**Drug treatment**

**Eye (Lond). 2017 Sep 22. [Epub ahead of print]**

**Comparison of effectiveness and safety between conbercept and ranibizumab for treatment of neovascular age-related macular degeneration. A retrospective case-controlled non-inferiority multiple center study.**


Purpose: To compare the efficacy and safety of conbercept and ranibizumab when administered according to a treat-and-extend (TREX) protocol for the treatment of neovascular age-related macular degeneration (AMD) in China.

Patients and methods: Between May 2014 and May 2015, 180 patients were treated in a 1:1 ratio using conbercept or ranibizumab from four hospitals. Patients received either conbercept 0.5 mg or ranibizumab 0.5 mg intravitreal injections. Follow-up time was 1 year and treated based on a TREX approach. Main outcomes and measures include best-corrected visual acuity (BCVA), using Early Treatment Diabetic Retinopathy Study (ETDRS); number of injections; central retinal thickness (CRT); and leakage of choroidal neovascularization before and after the treatment was analyzed by fluorescein fundus angiography and indocyanine green angiography.

Results: The 1-year visit was completed by 168 (93.3%) of patients. Mean BCVA was equivalent between two cohorts, and were improved by 12.7±7.770 and 12.3±7.269 letters in the conbercept and ranibizumab cohorts, respectively (P=0.624). There was no significant difference in measured CRT, with a mean decrease of 191.5 μm for conbercept and 187.8 μm for ranibizumab (P=0.773). There was a statistically significant difference (P=0.001) between the drugs regarding the number of treatments: 7.4 for conbercept and 8.7 for ranibizumab. The difference in the distribution of injection intervals was statistically significant between two groups (P=0.011). During the study, there were no cases of endophthalmitis or intraocular inflammation.

Conclusion: Both drugs had equivalent effects in visual and anatomic gains at 1 year when administered. In the conbercept group, longer treatment intervals were achieved with more patients.

PMID: 28937147

**Asia Pac J Ophthalmol (Phila). 2017 Sep 14. [Epub ahead of print]**

**New Treatment Modalities for Neovascular Age-Related Macular Degeneration.**

Schlottmann PG, Alezzandrini AA, Zas M, Rodriguez FJ, Luna JD, Wu L.
Abstract: Age-related macular degeneration (AMD) is considered one of the main causes of severe vision loss in older adults. The neovascular form (nAMD) is an advanced stage, which is responsible for the most severe vision loss. Vascular endothelial growth factor (VEGF) is at present the main factor that leads to the development of a neovascular membrane and the increased leakage from the membrane to the retina. At present, anti-VEGF therapy is the only treatment that achieves vision gains in many patients and halts progression in most of them. VEGF blockade can be achieved with several molecules and various treatment regimens, which have been studied with excellent results. Unfortunately, real-world data has shown to be far less efficacious than clinical trials. This gap between clinical trials and real-world results is an unmet medical need that supports the necessity of new treatment modalities for nAMD. Of the various treatments being studied, anti-VEGFs of higher efficacy and longer durability are those more advanced in their development. Brolucizumab and abicipar pegol are 2 new anti-VEGF drugs that had positive results in phase 2 studies and are being tested in phase 3 trials at present. Other promising therapies are antiangiopoietin 2 molecules, which are in phase 2 development. At earlier stages of development but with promising results are squalamine, anti-VEGF-C and -D, and gene therapy. The future will give retina specialists a broad armamentarium with which patients may achieve high visual gains for the long term with a low treatment burden.

PMID: 28933517

Ophthalmologica. 2017 Sep 20. [Epub ahead of print]

Different Clinical Courses on Long-Term Follow-Up of Age-Related Macular Degeneration Patients Treated with Intravitreal Anti-Vascular Endothelial Growth Factor Injections.

Sagiv O, Zloto O, Moroz I, Moisseiev J.

PURPOSE: To assess the long-term outcome of neovascular age-related macular degeneration (AMD) treated with multiple intravitreal anti-vascular endothelial growth factor (VEGF) injections.

METHODS: All patients treated with over 30 intravitreal anti-VEGF injections for neovascular AMD between 2007 and 2014 were retrospectively reviewed.

RESULTS: A total of 67 eyes received 2,960 (mean 45 ± 9.1 per eye) anti-VEGF injections. Eyes with good final visual acuity (VA) had better initial VA (p = 0.020) and maintained it. Patients with moderate-to-poor final VA improved significantly after the first 3 monthly injections, and thereafter deteriorated consistently, mostly during the third (p = 0.019) and fourth (p = 0.006) years. Eyes with worse final VA had more intraretinal fluid (p = 0.05) and subretinal fibrosis (p = 0.04).

CONCLUSION: Two distinct clinical courses were identified: good final VA was associated with initial and long-term stability of good VA; eyes with worse final VA had worse initial VA, progressive deterioration following the initial improvement, and more scarring and intraretinal fluid. This probably underscores the long-term benefits of early detection and treatment.

PMID: 28926846


An 8-year follow-up of anti-vascular endothelial growth factor treatment with a treat-and-extend modality for neovascular age-related macular degeneration.

Berg K, Roald AB, Navaratnam J, Bragadóttir R.

PURPOSE: To investigate long-term visual results of treatment with anti-vascular endothelial growth factor (VEGF) agents for neovascular age-related macular degeneration (nAMD) following a treat-and-extend
regimen.

METHODS: Retrospective review of 155 patients who initiated treatment with bevacizumab for nAMD in one eye. At the final 8-year visit, 40 patients (26%) remained for follow-up. Mean change in best-corrected visual acuity (BCVA) was calculated compared to baseline values.

RESULTS: Mean BCVA improved significantly from baseline during the first year of treatment, with -0.11 logMAR units equivalent to 6.1 approximate Early Treatment Diabetic Retinopathy Study (approxETDRS) letters (p < 0.001). Mean BCVA was still significantly improved after 4 years of treatment for the entire group of patients and after 6 years of treatment for the subgroup of 40 patients who remained at the final 8-year visit. Thereafter, BCVA gradually declined and at 8 years, there was a mean change of 0.05 logMAR units equivalent to 2.1 approxETDRS letters below baseline (p = 0.530). Mean number of injections during the first year was 6.1 ± 2.8 and during year 8 was 5.4 ± 3.5. At 5 years, fundus autofluorescence showed some degree of macular atrophy in all eyes. At the final 8-year visit, 87.5% of the eyes had stable neovascular lesions with no fluid on optical coherence tomography (OCT).

CONCLUSION: In an everyday clinical setting, treatment of nAMD patients with a treat-and-extend modality provided improvement and stability of vision for several years. After 8 years of follow-up, there was a decline in visual acuity (VA) that could be explained by macular atrophic development.

PMID: 28926190


RESOLUTION OF TREATMENT-RESISTANT SUBRETINAL FLUID IN A PATIENT WITH EXUDATIVE AGE-RELATED MACULAR DEGENERATION FOLLOWING ENDOPHTHALMITIS.

Kally PM, Sidikaro Y, McCannel CA.

PURPOSE: This is the first report to the best of the authors’ knowledge to show resolution of subretinal fluid and treatment requirement in a case of exudative age-related macular degeneration (eAMD) with persistent fluid despite treatment that resolved following an episode of culture-positive bacterial endophthalmitis.

METHODS: A 73-year-old man with history of eAMD of the right eye presented with acute postinjection bacterial endophthalmitis 3 days after injection. He had a history of only partially treatment-responsive eAMD that had been treated over a period of 8 years.

RESULTS: After tap-and-inject treatment of endophthalmitis with ceftazidime, vancomycin, and dexamethasone, the patient returned for follow-up with visual improvement and resolution of the subretinal fluid. The previously treatment-resistant eAMD remains quiescent without further treatment after 10 months of follow-up.

CONCLUSION: It is possible that some aspect of the infection, inflammation, or treatment of endophthalmitis had a disease-modifying impact on the eAMD. Further research into the components of endophthalmitis and its treatment may result in the discovery of new treatment approaches or treatment targets.

PMID: 28925926


Laser-Induced Choroidal Neovascularizations: Clinical Study of 3 Cases.

Laovirojjanakul W, Sanguansak T, Yospaiboony Y, Sinawat S, Sinawat S.
BACKGROUND: We report 3 patients with laser-induced choroidal neovascularization (CNV).

METHOD: Retrospective, observational case series. Medical charts and photographs were reviewed.

RESULTS: Two patients with central serous chorioretinopathy who developed iatrogenic CNV after focal laser photocoagulation were treated with intravitreal ranibizumab injections. One patient with CNV secondary to thermal laser photocoagulation for diabetic macular edema was treated with photodynamic therapy (PDT). Visual improvement has been demonstrated in the patients treated with intravitreal ranibizumab injections, and their successful visual outcome was stable for more than 2 years. Stable visual acuity was also observed in the patient treated with PDT, no visual improvement was observed possibly due to the macular scar and macular ischemia. No systemic or ocular complications were detected among the 3 cases.

CONCLUSION: To prevent a laser-induced CNV, it is critical to avoid heavy small-spot laser burns and repeated application. Patients should be monitored carefully for CNV after laser treatment. In our cases, PDT and intravitreal ranibizumab injections were effective for the treatment of laser-induced CNV.

PMID: 28924442 PMCID: PMC5597923

Clin Exp Optom. 2017 Sep 18. [Epub ahead of print]

Low frequency ranibizumab versus dexamethasone implant for macular oedema secondary to branch retinal vein occlusion.

Yuksel B, Karti O, Celik O, Kerci SG, Kusbeci T.

BACKGROUND: The aim was to make a real-world comparison of the efficacy of ranibizumab, dexamethasone and grid laser treatments in macular oedema due to branch retinal vein occlusion (BRVO).

METHODS: Forty-four eyes of 44 consecutive patients with macular oedema secondary to BRVO were included. Treatment arms comprised standard care (StCARE, n = 15), intravitreal ranibizumab (RNB, n = 14) and dexamethasone implant (DEX, n = 15). No rescue laser was performed in DEX and RNB groups. Main outcome measures were mean change in visual acuity (VA) and the percentage of patients who gained 10 or more letters from baseline to six months and central retinal thickness (CRT).

RESULTS: Improvements in mean logMAR VA (p = 0.642) and letter score from baseline to month 6 were not statistically significantly different in all three groups. Mean follow-up was 13.9 ± 10.7 months in RNB, 11.9 ± 6.3 in DEX and 11.4 ± 6.6 in StCARE. Mean number of injections was 2.4 ± 1.4 (range: 1-6) in RNB and 1.9 ± 0.7 (range: 1-3) in DEX group over the follow-up period. Mean letter gain was 13.5 in DEX (p = 0.067), 7.1 in RNB (p = 0.553) and 4.5 in StCARE (p = 0.362). Mean CRT at baseline was 512.8 μm in DEX, 505.1 μm in RNB and 345.5 μm in the StCARE group. At the last visit, RNB provided the maximum reduction in CRT. Mean CRT decrease was -146.5 μm (28.6 per cent) in DEX, -241.3 μm (47.8 per cent) in RNB and -45.6 μm (13.2 per cent) in StCARE (p = 0.030). A statistically significant intraocular pressure elevation occurred in the DEX group (p = 0.005).

CONCLUSION: Both RNB and DEX provided a significant resolution in macular oedema. Low frequency injections limited the visual gain in ranibizumab therapy. Visual results could be better with higher frequency injections and early start of treatment. Dexamethasone implants may be preferable in terms of visual improvement under low frequency injection conditions. Close follow-up is mandatory for detection of intraocular pressure elevations. Laser monotherapy is not a reasonable first-line option in the era of injection therapies.

PMID: 28922697

[Two-Year Follow-up Results of Patients with Macular Oedema Due to Retinal Vein Occlusion Treated with Ranibizumab]. [Article in Czech]

Hladíková Z, Klofáčová E, Kalvodová B.

PURPOSE: To evaluate 2-year follow-up results of patients with macular oedema (ME) caused by central (CRVO) and branch (BRVO) retinal vein occlusion treated with intravitreal ranibizumab at the Department of Ophthalmology, First Faculty of Medicine, Charles University and General University Hospital in Prague, Czech Republic.

METHODS: Retrospective study.

RESULTS: The 2-year follow-up was completed by 18 patients with ME caused by CRVO and 16 patients with ME caused by BRVO. In CRVO group mean age at diagnosis was 63 years, mean interval from diagnosis to the beginning of treatment was 3,6 months. During the first year of treatment the mean improvement of best corrected visual acuity (BCVA) was 17,4 letters of Early Treatment Diabetic Retinopathy Study (ETDRS) optotype, during the second year +2,4 letters. Mean number of injections was 6,8 in the first and 3,6 in the second year of treatment, mean total of 10,2 injections. In BRVO group the mean age at diagnosis was 68 years, mean interval from diagnosis to the beginning of treatment 6 month, mean gain in BCVA was +18,7 letters in the first and +1 letters in the second year of treatment, mean number of injections was 7 and 3,2 respectively, mean total of 9,6 injections. In both groups neither ocular nor systemic serious adverse effects were noted.

CONCLUSION: According to our results intravitreal ranibizumab is a safe and effective treatment for ME caused by retinal vein occlusion. Our results in BRVO group were in accordance with published international studies - BRAVO (BRVO) +18,3 letters, HORIZON -0,7 and even slightly better in CRVO group - CRUISE (CRVO) +13,9 letters, HORIZON study +4,1 letters.

Key words: macular oedema, ranibizumab, retinal vein occlusion, central retinal vein occlusion, branch retinal vein occlusion, 2-year follow-up.

PMID: 28931295

Other treatment & diagnosis


OCT-Angiography for monitoring and managing neovascular age-related macular degeneration.


PURPOSE: To evaluate the combined use of optical coherence tomography and angiography (OCT-A) for imaging choroidal neovascularization (CNV) secondary to neovascular age-related macular degeneration (nAMD).

MATERIALS AND METHODS: This prospective observational study was conducted from May 2015 to April 2017. Included in the study were 54 patients (n = 63 eyes), all of whom had CNV secondary to nAMD and all of whom had been examined by OCT-A. Angioscans (3x3 and 6 × 6) and conventional B-scan OCT scans were obtained for all patients at baseline and at various times during the 24-month follow-up period. For diagnostic confirmation, conventional imaging methods fluorescein angiography (FA) and indocyanine green angiography (ICGA) were performed at baseline. A total of 13 patients (n = 15 eyes) underwent serial imaging during 34 follow-up visits. The main outcomes included (i) determination of OCT-A sensitivity for the detection of CNV (classic and occult) and (ii) the correlation between B-scan OCT and OCT-A vis-à-vis consecutive follow-up changes.
RESULTS: At baseline, the detection rate (i.e., overall sensitivity) of OCT-A for detecting CNV was 64.4% (75.7 and 48.0% for classic and occult CNV, respectively), independent of prior treatment status. In terms of quality, 6 × 6 angioscans were superior to 3 × 3. Moreover, specific CNV morphologic patterns by B-scan OCT did not correlate with lesion composition. Correspondence between OCT-A and B-scan OCT was observed in only 53% of the cases.

CONCLUSIONS: OCT-A may prove to be a valuable adjunctive diagnostic tool for the interpretation of CNV, as it not only reduces the need for invasive angiographic procedures but also facilitates the follow-up process.

PMID: 28937833


Changes in Peripapillary Nerve Fiber Layer Thickness after Adjuvant Stereotactic Radiotherapy in Patients with Neovascular Age-Related Macular Degeneration.

Ranjbar M, Kurz M, Holzhey A, Rades D, Grisanti S.

PURPOSE: To evaluate the effect of stereotactic radiotherapy (SRT) in conjunction with intravitreal injections (IVI) of anti-vascular endothelial growth factor (anti-VEGF) drugs on peripapillary retinal nerve fiber layer (pRNFL) thickness in patients with neovascular age-related macular degeneration (nAMD).

METHODS: This was a retrospective, observational case series of patients with nAMD, who underwent SRT and subsequently had at least 12 months of complete follow-up. After SRT and one mandatory IVI, patients were examined monthly and received further treatment on a pro re nata basis. Examination included spectral-domain optical coherence tomography of the optic disc to measure pRNFL thickness. Patients’ data were retrieved from medical records including demographics, disease duration, best-corrected visual acuity, previous number of intravitreal injections, and the type of drug applied.

RESULTS: A total of 35 eyes of 35 patients (76.23 ± 7.05 years) were included. The mean duration of nAMD at time of irradiation was 34.57 ± 16.96 months. During that time, patients received a mean total number of 15.83 ± 6.29 intravitreal injections, 6.86 ± 1.57 within the last 12 months before SRT. After SRT, on average 3.46 ± 2.09 injections were administered over 12 months, resulting in a mean total number of 19.29 ± 6.92 injections at final follow-up. The mean global pRNFL thickness was 97.23 ± 12.55 µm at time of irradiation, 95.54 ± 11.07 µm at 6 month (P = 0.299), and 95.29 ± 12.07 µm at 12 month (P = 0.373) follow-up.

CONCLUSION: SRT in conjunction with anti-VEGF injections did not lead to any significant change in pRNFL thickness over 12 months in patients with nAMD. However, long-term results are not yet available. Therefore, prospective studies with longer follow-up are needed to corroborate these findings.

PMID: 28937877

Pathogenesis


Towards Treatment of Stargardt Disease: Workshop Organized and Sponsored by the Foundation Fighting Blindness.


Abstract: Accumulation of fluorescent metabolic byproducts of the visual (retinoid) cycle is associated with
photoreceptor and retinal pigment epithelial cell death in both Stargardt disease and atrophic (nonneovascular) age-related macular degeneration (AMD). As a consequence of this observation, small molecular inhibitors of enzymes in the visual cycle were recently tested in clinical trials as a strategy to protect the retina and retinal pigment epithelium in patients with atrophic AMD. To address the clinical translational needs for therapies aimed at both diseases, a workshop organized by the Foundation Fighting Blindness was hosted by the Department of Pharmacology at Case Western Reserve University on February 17, 2017, at the Tinkham Veale University Center, Cleveland, OH, USA. Invited speakers highlighted recent advances in the understanding of the pathophysiology of Stargardt disease, in terms of its clinical characterization and the development of endpoints for clinical trials, and discussed the comparability of therapeutic strategies between atrophic age-related macular degeneration (AMD) and Stargardt disease. Investigators speculated that reducing the concentrations of visual cycle precursor substances and/or their byproducts may provide valid therapeutic options for the treatment of Stargardt disease. Here we review the workshop’s presentations in the context of published literature to help shape the aims of ongoing research endeavors and aid the development of therapies for Stargardt disease.

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Hyperhomocysteinemia Alters Retinal Endothelial Cells Barrier Function and Angiogenic Potential via Activation of Oxidative Stress.


Abstract: Hyperhomocysteinemia (HHcy) is associated with several human visual disorders, such as diabetic retinopathy (DR) and age-related macular degeneration (AMD). Breakdown of the blood-retinal barrier (BRB) is linked to vision loss in DR and AMD. Our previous work revealed that HHcy altered BRB in retinal endothelial cells in vivo. Here we hypothesize that homocysteine (Hcy) alters retinal endothelial cell barrier function and angiogenic potential via activation of oxidative stress. Human retinal endothelial cells (HRECs) treated with and without different concentrations of Hcy showed a reduction of tight junction protein expression, increased FITC dextran leakage, decreased transcellular electrical resistance and increased angiogenic potential. In addition, HRECs treated with Hcy showed increased production of reactive oxygen species (ROS). The anti-oxidant N-acetyl-cysteine (NAC) reduced ROS formation and decreased FITC-dextran leakage in Hcy treated HRECs. A mouse model of HHcy, in which cystathionine-β-synthase is deficient (cbs-/-), was evaluated for oxidative stress by dichlorofluorescein (DCF), dihydroethidium (DHE) staining. There was a marked increase in ROS production and augmented GSH reductase and antioxidant regulator NRF2 activity, but decreased antioxidant gene expression in retinas of hyperhomocysteinemic mice. Our results suggest activation of oxidative stress as a possible mechanism of HHcy induced retinal endothelial cell dysfunction.

PMID: 28931831 PMCID: PMC5607263


Protective Effect of Combined Caffeic Acid Phenethyl Ester and Bevacizumab Against Hydrogen Peroxide-Induced Oxidative Stress in Human RPE Cells.

Dinc E, Ayaz L, Kurt AH.

PURPOSE: This study aimed to evaluate the protective effects of caffeic acid phenethyl ester (CAPE) and combined CAPE-bevacizumab against oxidative stress induced by hydrogen peroxide (H2O2) in human retinal pigment epithelium.
METHODS: ARPE-19 cells were pretreated with 5, 10, and 30 μM CAPE alone and in combination with bevacizumab for 3 h, then exposed to H2O2 for 16 h. Cell viability was evaluated with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Vascular endothelial growth factor (VEGF) protein levels in the medium were measured using a human VEGF ELISA kit. Total antioxidant status (TAS) and total oxidant status (TOS) were measured in ARPE-19 cells using the test kit from Rel Assay. Expression levels of VEGF, Bax, Bcl-2, cytochrome c, apoptotic protease activating factor-1 (apaf-1), and caspase-3 were determined using reverse transcription polymerase chain reaction.

RESULTS: Pretreatment of ARPE-19 cells with 30 μM CAPE and combined CAPE-bevacizumab reduced H2O2 mediated cell death. H2O2-induced oxidative stress increased TOS and VEGF production, which was significantly inhibited by CAPE and the CAPE-bevacizumab combination. VEGF, Bax, cytochrome c, apaf-1, and caspase-3 gene expressions were significantly decreased in cells pretreated with 5, 10, and 30 μM CAPE and combined CAPE-bevacizumab compared to the H2O2 group. In addition, Bcl-2 expression was significantly increased in both the CAPE and CAPE-bevacizumab combination groups compared to the H2O2 group.

CONCLUSIONS: CAPE has a protective effect on ARPE-19 cells against oxidative stress, and VEGF protein level and expression can be decreased by incubation with different concentrations of CAPE. These results demonstrate that CAPE suppresses the mitochondria-mediated apoptosis in ARPE-19 cells under oxidative stress. In addition, the use of CAPE in combination with bevacizumab has an additive effect.

PMID: 28937872


Lipid radicals cause light-induced retinal degeneration.


Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness worldwide. Although the cause of AMD remains unknown, lipid peroxidation (LPO) end-products are critical molecules for its development. Herein, we report the imaging of lipid radicals, which are key factors in the LPO reaction, and therapeutic information using animal models.

PMID: 28930310


Verteporfin Inhibits Cell Proliferation and Induces Apoptosis in Human Leukemia NB4 Cells without Light Activation.


Background and Aims: Verteporfin (VP), clinically used in photodynamic therapy for neovascular macular degeneration, has recently been proven a suppressor of yes-associated protein (YAP) and has shown potential in anticancer treatment. However, its anti-human leukemia effects in NB4 cells remain unclear. In this study, we investigated the effects of VP on proliferation and apoptosis in human leukemia NB4 cells. Methods: NB4 cells were treated with VP for 24 h. The effects of VP on cell proliferation were determined using a Cell-Counting Kit-8 assay (CCK-8) assay and colony forming assay. Apoptosis and cell cycle were evaluated by flow cytometry (FCM). The protein levels were detected by western blot.

Results: We found that VP inhibited the proliferation of NB4 cells in a concentration and time-dependent manner. FCM analysis showed that VP induced apoptosis in a concentration dependent manner and that
VP treatment led to cell cycle arrest at G0/G1 phase. Moreover, VP significantly decreased the protein expression of YAP, p-YAP, Survivin, c-Myc, cyclinD1, p-ERK, and p-AKT. In addition, VP increased the protein expression of cleaved caspase3, cleaved PARP, Bax, and p-p38 MAPK.

Conclusions: VP inhibited the proliferation and induced apoptosis in NB4 cells.

PMID: 28924376 PMCID: PMC5599928

Neuroscience. 2017 Sep 14. [Epub ahead of print]

Permissive role for mglu1 metabotropic glutamate receptors in excitotoxic retinal degeneration.


Abstract: Neuroprotection is an unmet need in eye disorders characterized by retinal ganglion cell (RGC) death, such as prematurity-induced retinal degeneration, glaucoma, and age-related macular degeneration. In all these disorders excitotoxicity is a prominent component of neuronal damage, but clinical data discourage the development of NMDA receptor antagonists as neuroprotectants. Here, we show that activation of mGlu1 metabotropic glutamate receptors largely contributes to excitotoxic degeneration of RGCs. Mice at postnatal day 9 were challenged with a toxic dose of monosodium glutamate (MSG, 3g/kg), which caused the death of >70% of Brn-3a+ RGCs. Systemic administration of the mGlu1 receptor negative allosteric modulator (NAM), JNJ16258695 (2.5mg/kg, s.c.), was largely protective against MSG-induced RGC death. This treatment did not cause changes in motor behavior in the pups. We also injected MSG to crv4 mice, which lack mGlu1 receptors because of a recessive mutation of the gene encoding the mGlu1 receptor. MSG did not cause retinal degeneration in crv4 mice, whereas it retained its toxic activity in their wild-type littermates. These findings demonstrate that mGlu1 receptors play a key role in excitotoxic degeneration of RGCs, and encourage the study of mGlu1 receptor NAMs in models of retinal neurodegeneration.

PMID: 28918254

Genetics & gene therapy


Gene expression levels of the insulin-like growth factor family in patients with AMD before and after ranibizumab intravitreal injections.


PURPOSE: The present study focused on the assessment of the mRNA levels of the insulin-like growth factor (IGF) family in patients with the exudative form of age-related macular degeneration (AMD) before and after ranibizumab intravitreal injections.

PATIENTS AND METHODS: An analysis of the expression profile of the IGF family of genes in patients with AMD was carried out using the oligonucleotide microarray and quantitative reverse transcriptase polymerase chain reaction (RT-qPCR) methods.

RESULTS: In the peripheral blood mononuclear cells (PBMCs) obtained from AMD group receiving ranibizumab compared to the peripheral blood mononuclear cells from AMD group before ranibizumab treatment using oligonucleotide microarray technique, six statistically significant differentially expressed transcripts related to the IGF family were detected (unpaired t-test, p<0.05, fold change >1.5). Moreover, analysis using the real-time RT-qPCR technique revealed statistically significant differences in the IGF2
and IGF2 mRNA levels (Mann-Whitney U test, p<0.05) between the two groups that were studied. Statistical analyses of both oligonucleotide microarray and real-time RT-qPCR results demonstrated a significant decreased expression only for IGF2 mRNA.

CONCLUSION: Our results revealed a changed expression of IGF2 mRNA after ranibizumab treatment.

PMID: 28919726 PMCID: PMC5592959


Novel pathogenic mutations in C1QTNF5 support a dominant negative disease mechanism in late-onset retinal degeneration.


Abstract: Late-onset retinal degeneration (L-ORD) is a rare autosomal dominant retinal dystrophy, characterised by extensive sub-retinal pigment epithelium (RPE) deposits, RPE atrophy, choroidal neovascularisation and photoreceptor cell death associated with severe visual loss. L-ORD shows striking phenotypic similarities to age-related macular degeneration (AMD), a common and genetically complex disorder, which can lead to misdiagnosis in the early stages. To date, a single missense mutation (S163R) in the C1QTNF5 gene, encoding C1q And Tumor Necrosis Factor Related Protein 5 (C1QTNF5) has been shown to cause L-ORD in a subset of affected families. Here, we describe the identification and characterisation of three novel pathogenic mutations in C1QTNF5 in order to elucidate disease mechanisms. In silico and in vitro characterisation show that these mutations perturb protein folding, assembly or polarity of secretion of C1QTNF5 and, importantly, all appear to destabilise the wildtype protein in co-transfection experiments in a human RPE cell line. This suggests that the heterozygous mutations in L-ORD show a dominant negative, rather than a haploinsufficient, disease mechanism. The function of C1QTNF5 remains unclear but this new insight into the pathogenetic basis of L-ORD has implications for future therapeutic strategies such as gene augmentation therapy.

PMID: 28939808

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VEGF Polymorphisms Among Neovascular Age-Related Macular Degenerative Subjects in a Multiethnic Population.


AIM: To determine the association of vascular endothelial growth factor (VEGF) polymorphisms with neovascular age-related macular degeneration (nAMD).

MATERIALS AND METHODS: One hundred thirty-five nAMD patients and 135 controls were recruited to determine the association of the -460 C/T, the -2549 I/D, and the +405 G/C polymorphisms with the VEGF gene. Genotyping was conducted using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) approach, and association analyses were conducted using chi-square analysis and logistic regression analysis.

RESULTS: A significant association was observed between nAMD and the VEGF +405 G/C genotypes (p = 0.002) and alleles (odds ratio = 1.36, 95% confidence interval = 1.12-1.62, p = < 0.001) compared with the controls. This association was confirmed by logistic regression analyses, using two different genetic models (additive and dominant) resulting in p-values of p = 0.001 and p < 0.001, respectively. In addition, the dominant model of VEGF +405 G/C was also found to be at risk of the CC genotype with nAMD among
subjects that were aged ≥60 years, female, of Chinese ethnicity, hypertensive, diabetic, and smokers.

CONCLUSION: With the exception of several limitations, the present study showed evidence of an association between the VEGF +405 G/C polymorphism and nAMD in Malaysian subjects.

PMID: 28926292


Association between CFH, CFB, ARMS2, SERPINF1, VEGFR1 and VEGF polymorphisms and anatomical and functional response to ranibizumab treatment in neovascular age-related macular degeneration.


PURPOSE: We sought to determine if specific genetic single nucleotide polymorphisms (SNPs) influence vascular endothelial growth factor inhibition response to ranibizumab in neovascular age-related macular degeneration (AMD).

METHODS: A total of 403 Caucasian patients diagnosed with exudative AMD were included. After a three-injection loading phase, a pro re nata regimen was followed. Nine SNPs from six different genes (CFH, CFB, ARMS2, SERPINF1, VEGFR1, VEGF) were genotyped. Non-genetic risk factors (gender, smoking habit and hypertension) were also assessed. Patients were classified as good or poor responders (GR or PR) according to functional (visual acuity), anatomical (foveal thickness measured by OCT) and fluid criteria (fluid/no fluid measured by OCT).

RESULTS: Hypertension was the environmental factor with the strongest poor response association with ranibizumab in the anatomical measure after the loading phase (p = 0.0004; OR 3.7; 95% CI, 2.4-5.8) and after 12 months of treatment (p = 10^-5; OR 2.3; 95% CI, 1.5-3.4). The genetic variants rs12614 (CFB), rs699947 (VEGFA) and rs7993418 (VEGFR1) predisposed patients to a good response, while rs12603486 and rs1136287 (SERPINF1) were associated with a poor response. The protective genotype of rs800292 variant (CFH) was also associated with a poor anatomical response (p = 0.004).

CONCLUSION: All these data suggest that genetics play an important role in treatment response in AMD patients.

PMID: 28926193

Prog Retin Eye Res. 2017 Sep 16. [Epub ahead of print]

Complement factor H in AMD: Bridging genetic associations and pathobiology.

Toomey CB, Johnson LV, Rickman CB.

Abstract: AMD is a complex multifactorial disease characterized in its early stages by lipoprotein accumulations in BrM, seen on fundoscopic exam as drusen, and in its late forms by neovascularization ("wet") or geographic atrophy of the RPE cell layer ("dry"). Genetic studies have strongly supported a relationship between the alternative complement cascade, in particular the common H402 variant in Complement Factor H (CFH) and development of AMD. However, the functional significance of the CFH Y402H polymorphism remains elusive. In this article, we critically review the literature surrounding the functional significance of this polymorphism. Furthermore, based on our group's studies we propose a model in which CFH H402 affects CFH binding to heparan sulfate proteoglycans leading to accelerated lipoprotein accumulation in BrM and drusen progression. We also review the literature on the role of other complement components in AMD pathobiologies, including C3a, C5a and membrane attack complex (MAC)
and on transgenic mouse models developed to interrogate in vivo the effects of the CFH H402 polymorphism.

PMID: 28928087

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**Associations of cholesteryl ester transfer protein (CETP) gene variants with predisposition to age-related macular degeneration.**


**PURPOSE:** To determine the frequency of the genotypes of single nucleotide polymorphisms (SNPs) in the gene encoding cholesteryl ester transfer protein (CETP) and their associations with age-related macular degeneration (AMD) in the Lithuanian population.

**STUDY DESIGN:** A total of 1264 subjects were examined: 251 patients with early AMD, 206 patients with exudative AMD, and 807 healthy controls.

**METHODS:** The genotyping of CETP (rs5882, rs708272, rs3764261, rs1800775, rs2303790) was carried out using the RT-PCR.

**RESULTS:** Binomial logistic regression analysis revealed that each copy of rs5882 allele A was associated with a 1.3-fold increased risk of exudative AMD (p=0.046). The G/A and A/A genotypes of the rs708272 polymorphism were associated with 1.5-fold and 1.7-fold increased risks of exudative AMD (p=0.049 and p=0.021, respectively). Combination of two genotypes (G+A/A) under the dominant model were associated with a 1.5-fold increased risk of exudative AMD (p=0.021). Analysis of rs708272 revealed that the G/A and A/A genotypes under the co-dominant model were associated with 1.5-fold and 1.7-fold increased risks of exudative AMD, respectively (OR=1.450, 95% CI=1.002-2.098; p=0.049 and OR=1.710, 95% CI=1.064-2.156; p=0.021, respectively). Both genotypes (G/A+A/A) under the dominant model were associated with the 1.5-fold increased risk of exudative AMD, as well (OR=1.514, 95% CI=1.064-2.156; p=0.021) and each additional copy A allele was associated with a 1.3-fold increased risk of exudative AMD (OR=1.316, 95% CI=1.051-1.646; p=0.016). The rs3764261 polymorphism was identified to be protective: the C/A genotype and the combination of two genotypes (C/A+A/A) were associated with 1.8-fold and 1.5-fold decreased risks of exudative AMD (p=0.001 and p=0.015, respectively).

**CONCLUSION:** Our study identified two polymorphisms with a higher risk of AMD development (rs5882 and rs708272) and a protective polymorphism for AMD (rs3764261).

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**Reducible PEG-POD/DNA Nanoparticles for Gene Transfer In Vitro and In Vivo: Application in a Mouse Model of Age-Related Macular Degeneration.**

Dasari BC, Cashman SM, Kumar-Singh R.

Abstract: Non-viral gene delivery systems are being developed to address limitations of viral gene delivery. Many of these non-viral systems are modeled on the properties of viruses including cell surface binding, endocytosis, endosomal escape, and nuclear targeting. Most non-viral gene transfer systems exhibit little correlation between in vitro and in vivo efficiency, hampering a systematic approach to their development. Previously, we have described a 3.5 kDa peptide (peptide for ocular delivery [POD]) that targets cell surface sialic acid. When functionalized with polyethylene glycol (PEG) via a sulphydryl group on the N-terminal cysteine of POD, PEG-POD could compact plasmid DNA, forming 120- to 180-nm homogeneous
nanoparticles. PEG-POD enabled modest gene transfer and rescue of retinal degeneration in vivo. Systematic investigation of different stages of gene transfer by PEG-POD nanoparticles was hampered by their inability to deliver genes in vitro. Herein, we describe functionalization of POD with PEG using a reducible orthopyridyl disulfide bond. These reducible nanoparticles enabled gene transfer in vitro while retaining their in vivo gene transfer properties. These reducible PEG-POD nanoparticles were utilized to deliver human FLT1 to the retina in vivo, achieving a 50% reduction in choroidal neovascularization in a murine model of age-related macular degeneration.

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**Adeno-Associated Viral Vector-Mediated mTOR Inhibition by Short Hairpin RNA Suppresses Laser-Induced Choroidal Neovascularization.**


Abstract: Choroidal neovascularization (CNV) is the defining characteristic feature of the wet subtype of age-related macular degeneration (AMD) and may result in irreversible blindness. Based on anti-vascular endothelial growth factor (anti-VEGF), the current therapeutic approaches to CNV are fraught with difficulties, and mammalian target of rapamycin (mTOR) has recently been proposed as a possible therapeutic target, although few studies have been conducted. Here, we show that a recombinant adeno-associated virus-delivered mTOR-inhibiting short hairpin RNA (rAAV-mTOR shRNA), which blocks the activity of both mTOR complex 1 and 2, represents a promising therapeutic approach for the treatment of CNV. Eight-week-old male C57/B6 mice were treated with the short hairpin RNA (shRNA) after generating CNV lesions in the eyes via laser photocoagulation. The recombinant adeno-associated virus (rAAV) delivery vehicle was able to effectively transduce cells in the inner retina, and significantly fewer inflammatory cells and less extensive CNV were observed in the animals treated with rAAV-mTOR shRNA when compared with control- and rAAV-scrambled shRNA-treated groups. Presumably related to the reduction of CNV, increased autophagy was detected in CNV lesions treated with rAAV-mTOR shRNA, whereas significantly fewer apoptotic cells detected in the outer nuclear layer around the CNV indicate that mTOR inhibition may also have neuroprotective effects. Taken together, these results demonstrate the therapeutic potential of mTOR inhibition, resulting from rAAV-mTOR shRNA activity, in the treatment of AMD-related CNV.

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**Diet, lifestyle & low vision**


**Relationships of orientation discrimination threshold and visual acuity with macular lesions in age-related macular degeneration.**


PURPOSE: To measure visual acuity and metamorphopsia in patients with age-related macular degeneration (AMD) and to explore their relationship with macular lesions.

METHODS: In this cross-sectional study, a total of 32 normal subjects (32 eyes) and 35 AMD patients (35 eyes) were recruited. They were categorized into 4 groups: normal, dry AMD, non-active wet AMD, and active wet AMD. Best-corrected visual acuity (BCVA) was measured using the Early Treatment Diabetic Retinopathy Study protocol. Metamorphopsia was quantified with the orientation discrimination threshold (ODT). Macular lesions, including drusen, sub-retinal fluid (SRF), intra-retinal fluid (IRF), pigmented...
epithelium detachment (PED), and scarring, were identified with spectral-domain optical coherence tomography (SD-OCT). A linear regression model was established to identify the relationships between the functional and structural changes.

RESULTS: BCVA progressively worsened across the normal, dry AMD, non-active wet AMD, and active wet AMD groups (P < 0.001), and ODT increased across the groups (P < 0.001). The correlation between BCVA and ODT varied among the groups. The partial correlation between BCVA and ODT was -0.61 (P < 0.001). Linear regression showed that ODT significantly depended on IRF (β = 0.61, P < 0.001), SRF (β = 0.34, P = 0.003), and scarring (β = 0.26, P = 0.050), while BCVA significantly depended only on scarring (β = -0.52, P < 0.001), and IRF (β = -0.36, P = 0.016).

CONCLUSIONS: From dry AMD to active wet AMD, BCVA gradually worsened while ODT increased. The correlation between BCVA and ODT varied among these groups, indicating that AMD lesions affect them differently. ODT and BCVA should be used concurrently for better monitoring of the disease.

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The Association between Dietary Intake of Antioxidants and Ocular Disease.

Braakhuis A, Raman R, Vaghefi E.

Abstract: To assess the association between dietary antioxidant intake and the incidence of the three major oxidative stress-related eye diseases, cataracts, glaucoma, and age-related macular degeneration, 78 cases from the University of Auckland Optometry and Vision Science clinic and 149 controls were recruited. Participants completed an antioxidant food-frequency questionnaire, analysed through multiple logistic regression. Protective associations were identified with higher consumption of fruit and vegetables (OR = 0.99; 95% CI: 0.98, 1.00; p = 0.004), vitamin C (OR = 0.63; 95% CI: 0.23, 1.03; p = 0.022), and β-carotene (OR = 0.56; 95% CI: 0.15, 0.98; p = 0.007). Meanwhile, harmful associations were observed with greater consumption of meat/nuts (OR = 1.03; 95% CI: 1.01, 1.05; p = 0.006) and cholesterol (OR = 1.09; 95% CI: 1.50, 2.46; p = 0.005). Diets rich in fruit and vegetables appear to be protective against cataracts, glaucoma, and age-related macular degeneration, while diets higher in meat and nuts may increase the risk of oxidative stress-related eye diseases. In addition, higher intakes of vitamin C and β-carotene from food, with reduction of dietary cholesterol intake, may be beneficial towards the outcome of oxidative stress-related eye diseases.

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The effect of prism on preferred retinal locus.

Lewerenz D, Blanco D, Ratzlaff C, Zodrow A.

BACKGROUND: Whether prism, especially base-up prism, affects the area of the retina used for fixation in a patient with central scotoma has been a controversial subject for 35 years. Our pilot study employed microperimetry to evaluate the effect of base-up prism on the fixation locus, or preferred retinal locus (PRL), in subjects with central scotoma.

METHODS: We used a microperimeter to assess the PRL in 13 visually impaired subjects with central scotoma under four conditions: no lens, a lens with no prism (control lens), 6Δ base-up, and 10Δ base-up. The PRL was measured in degrees in horizontal and vertical co-ordinates from the centre of the optic disc using graphical analysis.
RESULTS: The PRL with the control lens was not significantly different from the PRL with no lens. The preferred retinal loci with the two powers of prism were compared to the control lens and showed a superior shift in 22 of 26 cases (84.6 per cent). The amount of movement was significantly different from zero (p = 0.001 for 6Δ and p = 0.004 for 10Δ). The vertical movement with the 10Δ prism (1.73 ± 1.73 degrees) was not significantly greater (p = 0.562) than with the 6Δ prism (1.37 ± 1.08 degrees). The shift was significantly less than the prism powers used (p < 0.001), and the amount of vertical relocation was not significantly different from the amount of horizontal movement.

CONCLUSION: In our study, base-up prism appears to shift the PRL in the direction of the prism base most of the time, but our findings do not support the use of prism as a way of predictably relocating the PRL. More study is indicated to evaluate whether such a small shift is clinically or functionally significant.

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