases of late AMD (1151 neovascular, 384 geographic atrophy, and 192 mixed [neovascular AMD and geographic atrophy]) and 1153 controls. Early AMD cases (n = 574) were included only from the EUREYE Study. Data analysis was performed from August 1 to November 30, 2016. Four common single-nucleotide polymorphisms (rs1205, rs1130864, rs1800947, and rs3093077) were selected based on demonstrated influence on circulating CRP concentrations in the literature. In one study, genotyping of rs3093077 failed, and rs1800947 was typed in only 1 study.

MAIN OUTCOMES AND MEASURES: A genetic multiplicative model was used for the association of single-nucleotide polymorphisms with late AMD adjusted for age and sex.

RESULTS: Among the 1727 patients with late AMD, the mean (SD) age was 78.7 (7.4) years, and 668 (38.7%) were men. The mean (SD) age of the controls was 74.9 (7.0) years, and 510 (44.2%) were men. In the pooled results of all 3 studies, neither rs1205 (odds ratio [OR], 0.99; 95% CI, 0.86-1.14) nor rs1130864 (OR, 0.96; 95% CI, 0.83-1.11) was associated with late AMD. For geographic atrophy, rs1205 had an OR of 0.91 (95% CI, 0.74-1.13) and rs1130864 had an OR of 0.94 (95% CI, 0.76-1.16). For neovascular AMD, rs1205 had an OR of 1.01 (95% CI, 0.87-1.19) and rs1130864 had an OR of 0.99 (95% CI, 0.84-1.16). There was no association of rs3093077 and rs1800947 with late AMD or any late AMD phenotype. There were no significant findings for early AMD.

CONCLUSIONS AND RELEVANCE: Our results do not support a causal association between CRP concentrations and AMD.

PMID: 28750115

JAMA Ophthalmol. 2017 Jul 27. [Epub ahead of print]

Association Between C-Reactive Protein and Age-Related Macular Degeneration: Les Liaisons Dangereuses.

Keenan TD, Chew EY.

PMID: 28750126
Genetics


Identification of candidate protective variants for common diseases and evaluation of their protective potential.

Butler JM, Hall N, Narendran N, Yang YC, Paraoan L.

BACKGROUND: Human polymorphisms with derived alleles that are protective against disease may provide powerful translational opportunities. Here we report a method to identify such candidate polymorphisms and apply it to common non-synonymous SNPs (nsSNPs) associated with common diseases. Our study also sought to establish which of the identified protective nsSNPs show evidence of positive selection, taking this as indirect evidence that the protective variant has a beneficial effect on phenotype. Further, we performed an analysis to quantify the predicted effect of each protective variant on protein function/structure.

RESULTS: An initial analysis of eight SNPs previously identified as associated with age-related macular degeneration (AMD), revealed that two of them have a derived allele that is protective against developing the disease. One is in the complement component 2 gene (C2; E318D) and the other is in the complement factor B gene (CFB; R32Q). Then, combining genomewide ancestral allele information with known common disease-associated nsSNPs from the GWAS catalog, we found 32 additional SNPs which have a derived allele that is disease protective. Out of the total 34 identified candidate protective variants (CPVs), we found that 30 show stronger evidence of positive selection than the protective variant in lipoprotein lipase (LPL; S447X), which has already been translated into gene therapy. Furthermore, 11 of these CPVs have a higher probability of affecting protein structure than the lipoprotein lipase protective variant (LPL; S447X).

CONCLUSIONS: We identify 34 CPVs from the human genome. Diseases they confer protection against include, but are not limited to, type 2 diabetes, inflammatory bowel disease, age-related macular degeneration, multiple sclerosis and rheumatoid arthritis. We propose that those 30 CPVs with evidence of stronger positive selection than the LPL protective variant, may be considered as priority candidates for therapeutic approaches. The next step towards translation will require testing the hypotheses generated by our analyses, specifically whether the CPV arose from a gain-of-function or a loss-of-function mutation.

PMID: 28774272


A genome-wide association study identified a novel genetic loci STON1-GTF2A1L/LHCGR/FSHR for bilaterality of neovascular age-related macular degeneration.


Abstract: Bilateral neovascular age-related macular degeneration (AMD) causes much more handicaps for patients than unilateral neovascular AMD. Although several AMD-susceptibility genes have been evaluated for their associations to bilaterality, genome-wide association study (GWAS) on bilaterality has been rarely reported. In the present study, we performed GWAS using neovascular AMD cases in East Asian. The discovery stage compared 581,252 single nucleotide polymorphisms (SNPs) between 803 unilateral and 321 bilateral Japanese cases but no SNP showed genome-wide significance, while SNPs at six regions showed P-value < 1.0 × 10-5, STON1-GTF2A1/LHCGR/FSHR, PLXNA1, CTNNA3, ARMS2/HTRA1, LHFP, and FLJ38725. The first replication study for these six regions comparing 36 bilateral and 132 unilateral Japanese cases confirmed significant associations of rs4482537 (STON1-GTF2A1/LHCGR/ FSHR), rs2284665 (ARMS2/HTRA1), and rs8002574 (LHFP) to bilaterality. In the second replication study comparing 24 bilateral and 78 unilateral cases from Singapore, rs4482537 (STON1-GTF2A1/LHCGR/ FSHR) only showed significant association. Meta-analysis of discovery and replication studies confirmed genome-wide level significant association (P = 2.61 × 10-9) of rs4482537 (STON1-GTF2A1/LHCGR/
FSHR) and strong associations (\(P = 5.76 \times 10^{-7}\) and \(9.73 \times 10^{-7}\), respectively) of rs2284665 (ARMS2/HTRA1) and rs8002574 (LHFP). Our GWAS for neovascular AMD bilaterality found new genetic loci STON1-GTF2A1/LHCGR/FSHR and confirmed the previously reported association of ARMS2/HTRA1.

PMID: 28775256

**Nat Commun. 2017 Jul 24;8(1):112.**

**Genome editing abrogates angiogenesis in vivo.**


Abstract: Angiogenesis, in which vascular endothelial growth factor receptor (VEGFR) 2 plays an essential role, is associated with a variety of human diseases including proliferative diabetic retinopathy and wet age-related macular degeneration. Here we report that a system of adeno-associated virus (AAV)-mediated clustered regularly interspaced short palindromic repeats (CRISPR)-associated endonuclease (Cas)9 from Streptococcus pyogenes (SpCas9) is used to deplete VEGFR2 in vascular endothelial cells (ECs), whereby the expression of SpCas9 is driven by an endothelial-specific promoter of intercellular adhesion molecule 2. We further show that recombinant AAV serotype 1 (rAAV1) transduces ECs of pathologic vessels, and that editing of genomic VEGFR2 locus using rAAV1-mediated CRISPR/Cas9 abrogates angiogenesis in the mouse models of oxygen-induced retinopathy and laser-induced choroid neovascularization. This work establishes a strong foundation for genome editing as a strategy to treat angiogenesis-associated diseases. Abnormal angiogenesis causes many ocular diseases. Here the authors employ CRISPR/Cas9 gene editing technology to silence VEGFR2, a major regulator of angiogenesis, in retinal endothelium and abrogate angiogenesis in the mouse models of oxygen-induced retinopathy and laser-induced choroid neovascularization.

PMID: 28740073 PMCID: PMC5524639

**Hum Gene Ther Methods. 2017 Jul 27. [Epub ahead of print]**

**Suppression of choroidal neovascularization in mice by subretinal delivery of multigenic lentiviral vectors encoding anti-angiogenic microRNAs.**

Askou AL, Benckendorff JNE, Holmgaard A, Storm T, Aagaard L, Bek T, Mikkelsen JG, Corydon TJ.

Abstract: Lentivirus-based vectors have been used for the development of potent gene therapies. Here, we present application of a multigenic lentiviral vector (LV) producing multiple anti-angiogenic microRNAs following subretinal delivery in a laser-induced choroidal neovascularization (CNV) mouse model. This versatile LV, carrying back-to-back RNApolII-driven expression cassettes, enables combined expression of microRNAs targeting vascular endothelial growth factor A (Vegfa) mRNA, and fluorescent reporters. In addition, by including a vitelliform macular dystrophy 2 (VMD2) promoter, expression of microRNAs is restricted to the retinal pigment epithelial (RPE) cells. Already 6 days post injection (PI) robust and widespread fluorescent signals of eGFP are observed in the retina by fundoscopy. The eGFP expression peaks at day 21 PI and persists with stable expression for at least 9 months. In parallel, prominent AsRED co-expression, encoded from the VMD2-driven microRNA expression cassette, is evident in retinal sections and flat-mounts, revealing RPE-specific expression of microRNAs. Furthermore, LV-delivered microRNAs targeting the Vegfa gene in RPE cells reduced the size of laser-induced CNV in mice 28 days PI, as a consequence of diminished VEGF levels, suggesting that LVS delivered locally are powerful tools in the development of gene therapy-based strategies for treatment of age-related macular degeneration (AMD).

PMID: 28750559
Stem cells


Stem Cell Therapies for Reversing Vision Loss.

Higuchi A, Kumar SS, Benelli G, Alarfaj AA, Munusamy MA, Umezawa A, Murugan K.

Abstract: Current clinical trials that evaluate human pluripotent stem cell (hPSC)-based therapies predominantly target treating macular degeneration of the eyes because the eye is an isolated tissue that is naturally weakly immunogenic. Here, we discuss current bioengineering approaches and biomaterial usage in combination with stem cell therapy for macular degeneration disease treatment. Retinal pigment epithelium (RPE) differentiated from hPSCs is typically used in most clinical trials for treating patients, whereas bone marrow mononuclear cells (BMNCs) or mesenchymal stem cells (MSCs) are intravitreally transplanted, undifferentiated, into patient eyes. We also discuss reported negative effects of stem cell therapy, such as patients becoming blind following transplantation of adipose-derived stem cells, which are increasingly used by 'stem-cell clinics'.

PMID: 28751147

Diet, lifestyle & low vision

Exp Brain Res. 2017 Aug 1. [Epub ahead of print]

Effects of acute peripheral/central visual field loss on standing balance.

O'Connell C, Mahboobin A, Drexler S, Redfern MS, Perera S, Nau AC, Cham R.

Abstract: Vision impairments such as age-related macular degeneration (AMD) and glaucoma are among the top risk factors for geriatric falls and falls-related injuries. AMD and glaucoma lead to loss of the central and peripheral visual fields, respectively. This study utilized a custom contact lens model to occlude the peripheral or central visual fields in healthy adults, offering a novel within-subject approach to improve our understanding of the etiology of balance impairments that may lead to an increased fall risk in patients with visual field loss. Two dynamic posturography tests, including an adapted version of the Sensory Organization Test and a virtual reality environment with the visual scene moving sinusoidally, were used to evaluate standing balance. Balance stability was quantified by displacement and time-normalized path length of the center of pressure. Nine young and eleven older healthy adults wore visual field occluding contact lenses during posturography assessments to compare the effects of acute central and peripheral visual field occlusion. The results found that visual field occlusion had greater impact on older adults than young adults, specifically when proprioceptive cues are unreliable. Furthermore, the results suggest that both central and peripheral visions are important in postural control; however, peripheral vision may be more sensitive to movement in the environment.

PMID: 28765993


Adiponectin Mediates Dietary Omega-3 Long-Chain Polyunsaturated Fatty Acid Protection Against Choroidal Neovascularization in Mice.


PURPOSE: Neovascular age-related macular degeneration (AMD) is a major cause of legal blindness in...
the elderly. Diets with omega3-long-chain-polyunsaturated-fatty-acid (ω3-LCPUFA) correlate with a decreased risk of AMD. Dietary ω3-LCPUFA versus ω6-LCPUFA inhibits mouse ocular neovascularization, but the underlying mechanism needs further exploration. The aim of this study was to investigate if adiponectin (APN) mediated ω3-LCPUFA suppression of neovessels in AMD.

METHODS: The mouse laser-induced choroidal neovascularization (CNV) model was used to mimic some of the inflammatory aspect of AMD. CNV was compared between wild-type (WT) and Apn−/− mice fed either otherwise matched diets with 2% ω3 or 2% ω6-LCPUFAs. Vldlr−/− mice were used to mimic some of the metabolic aspects of AMD. Choroid assay ex vivo and human retinal microvascular endothelial cell (HRMEC) proliferation assay in vitro was used to investigate the APN pathway in angiogenesis. Western blot for p-AMPKα/AMPKα and qPCR for Apn, Mmps, and IL-10 were used to define mechanism.

RESULTS: ω3-LCPUFA intake suppressed laser-induced CNV in WT mice; suppression was abolished with APN deficiency. ω3-LCPUFA, mediated by APN, decreased mouse Mmps expression. APN deficiency decreased AMPKα phosphorylation in vivo and exacerbated choroid-sprouting ex vivo. APN pathway activation inhibited HRMEC proliferation and decreased Mmps. In Vldlr−/− mice, ω3-LCPUFA increased retinal AdipoR1 and inhibited NV. ω3-LCPUFA decreased IL-10 but did not affect Mmps in Vldlr−/− retinas.

CONCLUSIONS: APN in part mediated ω3-LCPUFA inhibition of neovascularization in two mouse models of AMD. Modulating the APN pathway in conjunction with a ω3-LCPUFA-enriched-diet may augment the beneficial effects of ω3-LCPUFA in AMD patients.

PMID: 28763559 PMCID: PMC5539800

Curr Med Chem. 2017 Aug 1. [Epub ahead of print]

Therapeutic potential of co-enzyme Q10 in retinal diseases.
Zhang X, Tohari AM, Marcheggiani F, Zhou X, Reilly J, Tiano L, Shu X.

Abstract: Coenzyme Q10 (CoQ10) plays a critical role in mitochondrial oxidative phosphorylation by serving as an electron carrier in the respiratory electron transport chain. CoQ10 also functions as a lipid-soluble antioxidant by protecting lipids, proteins and DNA damaged by oxidative stress. CoQ10 deficiency has been associated with a number of human diseases including mitochondrial diseases, neurodegenerative disorders, cardiovascular diseases, diabetes, cancer, and with the ageing process. In many of these conditions CoQ10 supplementation therapy has been effective in slowing or reversing pathological changes. Oxidative stress is a major contributory factor in the process of retinal degeneration. In this brief review, we summarize the functions of CoQ10 and highlight its use in the treatment of age-related macular degeneration and glaucoma. In light of these data we propose that CoQ10 could have therapeutic potential for other retinal diseases.

PMID: 28762311


Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration.

Evans JR, Lawrenson JG.

BACKGROUND: It has been proposed that antioxidants may prevent cellular damage in the retina by reacting with free radicals that are produced in the process of light absorption. Higher dietary levels of antioxidant vitamins and minerals may reduce the risk of progression of age-related macular degeneration (AMD).
OBJECTIVES: The objective of this review was to assess the effects of antioxidant vitamin or mineral supplementation on the progression of AMD in people with AMD.

SEARCH METHODS: We searched CENTRAL (2017, Issue 2), MEDLINE Ovid (1946 to March 2017), Embase Ovid (1947 to March 2017), AMED (1985 to March 2017), OpenGrey (System for Information on Grey Literature in Europe), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 29 March 2017.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) that compared antioxidant vitamin or mineral supplementation (alone or in combination) to placebo or no intervention, in people with AMD.

DATA COLLECTION AND ANALYSIS: Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5; the other author checked the data entry. We graded the certainty of the evidence using GRADE.

MAIN RESULTS: We included 19 studies conducted in USA, Europe, China, and Australia. We judged the trials that contributed data to the review to be at low or unclear risk of bias. Nine studies compared multivitamins with placebo (7 studies) or no treatment (2 studies) in people with early and moderate AMD. The duration of supplementation and follow-up ranged from nine months to six years; one trial followed up beyond two years. Most evidence came from the Age-Related Eye Disease Study (AREDS) in the USA. People taking antioxidant vitamins were less likely to progress to late AMD (odds ratio (OR) 0.72, 95% confidence interval (CI) 0.58 to 0.90; 2445 participants; 3 RCTs; moderate-certainty evidence). In people with very early signs of AMD, who are at low risk of progression, this would mean that there would be approximately 4 fewer cases of progression to late AMD for every 1000 people taking vitamins (1 fewer to 6 fewer cases). In people at high risk of progression (i.e. people with moderate AMD) this would correspond to approximately 8 fewer cases of progression for every 100 people taking vitamins (3 fewer to 13 fewer). In one study of 1206 people, there was a lower risk of progression for both neovascular AMD (OR 0.62, 95% CI 0.47 to 0.82; moderate-certainty evidence) and geographic atrophy (OR 0.75, 95% CI 0.51 to 1.10; moderate-certainty evidence) and a lower risk of losing 3 or more lines of visual acuity (OR 0.77, 95% CI 0.62 to 0.96; 1791 participants; moderate-certainty evidence). Low-certainty evidence from one study of 110 people suggested higher quality of life scores (National Eye Institute Visual Function Questionnaire) in treated compared with the non-treated people after 24 months (mean difference (MD) 12.30, 95% CI 4.24 to 20.36). Six studies compared lutein (with or without zeaxanthin) with placebo. The duration of supplementation and follow-up ranged from six months to five years. Most evidence came from the AREDS2 study in the USA. People taking lutein or zeaxanthin may have similar or slightly reduced risk of progression to late AMD (RR 0.94, 95% CI 0.87 to 1.01; 6891 eyes; low-certainty evidence), neovascular AMD (RR 0.92, 95% CI 0.84 to 1.02; 6891 eyes; low-certainty evidence), and geographic atrophy (RR 0.92, 95% CI 0.80 to 1.05; 6891 eyes; low-certainty evidence). A similar risk of progression to visual loss of 15 or more letters was seen in the lutein and control groups (RR 0.98, 95% CI 0.91 to 1.05; 6656 eyes; low-certainty evidence). Quality of life (measured with Visual Function Questionnaire) was similar between groups in one study of 108 participants (MD 1.48, 95% -5.53 to 8.49, moderate-certainty evidence). One study, conducted in Australia, compared vitamin E with placebo. This study randomised 1204 people to vitamin E or placebo, and followed up for four years. Participants were enrolled from the general population; 19% had AMD. The number of late AMD events was low (N = 7) and the estimate of effect was uncertain (RR 1.36, 95% CI 0.31 to 6.05, very low-certainty evidence). There were no data on neovascular AMD or geographic atrophy. There was no evidence of any effect of treatment on visual loss (RR 1.04, 95% CI 0.74 to 1.47, low-certainty evidence). There were no data on quality of life. Five studies compared zinc with placebo. The duration of supplementation and follow-up ranged from six months to seven years. People taking zinc supplements may be less likely to progress to late AMD (OR 0.83, 95% CI 0.70 to 0.98; 3790 participants; 3 RCTs; low-certainty evidence), neovascular AMD (OR 0.76, 95% CI 0.62 to 0.93; 2442 participants; 1 RCT; moderate-certainty evidence), geographic atrophy (OR 0.84, 95% CI 0.64 to 1.10; 2442 participants; 1 RCT; moderate-certainty evidence), or visual loss (OR 0.87, 95% CI 0.75 to 1.00; 3791
participants; 2 RCTs; moderate-certainty evidence). There were no data reported on quality of life. Very low-certainty evidence was available on adverse effects because the included studies were underpowered and adverse effects inconsistently reported.

AUTHORS’ CONCLUSIONS:

People with AMD may experience some delay in progression of the disease with multivitamin antioxidant vitamin and mineral supplementation. This finding was largely drawn from one large trial, conducted in a relatively well-nourished American population. We do not know the generalisability of these findings to other populations. Although generally regarded as safe, vitamin supplements may have harmful effects. A systematic review of the evidence on harms of vitamin supplements is needed. Supplements containing lutein and zeaxanthin are heavily marketed for people with age-related macular degeneration but our review shows they may have little or no effect on the progression of AMD.

PMID: 28756618


Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration.

Evans JR, Lawrenson JG.

BACKGROUND: There is inconclusive evidence from observational studies to suggest that people who eat a diet rich in antioxidant vitamins (carotenoids, vitamins C, and E) or minerals (selenium and zinc) may be less likely to develop age-related macular degeneration (AMD).

OBJECTIVES: To determine whether or not taking antioxidant vitamin or mineral supplements, or both, prevent the development of AMD.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2017, Issue 2), MEDLINE Ovid (1946 to 29 March 2017), Embase Ovid (1947 to 29 March 2017), AMED (Allied and Complementary Medicine Database) (1985 to 29 March 2017), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/); searched 29 March 2017, the ISRCTN registry (www.isrctn.com/editAdvancedSearch); searched 29 March 2017, ClinicalTrials.gov (www.clinicaltrials.gov); searched 29 March 2017 and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en); searched 29 March 2017. We did not use any date or language restrictions in the electronic searches for trials.

SELECTION CRITERIA: We included all randomised controlled trials (RCTs) comparing an antioxidant vitamin or mineral supplement (alone or in combination) to control.

DATA COLLECTION AND ANALYSIS: Both review authors independently assessed risk of bias in the included studies and extracted data. One author entered data into RevMan 5; the other author checked the data entry. We pooled data using a fixed-effect model. We graded the certainty of the evidence using GRADE.

MAIN RESULTS: We included a total of five RCTs in this review with data available for 76,756 people. The trials were conducted in Australia, Finland, and the USA, and investigated vitamin C, vitamin E, beta-carotene, and multivitamin supplements. All trials were judged to be at low risk of bias. Four studies reported the comparison of vitamin E with placebo. Average treatment and follow-up duration ranged from 4 to 10 years. Data were available for a total of 55,614 participants. There was evidence that vitamin E supplements do not prevent the development of any AMD (risk ratio (RR) 0.97, 95% confidence interval (CI) 0.90 to 1.06; high-certainty evidence), and may slightly increase the risk of late AMD (RR 1.22, 95% CI 0.89 to 1.67; moderate-certainty evidence) compared with placebo. Only one study (941 participants) reported data separately for neovascular AMD and geographic atrophy. There were 10 cases of
neovascular AMD (RR 3.62, 95% CI 0.77 to 16.95; very low-certainty evidence), and four cases of geographic atrophy (RR 2.71, 95% CI 0.28 to 26.0; very low-certainty evidence). Two trials reported similar numbers of adverse events in the vitamin E and placebo groups. Another trial reported excess of haemorrhagic strokes in the vitamin E group (39 versus 23 events, hazard ratio 1.74, 95% CI 1.04 to 2.91, low-certainty evidence). Two studies reported the comparison of beta-carotene with placebo. These studies took place in Finland and the USA. Both trials enrolled men only. Average treatment and follow-up duration was 6 years and 12 years. Data were available for a total of 22,083 participants. There was evidence that beta-carotene supplements did not prevent any AMD (RR 1.00, 95% CI 0.88 to 1.14; high-certainty evidence) nor have an important effect on late AMD (RR 0.90, 95% CI 0.65 to 1.24; moderate-certainty evidence). Only one study (941 participants) reported data separately for neovascular AMD and geographic atrophy. There were 10 cases of neovascular AMD (RR 0.61, 95% CI 0.17 to 2.15; very low-certainty evidence) and 4 cases of geographic atrophy (RR 0.31 95% CI 0.03 to 2.93; very low-certainty evidence). Beta-carotene was associated with increased risk of lung cancer in people who smoked. One study reported the comparison of vitamin C with placebo, and multivitamin (Centrum Silver) versus placebo. This was a study in men in the USA with average treatment duration and follow-up of 8 years for vitamin C and 11 years for multivitamin. Data were available for a total of 14,236 participants. AMD was assessed by self-report followed by medical record review. There was evidence that vitamin C supplementation did not prevent any AMD (RR 0.96, 95% CI 0.79 to 1.18; high-certainty evidence) or late AMD (RR 0.94, 0.61 to 1.46; moderate-certainty evidence). There was a slight increased risk of any AMD (RR 1.21, 95% CI 1.02 to 1.43; moderate-certainty evidence) and late AMD (RR 1.22, 95% CI 0.88 to 1.69; moderate-certainty evidence) in the multivitamin group. Neovascular AMD and geographic atrophy were not reported separately. Adverse effects were not reported but there was possible increased risk of skin rashes in the multivitamin group. Adverse effects were not consistently reported in these eye studies, but there is evidence from other large studies that beta-carotene increases the risk of lung cancer in people who smoke or who have been exposed to asbestos. None of the studies reported quality of life or resource use and costs.

AUTHORS’ CONCLUSIONS: Taking vitamin E or beta-carotene supplements will not prevent or delay the onset of AMD. The same probably applies to vitamin C and the multivitamin (Centrum Silver) investigated in the one trial reported to date. There is no evidence with respect to other antioxidant supplements, such as lutein and zeaxanthin. Although generally regarded as safe, vitamin supplements may have harmful effects, and clear evidence of benefit is needed before they can be recommended. People with AMD should see the related Cochrane Review on antioxidant vitamin and mineral supplements for slowing the progression of AMD, written by the same review team.

PMID: 28756617


Visual processing in patients with age-related macular degeneration performing a face detection test.

Vottonen P, Kaarniranta K, Pääkkönen A, Tarkka IM.

PURPOSE: People with age-related macular degeneration (AMD) have difficulties in familiar face recognition and facial expression discrimination. Our aim was to evaluate the visual processing of faces in AMD patients and whether this would be improved by anti-vascular endothelial growth factor therapy. This was a prospective interventional cohort study.

PATIENTS: Twelve patients with monocular wet AMD and 6 control subjects were recruited. Face detection processes were studied using cortical event-related potentials (ERPs). Patients received 3 bevacizumab intravitreal injections to the single affected eye. At baseline and 4-6 weeks after the last injection, clinical presentation and ERPs of the face task were evaluated. Face pictures were shown as targets (16.7%) among standard pictures of pixelated faces in an oddball-type paradigm.
RESULTS: Face pictures elicited well-defined electrical components in occipital and parieto-occipital cortical areas at baseline and after treatment. The face-specific N170 component was evident in all subjects with longer peak latency in patients than in controls (170±13 vs 155±14, P=0.032). Unexpectedly, an early component reflecting unintentional prediction of perceiving a face, that is, deviance-related negativity, was present in patients and controls. Visual acuity of the affected eye seemed improved in patients from logarithm of the minimum angle of resolution 0.71 (±0.33) to 0.52 (±0.39) by 119 (±23) days without accompanying significant change in face-specific ERPs.

CONCLUSIONS: Monocular wet AMD distinctly influenced face-specific brain electrophysiological components. However, the anti-vascular endothelial growth factor treatment did not improve the binocular face detection ability. The EudraCT number of this study is 2012-000765-20.

PMID: 28740360 PMCID: PMC5505620


Lutein and zeaxanthin isomers modulates lipid metabolism and the inflammatory state of retina in obesity-induced high-fat diet rodent model.

Tuzcu M, Orhan C, Muz OE, Sahin N, Juturu V, Sahin K.

BACKGROUND: Several studies associated high-fat intakes with a high incidence of age-related macular degeneration (AMD). Lutein and Zeaxanthin isomers (L/Zi) may counteract reactive oxygen species produced by oxidative stress. The present study was conducted to determine the possible effects of L/Zi administration on lipid profile, protein genes associated with oxidative stress and inflammation pathways in the obesity induced by a high-fat diet (HFD) in rodents.

METHODS: Twenty-eight male Wistar rats were allocated into four groups as follows: (i) Control, (ii) Control + L/Zi, (iii) High Fat Diet (HFD), and (iv) HFD+ L/Zi. L/Zi was administrated for 8 weeks at a daily dose of 100 mg/kg BW.

RESULTS: L/Zi administration significantly reduced insulin and free fatty acid (FFA) levels (P < 0.001) and ameliorated the oxidative damage by reducing malondialdehyde (MDA) concentration and increasing antioxidant enzymes activities of retina induced by HFD. In addition, supplementation decreased the levels of vascular endothelial growth factor (VEGF), inducible nitric oxide synthase (iNOS), nuclear factor-kappa B (NF-κB) and intercellular adhesion molecule-1 (ICAM) (P < 0.001, respectively) and improved nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase 1 (HO-1) gene proteins in retinal tissues (P < 0.001).

CONCLUSION: Rats fed with HFD exhibited increased oxidative stress and upregulation of inflammatory indicators. However, L/Zi supplementation modulates genes involved oxidative stress and inflammation including NF-κB and Nrf2 signaling pathways in the retina which may contribute to ameliorating retinal damage induced by HFD.

PMID: 28738845 PMCID: PMC5525211

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