

Issue 184

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Drug treatment

Biomed Res Int. 2014;2014:273754. doi: 10.1155/2014/273754. Epub 2014 May 7.

Visual and anatomical outcomes of intravitreal aflibercept for treatment-resistant neovascular age-related macular degeneration.

Gharbiya M, Iannetti L, Parisi F, De Vico U, Mungo ML, Marengo M.

Abstract: A retrospective chart review of patients with persistent subretinal and/or intraretinal fluid, despite previous treatment with intravitreal ranibizumab (0.5 mg), who were switched to aflibercept injections, was performed. Treatment was three monthly aflibercept (2 mg) injections followed by dosing on pro re nata basis. Main outcome measures included changes in best corrected visual acuity (BCVA), 1 mm central subfield (CSF) retinal thickness, the height of the pigment epithelial detachment (PED), and subfoveal choroidal thickness on optical coherence tomography at 6 months. Thirty-one eyes of 30 patients were analyzed. The mean number of injections before aflibercept conversion was 34.4 ± 11.9 . After an average of 4.5 aflibercept injections (range 3 to 6) over 6 months, no significant change in BCVA was observed ($P > 0.05$). Compared with baseline, there was a significant reduction of the CSF retinal thickness (449 ± 179 versus 269 ± 145 μm , $P < 0.001$), maximum PED height (262 ± 134 versus 183 ± 100 μm , $P < 0.001$), and choroidal thickness (192 ± 67 versus 167 ± 51 μm , $P < 0.01$). Stable visual acuity and anatomical improvement were obtained for up to 6 months after aflibercept conversion. However, choroidal thinning related to treatment was observed.

PMID: 24895562 [PubMed - in process] PMCID: PMC4033502

Clin Ophthalmol. 2014 May 19;8:981-8. doi: 10.2147/OPHTH.S61871. eCollection 2014.

The effects of ranibizumab injections on fluorescein angiographic findings and visual acuity recovery in age-related macular degeneration.

Gungel H, Osmanbasoglu OA, Altan C, Baylancicek DO, Pasaoglu IB.

AIM: The objective of the study reported here was to evaluate the effect of ranibizumab on retinal circulation times and vessel caliber and to analyze the correlation of these factors with visual acuity (VA) prognosis in patients with age-related macular degeneration (AMD).

SUBJECTS AND METHODS: This prospective cohort study included 52 eyes of 46 patients (mean age 73.5 years [standard deviation 7.7]; 28 males, 18 females). The study parameters were best-corrected visual acuity (BCVA), central macular thickness (CMT) (pre- and posttreatment: for 3 months after the last injection), retinal circulation times, diameter of retinal arteriole (DRA), and diameter of retinal vein (DRV)

(pre- and posttreatment: after a loading dose of three consecutive injections of ranibizumab with a 4-week interval in the initial phase). The pretreatment, posttreatment measurements, and their differences were recorded for analyses. The injections were repeated when needed. Eyes were grouped into one of two groups according to VA recovery: Group 1, cases showing significant recovery of VA (n=21, 37%), and Group 2, cases showing preservation of VA (n=22, 42%) and deterioration of VA (n=11, 21%). Differences were compared statistically in and between groups. Logistic regression analysis was undertaken to determine the correlation of these parameters with VA recovery.

RESULTS: There was a significant reduction in DRA (P=0.007) and CMT levels (P<0.001) in both study groups after treatment. When the two groups were compared, the differences in pretreatment values of DRA (P=0.001), DRV (P=0.017), CMT (P=0.039), and mean BCVA (P=0.00) were found to be statistically significant. Posttreatment changes in DRA (P=0.013) and mean CMT (P=0.010) were found to be factors related to VA recovery by logistic regression analysis.

CONCLUSION: Our findings reveal that ranibizumab treatment is associated with decrease in DRA, CMT, and significant improvement in VA recovery. Further, taking into account the cases in which VA was preserved, when needed, ranibizumab should be re-injected after the loading dose.

PMID: 24899794 [PubMed] PMCID: PMC4038425

Pharmacogenomics. 2014 Apr;15(6):833-43. doi: 10.2217/pgs.14.51.

Evaluation of clinical and genetic indicators for the early response to intravitreal ranibizumab in exudative age-related macular degeneration.

Matsumiya W, Honda S, Yanagisawa S, Miki A, Nagai T, Tsukahara Y.

Aim: This study was conducted to evaluate the possible clinical and genetic indicators for an early response to intravitreal ranibizumab (IVR) in exudative age-related macular degeneration (AMD).

Patients & methods: The records of 120 eyes from 120 Japanese patients with treatment-naïve exudative AMD were retrospectively reviewed. Three consecutive IVR treatments were performed every month. Achievement of anatomical resolution was evaluated by ophthalmoscopy and optical coherence tomography. Multivariable logistic regression analysis was conducted by analyzing SNPs in the ARMS2 locus (A69S) and in the CFH gene (I62V and Y402H), in addition to clinical factors.

Results: The mean central retinal thickness of overall patients was significantly decreased ($-120.1 \pm 122.8 \mu\text{m}$, $p = 2.7 \times 10^{-19}$) at 3 months after the initial treatment. In the logistic regression analysis, the poor anatomical resolution of the lesion at 3 months was associated with the combination of CFH I62V + CFH Y402H variants ($p = 0.0021$), and the polypoidal choroidal vasculopathy lesions ($p = 0.044$).

Conclusion: The CFH variants and the polypoidal choroidal vasculopathy lesion may influence the early anatomical resolution with IVR in exudative AMD.

PMID: 24897289 [PubMed - in process]

Retina. 2014 Jun 3. [Epub ahead of print]

CLINICAL EVALUATION OF PAZOPANIB EYE DROPS IN HEALTHY SUBJECTS AND IN SUBJECTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Singh R, Wurzelmann J, Ye L, Henderson L, Hossain M, Trivedi T, Kelly DS.

PURPOSE: To evaluate pazopanib 10 mg/mL eye drops (pazopanib) in healthy subjects and in subjects with previously untreated subfoveal choroidal neovascularization secondary to age-related macular

degeneration.

METHODS: Study 1 (single center, randomized, placebo-controlled, double-masked) included 3 cohorts of 12 to 13 healthy subjects each who instilled pazopanib or placebo 4 times daily for 2 weeks. Study 2 (multicenter open-label) included 19 subjects with neovascular age-related macular degeneration who instilled pazopanib 4 times daily for 12 weeks. Both studies evaluated pharmacokinetics and safety. Study 2 also evaluated efficacy.

RESULTS: Steady-state concentrations of pazopanib in plasma seemed to be reached by Week 2. At Week 4 (Study 2), there were no meaningful changes from baseline in the mean central retinal thickness (37.9 μ m) or best-corrected visual acuity (0.1 letters) (primary endpoint), retinal morphology, choroidal neovascularization size, or total lesion size. Complement Factor H genotype had no effect on changes from baseline in the best-corrected visual acuity or central retinal thickness. The most common pazopanib-related ocular adverse events included eye irritation (Study 1, n = 7) and instillation site pain (Study 2, n = 3). No serious adverse events were reported.

CONCLUSION: Pazopanib was well tolerated. In subjects with previously untreated neovascular age-related macular degeneration, pazopanib instilled 4 times daily because monotherapy did not seem to improve the best-corrected visual acuity or decrease the central retinal thickness.

PMID: 24896137 [PubMed - as supplied by publisher]

BMJ Case Rep. 2014 Jun 3;2014. pii: bcr2013010247. doi: 10.1136/bcr-2013-010247.

Treatment of choroidal neovascularisation secondary to membranoproliferative glomerulonephritis type II with intravitreal ranibizumab.

McCullagh D, Silvestri G, Maxwell AP.

Abstract: Membranoproliferative glomerulonephritis type II (MPGN II) is characterised by electron-dense deposits of complement components in the glomerular basement membrane and retinal pigment epithelium. Approximately, 10% of affected individuals develop serious ocular complications similar to age-related macular degeneration such as choroidal neovascularisation (CNV), which has been managed with photocoagulation or photodynamic therapy; however, these treatments can impact visual acuity. We report the case of a 42-year-old woman with MPGN II presenting with decreased visual acuity and paracentral scotoma in her left eye due to an extrafoveal choroidal neovascular membrane (growth of new vessels under the retina). The patient was successfully treated with intravitreal ranibizumab (Lucentis) with restoration of visual function. This case highlights the successful management of CNV secondary to MPGN II with the antivascular endothelial growth factor agent ranibizumab and emphasises the importance of early referral of patients with MPGN II who are reporting of visual 'distortion'.

PMID: 24895384 [PubMed - in process]

Indian J Ophthalmol. 2014 May;62(5):554-60. doi: 10.4103/0301-4738.133485.

Morphological changes in spectral domain optical coherence tomography guided bevacizumab injections in wet age-related macular degeneration, 12-months results.

Michalewski J, Nawrocki J, Izdebski B, Michalewska Z.

Purpose: To describe retinal changes during Spectral Domain Optical Coherence Tomography (SD-OCT) guided bevacizumab treatment for neovascular age-related macular degeneration (AMD).

Settings and Design: Single center observational study.

Materials and Methods: We confirmed wet AMD in 47 eyes of 45 patients by fluorescein angiography and SD-OCT. After bevacizumab injection, we examined the patients at 4-week intervals. During each follow-up control, we performed SD-OCT and a complete ophthalmic examination. Criteria for reinjection were visual acuity loss of more than five ETDRS letters, and/or increase of central retinal thickness, sub-retinal fluid, intra-retinal fluid, pigment epithelium detachment. If reinjection criteria were not met, we advised the patient to return in 4 weeks' time for the next scheduled follow-up. We used 3-dimensional SD-OCT to measure photoreceptor defects and sub-retinal fibrosis. The main efficacy endpoints were the SD-OCT measurements of the size of photoreceptor defects, the size of external membrane defects and the central retinal thickness.

Results: Over the 12 months study period, the percentage of scans in 3-D imaging mode showing visible defects of the junction between inner and outer segments of photoreceptors increased from 38.96 to 53.8%. The percentage of scans in 3-D imaging mode with visible sub-retinal fibrosis increased from 33 to 52% and mean central retinal thickness decreased from 333 μ m (96-900 μ m) to 272 μ m ($P = 0.011$).

Conclusion: In long-term anti- Vascular endothelial growth factor (VEGF) treatment for neovascular AMD, photoreceptor defects and fibrosis progress despite a decrease in central retinal thickness and improvements in visual acuity. We would encourage further discussion as to whether this is the natural course of the disease or a result of the treatment.

PMID: 24881600 [PubMed - in process]

Am J Ophthalmol. 2014 Jun 4. pii: S0002-9394(14)00326-2. doi: 10.1016/j.ajo.2014.05.037. [Epub ahead of print]

Treatment of Exudative Age-Related Macular Degeneration with a Designed Ankyrin Repeat Protein that Binds Vascular Endothelial Growth Factor: A Phase I/II Study.

Souied EH, Devin F, Mauget-Faÿsse M, Kolář P, Wolf-Schnurrbusch U, Framme C, Gaucher D, Querques G, Stumpp MT, Wolf S; MP0112 Study Group.

PURPOSE: To evaluate the safety, tolerability, and bioactivity of ascending doses of MP0112, a designed ankyrin repeat protein (DARPin) that binds with high affinity to vascular endothelial growth factor-A (VEGF-A), in treatment-naïve patients with exudative age-related macular degeneration (AMD).

DESIGN: Phase I/II, open-label, multicenter, dose-escalation study.

METHODS: Patients were to receive a single intravitreal injection of MP0112 at doses ranging from 0.04 to 3.6 mg, and be monitored for 16 weeks for safety, efficacy, pharmacokinetics, and dose response.

RESULTS: 32 patients received a single injection of MP0112. The maximum tolerated dose was 1.0 mg, due to a case of endophthalmitis in the 2.0 mg cohort. Drug-related adverse events were reported by 13 (41%) of 32 patients, including ocular inflammation in 11 patients; 7/11 were mild and 4/11 were moderate in severity. Visual acuity scores were stable or improved compared with baseline for ≥ 4 weeks following injection; both retinal thickness and fluorescein angiography leakage decreased in a dose-dependent manner. Rescue therapy was administered to 20 (91%) of 22 patients who received 0.04-0.4 mg MP0112 compared with 4 (40%) patients who received 1.0 or 2.0 mg. 83% (5/6) of patients in the higher-dose cohorts who did not require rescue treatment maintained reductions in central retinal thickness through Week 16.

CONCLUSIONS: A single injection of 1.0 or 2.0 mg MP0112 resulted in mean decreases in retinal thickness and leakage area despite ocular inflammation. Larger-scale studies are warranted to confirm these observations.

PMID: 24907435 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Br J Ophthalmol. 2014 Jun 5. pii: bjophthalmol-2013-304399. doi: 10.1136/bjophthalmol-2013-304399. [Epub ahead of print]

Visual acuity and central retinal thickness: fulfilment of retreatment criteria for recurrent neovascular AMD in routine clinical care.

Reznicek L, Muhr J, Ulbig M, Kampik A, Mayer WJ, Haritoglou C, Neubauer A, Wolf A.

BACKGROUND: To evaluate the fulfilment of retreatment criteria in recurrent neovascular age-related macular degeneration (nAMD) for a pro-re-nata treatment regime with ranibizumab in routine clinical care.

METHODS: Data from patients with treatment-naïve nAMD were analysed retrospectively. As an 'upload', all patients had received three-monthly intravitreal ranibizumab injections in a university eye hospital and were then seen by ophthalmologists in private practice who referred them back in case of recurrence. Recurrence was defined as a decrease of visual acuity (VA) of one line or more (functional retreatment criteria), a central retinal thickness (CRT) increase of at least 100 µm upon Optical Coherence Tomography (OCT) examination (morphological retreatment criteria) or a new macular haemorrhage (clinical retreatment criteria).

RESULTS: We included 92 patients (36 men and 56 women). The mean VA before retreatment of a recurrence was -0.63 ± 0.33 logMAR and improved significantly ($p < 0.001$) by 0.10 ± 0.16 logMAR to -0.53 ± 0.28 logMAR thereafter. Mean CRT before retreatment was 278.07 ± 87.56 µm and decreased significantly ($p < 0.001$) by 71.22 ± 106.93 to 206.85 ± 60.30 µm. Evaluation of the fulfilment of retreatment criteria revealed functional retreatment criteria in 82.6% of patients. However, upon re-evaluation of VA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts in the treatment centre, mean decrease of VA was 10 letters as compared with the end of upload therapy. All patients presented an increased CRT when treated for recurrence of nAMD (mean increase 69.47 µm), but the morphological retreatment criteria (CRT increase of 100 µm or more) were fulfilled in only 44.4% of patients upon Spectral Domain OCT (SD-OCT) evaluation in the treatment centre.

CONCLUSIONS: In a routine clinical care, evaluation of VA using ETDRS charts seems to be more sensitive than Snellen VA testing. Quantitative OCT-based retreatment criteria (eg, increase of CRT of 100 µm or more) appear to be not sensitive enough in a clinical setting with referring ophthalmologists.

PMID: 24903670 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jun 6. pii: IOVS-14-14542. doi: 10.1167/iovs.14-14542. [Epub ahead of print]

IN VIVO IMAGING OF HUMAN CONE PHOTORECEPTOR INNER SEGMENTS.

Scoles DH, Sulai YN, Langlo C, Fishman GA, Curcio CA, Carroll J, Dubra A.

Purpose: An often-overlooked prerequisite to cone photoreceptor gene therapies development is residual photoreceptor structure that can be rescued. While advances in adaptive optics (AO) retinal imaging have recently enabled direct visualization of individual cone and rod photoreceptors in the living human retina, these techniques largely detect strongly directionally-backscattered (waveguided) light from normal intact photoreceptors. This represents a major limitation in using existing AO-imaging tools to quantify remnant cone structure in the degenerating retina.

Methods: Photoreceptor inner segment structure was assessed with a novel AO scanning light ophthalmoscopy (AOSLO) differential phase technique, that we termed non-confocal split-detector, in two normal subjects and four subjects with achromatopsia. Ex vivo preparations of five donor eyes were analyzed for comparison of inner segment diameter to that measured in in vivo images from split-detector

AOSLO.

Results: Non-confocal split-detector AOSLO reveals the photoreceptor inner segment with or without the presence of a waveguiding outer segment. The diameter of inner segments measured in vivo is in good agreement with histology. A substantial number of foveal and parafoveal cone photoreceptors with apparently intact inner segments were identified in patients with the inherited disease achromatopsia.

Conclusions: The application of non-confocal split-detector to emerging human gene therapy trials will improve the likelihood of therapeutic success, by identifying patients with sufficient retained photoreceptor structure to benefit the most from intervention. Additionally, split-detector may be useful for studies of other retinal degenerations such as age related macular degeneration, retinitis pigmentosa and choroideremia where the outer segment is lost before the photoreceptor cell.

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Invest Ophthalmol Vis Sci. 2014 Jun 3. pii: IOVS-14-14447. doi: 10.1167/iov.14-14447. [Epub ahead of print]

Choroidal structure in normal eyes and after photodynamic therapy determined by binarization of optical coherence tomographic images.

Sonoda S, Sakamoto T, Yamashita T, Shirasawa M, Uchino E, Terasaki H, Tomita M.

Purpose: To determine the changes of choroidal structure by binarization of the optical coherence tomographic (OCT) images.

Methods: Choroidal images were recorded by enhanced depth imaging-OCT. The subfoveal choroidal images were analyzed, and the luminal and interstitial areas were converted to binary images by the Niblack method. The inter-rater, intra-rater, and inter-session agreements of the binary images were determined for healthy eyes. In eyes with age-related macular degeneration (AMD), the binary images of the choroid before photodynamic therapy (PDT) were compared to those after PDT. The untreated fellow eyes were studied as controls.

Results: In healthy eyes, the average ratio of the luminal/choroidal area was 65.4%. The inter-rater agreement rate was high: intraclass correlation coefficient (ICC) 0.985 and 0.988 for the choroid and luminal areas, respectively. The intra-rater ICC was 0.996 for the choroid and 0.997 for the luminal areas. The intersession ICC was 0.993 for the choroid and 0.984 for the luminal areas. In eyes with AMD, the subfoveal choroidal area, the luminal area, and the interstitial areas were thinner six months after PDT ($P < 0.01$ all, Wilcoxon signed-rank sum test). The ratio of the luminal/choroidal area was significantly decreased to 62.8% ($P < 0.01$, Wilcoxon signed-rank sum test). The ratio of the fellow eyes was not significantly changed.

Conclusions: The Niblack binarization method can be used to analyze the luminal area of choroid in the OCT image with good repeatability and reproducibility. The change in the subfoveal choroidal area after PDT is due mainly to a decrease in the luminal areas.

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Curr Eye Res. 2014 Jun 3;1-12. [Epub ahead of print]

Gender Differences in Ocular Blood Flow.

Schmidl D, Schmetterer L, Garhöfer G, Popa-Cherecheanu A.

Abstract: Gender medicine has been a major focus of research in recent years. The present review focuses

on gender differences in the epidemiology of the most frequent ocular diseases that have been found to be associated with impaired ocular blood flow, such as age-related macular degeneration, glaucoma and diabetic retinopathy. Data have accumulated indicating that hormones have an important role in these diseases, since there are major differences in the prevalence and incidence between men and pre- and post-menopausal women. Whether this is related to vascular factors is, however, not entirely clear. Interestingly, the current knowledge about differences in ocular vascular parameters between men and women is sparse. Although little data is available, estrogen, progesterone and testosterone are most likely important regulators of blood flow in the retina and choroid, because they are key regulators of vascular tone in other organs. Estrogen seems to play a protective role since it decreases vascular resistance in large ocular vessels. Some studies indicate that hormone therapy is beneficial for ocular vascular disease in post-menopausal women. This evidence is, however, not sufficient to give any recommendation. Generally, remarkably few data are available on the role of sex hormones on ocular blood flow regulation, a topic that requires more attention in the future.

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Am J Ophthalmol. 2014 Jun 4. pii: S0002-9394(14)00327-4. doi: 10.1016/j.ajo.2014.05.038. [Epub ahead of print]

Photoreceptor perturbation around subretinal drusenoid deposits revealed by adaptive optics scanning laser ophthalmoscopy.

Zhang Y, Wang X, Rivero EB, Clark ME, Witherspoon CD, Spaide RF, Girkin CA, Owsley C, Curcio CA.

PURPOSE: To describe the microscopic structure of photoreceptors impacted by subretinal drusenoid deposits, also called pseudodrusen, an extracellular lesion associated with age-related macular degeneration (AMD), using adaptive optics scanning laser ophthalmoscopy (AOSLO).

DESIGN: Observational case series.

METHODS: Fifty-three patients with AMD and 10 age-similar subjects in normal retinal health were recruited. All subjects underwent color fundus photography, infrared reflectance, red-free reflectance, autofluorescence, and spectral-domain optical coherence tomography (SD-OCT). Subretinal drusenoid deposits were classified with a 3-stage OCT-based grading system. Lesions and surrounding photoreceptors were examined with AOSLO.

RESULTS: Subretinal drusenoid deposits were found in 26 eyes of 13 patients with AMD and imaged by AOSLO and SD-OCT in 18 eyes (n=342 lesions). SD-OCT showed subretinal drusenoid deposits as highly reflective material accumulated internal to the retinal pigment epithelium. AOSLO revealed that photoreceptor reflectivity was qualitatively reduced by stage 1 subretinal drusenoid deposits and greatly reduced by stage 2. AOSLO presented a distinct structure in stage 3, a hyporeflective annulus consisting of deflected, degenerated or absent photoreceptors. A central core with a reflectivity superficially resembling photoreceptors is formed by the lesion material itself. A hyporeflective gap in the photoreceptor ellipsoid zone on either side of this core shown in SD-OCT corresponded to the hyporeflective annulus seen by AOSLO.

CONCLUSIONS: AOSLO and multimodal imaging of subretinal drusenoid deposits indicate solid, space filling lesions in the subretinal space. Associated retinal reflectivity changes are related to lesion stages and are consistent with perturbations to photoreceptors, as suggested by histology.

PMID: 24907433 [PubMed - as supplied by publisher]

Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2014 Jun 2. doi: 10.1002/wnan.1272. [Epub ahead of print]

Controlled ocular drug delivery with nanomicelles.

Vaishya RD, Khurana V, Patel S, Mitra AK.

Abstract: Many vision threatening ocular diseases such as age-related macular degeneration (AMD), diabetic retinopathy, glaucoma, and proliferative vitreoretinopathy may result in blindness. Ocular drug delivery specifically to the intraocular tissues remains a challenging task due to the presence of various physiological barriers. Nonetheless, recent advancements in the field of nanomicelle-based novel drug delivery system could fulfil these unmet needs. Nanomicelles consists of amphiphilic molecules that self-assemble in aqueous media to form organized supramolecular structures. Micelles can be prepared in various sizes (10-1000 nm) and shapes depending on the molecular weights of the core and corona forming blocks. Nanomicelles have been an attractive carrier for their potential to solubilize hydrophobic molecules in aqueous solution. In addition, small size in nanometer range and highly modifiable surface properties have been reported to be advantageous in ocular drug delivery. In this review, various factors influencing rationale design of nanomicelles formulation and disposition are discussed along with case studies. Despite the progress in the field, influence of various properties of nanomicelles such as size, shape, surface charge, rigidity of structure on ocular disposition need to be studied in further details to develop an efficient nanocarrier system. For further resources related to this article, please visit the WIREs website. Conflict of interest: The authors have declared no conflicts of interest for this article.

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ACS Med Chem Lett. 2014 Jan 30;5(2):106-7. doi: 10.1021/ml500037a. eCollection 2014.

Inhibitors of factor d may provide a treatment for age-related macular degeneration.

Abdel-Magid AF.

PMID: 24900799 [PubMed] PMCID: PMC4027787 [Available on 2015/2/13]

Pathogenesis

Acta Med Iran. 2014 Apr;52(4):265-70.

Osteoprotegerin and soluble receptor activator of nuclear factor-kappa B ligand in exudative age-related macular degeneration.

Ghorbanihaghjo A, Javadzadeh A, Rashtchizadeh N, Sorkhabi R, Khalili H, Rahimi-Ardabili B.

Abstract: Calcification and inflammation are among the important cases of exudative age-related macular degeneration (E-ARMD). The aim of the present study was to elucidate if there is any relationship between serum Osteoprotegerin (OPG), soluble receptor activator of nuclear factor-kappa B ligand (RANK-ligand) and E-ARMD. In a cross-sectional study, we compared 45 E-ARMD patients with 45 matched controls. Diagnosis was confirmed by fluorescein angiography. Serum samples were analyzed for OPG, RANK-ligand, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride (TG). The levels of OPG and RANK-ligand were measured by ELISA methods. The mean age was 72.0±11.5 years in the E-ARMD group and 68.2±8.9 years in the control group (p=0.09). The level of serum OPG was 132.10±75.49 pg/ml in the E-ARMD group and 94.88±61.65 pg/ml in the control subjects. E-ARMD patients had significantly high levels of OPG (p=0.012), as well as significantly high levels of LDL-C and TC (p=0.001 and p=0.005, respectively). We could not find any significant difference in RANK-ligand, HDL-C, or TG between two study groups (p>0.05). To the best of our

knowledge, this is the first study investigating the levels of OPG in E-ARMD patients. The present study showed that E-ARMD patients had high levels of serum OPG. It may act as a protective factor for E-ARMD or only as a secondary phenomenon of different processes of E-ARMD. Further prospective studies would be necessary for prognostic and predictive significance of OPG in patients affected by E-ARMD.

PMID: 24901855 [PubMed - in process]

J Tissue Eng Regen Med. 2014 Jun 1. doi: 10.1002/term.1882. [Epub ahead of print]

Effects of small intestinal submucosa content on the adhesion and proliferation of retinal pigment epithelial cells on SIS-PLGA films.

Lee GY, Kang SJ, Lee SJ, Song JE, Joo CK, Lee D, Khang G.

Abstract: The retinal pigment epithelium (RPE) plays a critical role in the maintenance of the normal functions of the retina, particularly the photoreceptors. RPE dysfunction, vision loss and degeneration have been implicated as the cause of many retinal diseases, including retinitis pigmentosa and age-related macular degeneration (AMD). To overcome such disorders, tissue engineering could offer useful strategies, using biodegradable polymeric films to replace diseased or lost RPE. Synthetic/natural hybrid films have been studied as a temporary substrate for growing RPEs in biological implantations. In this study, we prepared small intestinal submucosa (SIS)-poly(lactic-co-glycolic) (PLGA) hybrid films and seeded human RPE cells (ARPE-19 cells) onto the film surface. We investigated the film suitability for RPE cell proliferation by MTT assay. The morphology of cellular adhesion on the film was confirmed by scanning electron microscopy (SEM). Reverse transcription-polymerase chain reaction (RT-PCR) and 3-amino-9-ethylcarbazole (AEC) staining were performed to examine mRNA expression and to compare cell proliferation on the films, using cytokeratin as a marker of RPE. Conclusively, we confirmed the higher cell survival rate and much stronger phenotype expression of RPEs on SIS-PLGA films compared to pure PLGA films. These results demonstrated the potential application of SIS-PLGA films in tissue-engineering strategies. Copyright © 2014 John Wiley & Sons, Ltd.

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Genetics

Invest Ophthalmol Vis Sci. 2014 Jun 6. pii: IOVS-13-13684. doi: 10.1167/iov.13-13684. [Epub ahead of print]

Rare Complement Factor H Variant Associated with Age-related Macular Degeneration in the Amish.

Hoffman JD, Cooke Bailey JN, D'Aoust LN, Cade W, Ayala-Haedo J, Fuzzell MD, Laux RA, Adams L, Reinhart-Mercer L, Caywood L, Whitehead-Gay P, Agarwal A, Wang G, Scott WK, Pericak-Vance M, Haines JL.

Purpose: Age-related macular degeneration (AMD) is the leading cause of blindness among the adult population in the developed world. To further the understanding of this disease, we have studied the genetically isolated Amish population of Ohio and Indiana.

Methods: Cumulative genetic risk scores were calculated using the 19 known allelic associations. Exome sequencing was performed in three members of a small Amish family with AMD who lack the common risk alleles in CFH and ARMS2/HTRA1. Follow-up genotyping and association analysis was performed in a cohort of 973 Amish individuals including 95 with self-reported AMD.

Results: The cumulative genetic risk score analysis generated a mean genetic risk score of 1.12 (95% CI [1.10,1.13]) in the Amish controls and 1.18 (95% CI [1.13,1.22]) in the Amish cases. This mean difference

in genetic risk scores is statistically significant ($p=0.0042$). Exome sequencing identified a rare variant (P503A) in CFH. Association analysis in the remainder of the Amish sample revealed that the P503A variant is significantly associated with AMD ($p=9.27 \times 10^{-13}$). P503A was absent when evaluated in a cohort of 791 elderly non-Amish controls, and 1,456 non-Amish cases.

Conclusions: The cumulative genetic risk score analysis suggests that the variants reported by the AMDGene consortium account for a smaller genetic burden of disease in the Amish as compared to the non-Amish Caucasian population. Using exome sequencing data, we identified a novel missense mutation that is shared among a densely affected nuclear Amish family and located in a gene that has been previously implicated in AMD risk.

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PLoS Comput Biol. 2014 Jun 5;10(6):e1003627. doi: 10.1371/journal.pcbi.1003627. eCollection 2014.

AprioriGWAS, a New Pattern Mining Strategy for Detecting Genetic Variants Associated with Disease through Interaction Effects.

Zhang Q, Long Q, Ott J.

Abstract: Identifying gene-gene interaction is a hot topic in genome wide association studies. Two fundamental challenges are: (1) how to smartly identify combinations of variants that may be associated with the trait from astronomical number of all possible combinations; and (2) how to test epistatic interaction when all potential combinations are available. We developed AprioriGWAS, which brings two innovations. (1) Based on Apriori, a successful method in field of Frequent Itemset Mining (FIM) in which a pattern growth strategy is leveraged to effectively and accurately reduce search space, AprioriGWAS can efficiently identify genetically associated genotype patterns. (2) To test the hypotheses of epistasis, we adopt a new conditional permutation procedure to obtain reliable statistical inference of Pearson's chi-square test for the [Formula: see text] contingency table generated by associated variants. By applying AprioriGWAS to age-related macular degeneration (AMD) data, we found that: (1) angiopoietin 1 (ANGPT1) and four retinal genes interact with Complement Factor H (CFH). (2) GO term "glycosaminoglycan biosynthetic process" was enriched in AMD interacting genes. The epistatic interactions newly found by AprioriGWAS on AMD data are likely true interactions, since genes interacting with CFH are retinal genes, and GO term enrichment also verified that interaction between glycosaminoglycans (GAGs) and CFH plays an important role in disease pathology of AMD. By applying AprioriGWAS on Bipolar disorder in WTCCC data, we found variants without marginal effect show significant interactions. For example, multiple-SNP genotype patterns inside gene GABRB2 and GRIA1 (AMPA subunit 1 receptor gene). AMPARs are found in many parts of the brain and are the most commonly found receptor in the nervous system. The GABRB2 mediates the fastest inhibitory synaptic transmission in the central nervous system. GRIA1 and GABRB2 are relevant to mental disorders supported by multiple evidences.

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Rare and common variants in extracellular matrix gene Fibrillin 2 (FBN2) are associated with macular degeneration.

Ratnapriya R, Zhan X et al

Abstract: Neurodegenerative diseases affecting the macula constitute a major cause of incurable vision loss and exhibit considerable clinical and genetic heterogeneity, from early-onset monogenic disease to multifactorial late-onset age-related macular degeneration (AMD). As part of our continued efforts to define genetic causes of macular degeneration, we performed whole exome sequencing in four individuals of a

two-generation family with autosomal dominant maculopathy and identified a rare variant p.Glu1144Lys in Fibrillin 2 (FBN2), a glycoprotein of the elastin-rich extracellular matrix (ECM). Sanger sequencing validated the segregation of this variant in the complete pedigree, including two additional affected and one unaffected individual. Sequencing of 192 maculopathy patients revealed additional rare variants, predicted to disrupt FBN2 function. We then undertook additional studies to explore the relationship of FBN2 to macular disease. We show that FBN2 localizes to Bruch's membrane and its expression appears to be reduced in aging and AMD eyes, prompting us to examine its relationship with AMD. We detect suggestive association of a common FBN2 non-synonymous variant, rs154001 (p.Val965Ile) with AMD in 10,337 cases and 11,174 controls (OR=1.10; p-value=3.79×10⁻⁵). Thus, it appears that rare and common variants in a single gene - FBN2 - can contribute to Mendelian and complex forms of macular degeneration. Our studies provide genetic evidence for a key role of elastin microfibers and Bruch's membrane in maintaining blood-retina homeostasis and establish the importance of studying orphan diseases for understanding more common clinical phenotypes.

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Expert Opin Drug Deliv. 2014 Jun 5:1-10. [Epub ahead of print]

RNA interference technology for anti-VEGF treatment.

Chen S, Feng J, Ma L, Liu Z, Yuan W.

Introduction: Overexpression of VEGF has been identified to be associated with many pathologic processes such as tumors and retinopathy. Inhibiting uncontrolled growth of VEGF is a promising strategy to treat these diseases. Currently small molecule inhibitors and monoclonal antibodies are the primary treatment. However, complex development, short half-life, limited effectiveness and potential systemic side effects limited their applications. Highly effective and safe therapeutic technologies are highly desirable to meet the growing clinical needs. RNA interference (RNAi) technology, inhibits special gene activity at the post transcriptional level and reduces the expression of relevant proteins, holding great potential due to its easy design and high efficacy. Some molecules based on RNAi have been investigating in different clinical trials.

Areas covered: In this article, we review and consider current advances in the application of RNAi technology and potential future clinical strategies.

Expert opinion: RNAi technology has a promising future in anti-VEGF treatment, most of the investigations are encouraging and exciting. More anti-VEGF candidates will enter clinical trials and may be a novel therapeutic strategy.

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Diet & lifestyle

Ophthalmic Physiol Opt. 2014 Jun 5. doi: 10.1111/opo.12142. [Epub ahead of print]

A review of the evidence for dietary interventions in preventing or slowing the progression of age-related macular degeneration.

Evans JR, Lawrenson JG.

PURPOSE: To summarise the results of recent Cochrane systematic reviews that have investigated whether nutritional supplements prevent or slow the progression of age-related macular degeneration (AMD).

RECENT FINDINGS: There is no good evidence from randomised controlled trials that the general

population should be taking antioxidant vitamin supplements to reduce their risk of developing AMD later on in life. By contrast, there is moderate quality evidence that people with AMD may experience a delay in progression by taking specific antioxidant vitamin and mineral supplements. This finding is drawn from one large randomised controlled trial conducted in the USA in a relatively well-nourished population. Although observational studies have shown that the consumption of dietary omega 3 long chain polyunsaturated fatty acids may reduce the risk of progression to advanced AMD, two recently published randomised controlled trials failed to show any benefit of omega 3 supplements on AMD progression.

SUMMARY: There is no high quality experimental evidence that nutritional supplementation is beneficial for the primary prevention of AMD. However, people with AMD may benefit from supplementation with antioxidant vitamins. There is currently no evidence to support increasing levels of omega 3 long chain polyunsaturated fatty acids in the diet for the explicit purpose of preventing or slowing the progression of AMD.

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Why has Nature Chosen Lutein and Zeaxanthin to Protect the Retina?

Widomska J, Subczynski WK.

Abstract: Age-related macular degeneration (AMD) is associated with a low level of macular carotenoids in the eye retina. Only two carotenoids, namely lutein and zeaxanthin are selectively accumulated in the human eye retina from blood plasma where more than twenty other carotenoids are available. The third carotenoid which is found in the human retina, meso-zeaxanthin is formed directly in the retina from lutein. All these carotenoids, named also macular xanthophylls, play key roles in eye health and retinal disease. Macular xanthophylls are thought to combat light-induced damage mediated by reactive oxygen species by absorbing the most damaging incoming wavelength of light prior to the formation of reactive oxygen species (a function expected of carotenoids in nerve fibers) and by chemically and physically quenching reactive oxygen species once they are formed (a function expected of carotenoids in photoreceptor outer segments). There are two major hypotheses about the precise location of macular xanthophylls in the nerve fiber layer of photoreceptor axons and in photoreceptor outer segments. According to the first, macular xanthophylls transversely incorporate in the lipid-bilayer portion of membranes of the human retina. According to the second, macular xanthophylls are protein-bound by membrane-associated, xanthophyll-binding proteins. In this review we indicate specific properties of macular xanthophylls that could help explain their selective accumulation in the primate retina with special attention paid to xanthophyll-membrane interactions.

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SUPPLEMENTATION WITH THREE DIFFERENT MACULAR CAROTENOID FORMULATIONS IN PATIENTS WITH EARLY AGE-RELATED MACULAR DEGENERATION.

Sabour-Pickett S, Beatty S, Connolly E, Loughman J, Stack J, Howard A, Klein R, Klein BE, Meuer SM, Myers CE, Akuffo KO, Nolan JM.

PURPOSE: To investigate the impact of three different macular carotenoid formulations on macular pigment optical density and visual performance in subjects with early age-related macular degeneration.

METHODS: Fifty-two subjects were supplemented and followed for 12 months, 17 of them were in intervention Group 1 (20 mg/day lutein and 2 mg/day zeaxanthin); 21 in Group 2 (10 mg/day meso-

zeaxanthin, 10 mg/day lutein, and 2 mg/day zeaxanthin); and 14 in Group 3 (17 mg/day meso-zeaxanthin, 3 mg/day lutein, and 2 mg/day zeaxanthin). The macular pigment optical density was measured using customized heterochromatic flicker photometry, and visual function was assessed using corrected distance visual acuity and by letter contrast sensitivity.

RESULTS: A statistically significant increase in the macular pigment optical density was observed at all measured eccentricities in Group 2 ($P \leq 0.005$) and in Group 3 ($P < 0.05$, for all), but only at 1.75° in Group 1 ($P = 0.018$). Statistically significant ($P < 0.05$) improvements in letter contrast sensitivity were seen at all spatial frequencies (except 1.2 cycles per degree) in Group 3, and at low spatial frequencies in Groups 1 and 2.

CONCLUSION: Augmentation of the macular pigment optical density across its spatial profile and enhancements in contrast sensitivity were best achieved after supplementation with a formulation containing high doses of meso-zeaxanthin in combination with lutein and zeaxanthin.

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