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Drug treatment

Ophthalmology. 2014 Aug 19. pii: S0161-6420(14)00592-2. doi: 10.1016/j.ophtha.2014.07.008. [Epub ahead of print]

Vision-Related Function after Ranibizumab Treatment for Diabetic Macular Edema: Results from RIDE and RISE.

Bressler NM, Varma R, Suñer IJ, Dolan CM, Ward J, Ehrlich JS, Colman S, Turpcu A; RIDE and RISE Research Groups.

OBJECTIVE: To examine the effects of intravitreal ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA) treatment on patient-reported vision-related function, as assessed by 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) scores, in patients with visual impairment secondary to center-involved diabetic macular edema (DME).

DESIGN: Within 2 randomized, double-masked, phase 3 clinical trials (RIDE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema {ME} With Center Involvement Secondary to Diabetes Mellitus; NCT00473382] and RISE [A Study of Ranibizumab Injection in Subjects With Clinically Significant Macular Edema {ME} With Center Involvement Secondary to Diabetes Mellitus; NCT00473330]), the NEI VFQ-25 was administered at baseline and at the 6-, 12-, 18-, and 24-month follow-up visits.

PARTICIPANTS: Three hundred eighty-two (100%) RIDE patients and 377 (100%) RISE patients.

INTERVENTION: Patients were randomized 1:1:1 to monthly injections of intravitreal ranibizumab 0.3 or 0.5 mg or sham. Study participants could receive macular laser for DME from month 3 onward if specific criteria were met.

MAIN OUTCOME MEASURES: Exploratory post hoc analysis of mean change from baseline in NEI VFQ-25 scores at 12 and 24 months.

RESULTS: Across all treatment arms, 13% to 28% of enrolled eyes were the better-seeing eye. For all eyes in RIDE and RISE, the mean change in NEI VFQ-25 composite score improved more in ranibizumab-treated eyes at both the 12- and 24-month visits compared with sham treatment. For the better-seeing eyes at baseline, the mean change in composite score with 0.3 mg ranibizumab at the 24-month visit was 10.9 more (95% confidence interval [CI], 2.5-19.2) than sham for RIDE patients and 1.3 more (95% CI, -10.5 to 13.0) than sham for RISE patients. For the worse-seeing eyes at baseline, the mean change in composite score with 0.3 mg ranibizumab at the 24-month visit was 1.0 more (95% CI, -4.7 to 6.7) than sham for RIDE patients and 1.8 more (95% CI, -2.7 to 6.2) than sham for RISE patients. Similar results for most of these outcomes were seen with 0.5 mg ranibizumab.

CONCLUSIONS: These phase 3 trials demonstrated that ranibizumab treatment for DME likely improves patient-reported vision-related function outcomes compared with sham, further supporting treatment of DME with ranibizumab.

PMID: 25148789 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2014 Aug 29;8:CD005139. [Epub ahead of print]

Anti-vascular endothelial growth factor for neovascular age-related macular degeneration.

Solomon SD, Lindsley K, Vedula SS, Krzystolik MG, Hawkins BS.

BACKGROUND: Age-related macular degeneration (AMD) is the most common cause of uncorrectable severe vision loss in people aged 55 years and older in the developed world. Choroidal neovascularization (CNV) secondary to neovascular AMD accounts for most AMD-related severe vision loss. Anti-vascular endothelial growth factor (anti-VEGF) agents, injected intravitreally, aim to block the growth of abnormal blood vessels in the eye to prevent vision loss and, in some instances, improve vision.

OBJECTIVES: To investigate: (1) the ocular and systemic effects of, and quality of life associated with, intravitreally injected anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) for the treatment of neovascular AMD compared with no anti-VEGF treatment; and (2) the relative effects of one anti-VEGF agent compared with another when administered in comparable dosages and regimens.

SEARCH METHODS: We searched Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 3), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to March 2014), EMBASE (January 1980 to March 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to March 2014), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip/search/en). We used no date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 27 March 2014.

SELECTION CRITERIA: We included randomized controlled trials (RCTs) that evaluated pegaptanib, ranibizumab, or bevacizumab versus each other or a control treatment (e.g., sham treatment or photodynamic therapy). All trials followed participants for at least one year.

DATA COLLECTION AND ANALYSIS: Two review authors independently screened records, extracted data, and assessed risks of bias. We contacted trial authors for additional data. We analyzed outcomes as risk ratios (RRs) or mean differences (MDs). We used the standard methodological procedures expected by The Cochrane Collaboration.

MAIN RESULTS: We included 12 RCTs including a total of 5496 participants with neovascular AMD (the number of participants per trial ranged from 28 to 1208). One trial compared pegaptanib, three trials ranibizumab, and two trials bevacizumab versus controls; six trials compared bevacizumab with ranibizumab. Four trials were conducted by pharmaceutical companies; none of the eight studies which evaluated bevacizumab were funded by pharmaceutical companies. The trials were conducted at various centers across five continents (North and South America, Europe, Asia and Australia). The overall quality of the evidence was very good, with most trials having an overall low risk of bias. When compared with control treatments, participants who received any of the three anti-VEGF agents were more likely to have gained 15 letters or more of visual acuity, lost fewer than 15 letters of visual acuity, and had vision 20/200 or better after one year of follow up. Visual acuity outcomes after bevacizumab and ranibizumab were similar when the same regimens were compared in the same RCTs, despite the substantially lower cost for bevacizumab compared with ranibizumab. No trial directly compared pegaptanib with other anti-VEGF agents; however, when compared with controls, ranibizumab or bevacizumab yielded larger improvements in visual acuity

outcomes than pegaptanib. Participants treated with anti-VEGFs showed improvements in morphologic outcomes (e.g., size of CNV or central retinal thickness) compared with participants not treated with anti-VEGF agents. There was less reduction in central retinal thickness among bevacizumab-treated participants than among ranibizumab-treated participants after one year (MD -13.97 μ m; 95% confidence interval (CI) -26.52 to -1.41); however, this difference is within the range of measurement error and we did not interpret it as being clinically meaningful. Ocular inflammation and increased intraocular pressure after intravitreal injection were the most frequently reported serious ocular adverse events. Endophthalmitis was reported in fewer than 1% of anti-VEGF treated participants; no cases were reported in control groups. The occurrence of serious systemic adverse events was comparable across anti-VEGF-treated groups and control groups; however, the numbers of events and trial participants may have been insufficient to detect a meaningful difference between groups. Data for visual function, quality of life, and economic outcomes were sparsely measured and reported.

AUTHORS' CONCLUSIONS: The results of this review indicate the effectiveness of anti-VEGF agents (pegaptanib, ranibizumab, and bevacizumab) in terms of maintaining visual acuity; ranibizumab and bevacizumab were also shown to improve visual acuity. The information available on the adverse effects of each medication do not suggest a higher incidence of potentially vision-threatening complications with intravitreal injection compared with control interventions; however, clinical trial sample sizes may not have been sufficient to detect rare safety outcomes. Research evaluating variable dosing regimens with anti-VEGF agents, effects of long-term use, combination therapies (e.g., anti-VEGF treatment plus photodynamic therapy), and other methods of delivering the agents should be incorporated into future Cochrane reviews.

PMID: 25170575 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Aug 27. [Epub ahead of print]

Effect of Macular Ischemia on Intravitreal Ranibizumab Treatment for Diabetic Macular Edema.

Douvali M, Chatziralli IP, Theodossiadis PG, Chatzistefanou KI, Giannakaki E, Rouvas AA.

Purpose: To evaluate the impact of macular ischemia on the functional and anatomical outcome after intravitreal injections of ranibizumab for the treatment of diabetic macular edema (DME).

Procedures: Participants were 49 patients with diabetes mellitus, divided into two groups based on the presence of ischemia on fluorescein angiography: (i) nonischemic group (n = 32) and (ii) ischemic group (n = 17). All patients were treated with intravitreal ranibizumab and were followed up for 6 months. The main outcome measures were changes in visual acuity (VA) and central foveal thickness (CFT).

Results: There was a statistically significant improvement in VA and CFT between baseline and the end of the follow-up in the nonischemic group, while in the ischemic group there was no significant difference in VA but CFT differed significantly at the 6-month follow-up.

Conclusions: Macular ischemia may have a negative impact on functional outcomes 6 months after intravitreal ranibizumab treatment in patients with DME but has no effect on anatomical outcomes.

PMID: 25171753 [PubMed - as supplied by publisher]

Expert Opin Drug Saf. 2014 Aug 29:1-5. [Epub ahead of print]

Safety and efficacy of various concentrations of topical lidocaine gel for intravitreal injection.

Shiroma HF, Rodrigues EB, Farah ME, Penha FM, Lorenzo JC, Grumann A, Nunes RP.

Introduction: Intravitreal injection (IVT) is one of the most common vitreoretinal procedures, a large majority

are performed with local anesthesia. The purpose of this study was to investigate the safety to the cornea and anesthetic efficacy of five concentrations of lidocaine gel.

Methods: A prospective clinical trial was conducted testing lidocaine gel in five preparations: 2, 3.5, 5, 8 and 12%. Patients with macular degeneration, diabetic edema or retina vein occlusion were scheduled for intravitreal treatment received topical anesthesia with lidocaine gel 5 and 10 min before the procedure. Patients answered the visual analog scale for pain during the procedure. Corneal and conjunctival was evaluated using the Oxford scale.

Results: In total, 260 patients were randomized into five groups. The mean pain scores ($\pm$ standard deviation) were 2.63 ($\pm$ 1.68) in the 2% group, 2.08 ($\pm$ 1.35) in the 3.5%; 2.00 ($\pm$ 1.65) in the 5%, 1.93 ($\pm$ 1.40) in the 8% and 1.83 ($\pm$ 1.35) in the 12% group. Mean pain score among all groups was similar ($p = 0.077$). There was no significant difference between groups in regard to keratitis mean score ($p = 0.897$).

Conclusions: Lidocaine gel at concentrations from 2 to 12% induced similar anesthetic effect for IVTs, without adverse effects on cornea and conjunctiva.

PMID: 25171074 [PubMed - as supplied by publisher]

Retina. 2014 Aug 28. [Epub ahead of print]

LONG-TERM ALTERATIONS OF SYSTEMIC VASCULAR ENDOTHELIAL GROWTH FACTOR LEVELS IN PATIENTS TREATED WITH RANIBIZUMAB FOR AGE-RELATED MACULAR DEGENERATION.

Enders P, Muether PS, Hermann M, Ristau T, Fauser S.

PURPOSE: To analyze long-term changes of systemic vascular endothelial growth factor (VEGF) levels in patients treated with ranibizumab for neovascular age-related macular degeneration.

METHODS: Sixty-one patients with neovascular age-related macular degeneration and 68 age-matched controls were included in the study. Patients were treated with ranibizumab on a pro re nata regimen. Plasma samples were collected before initiation of treatment and after 1 year (30 patients) or 2 years (31 patients) of treatment. Vascular endothelial growth factor was measured by Luminex microbead analysis.

RESULTS: At baseline, patients with neovascular age-related macular degeneration and controls did not differ significantly in VEGF levels ($P = 0.062$). There was a significant decline in systemic VEGF levels of 39.5% after 1 year (34.2 ± 17.2 pg/mL to 20.7 ± 14.0 pg/mL; $P = 7.50 \times 10^{-5}$) and of 46.7% after 2 years (40.4 ± 24.1 pg/mL to 21.5 ± 23.3 pg/mL; $P = 2.48 \times 10^{-5}$) of treatment. Patients with persistent activity of choroidal neovascularization showed a significantly smaller decrease of plasma VEGF levels than patients with dry intervals despite the higher number of injections ($P = 0.048$).

CONCLUSION: In addition to immediate effects limited to days if not hours, ranibizumab also leads to long-term alterations of systemic VEGF to subnormal levels. Patients with persistent choroidal neovascularization activity showed a less pronounced VEGF decrease. Therefore, VEGF levels might be a useful marker for treatment response.

PMID: 25170863 [PubMed - as supplied by publisher]

Retina. 2014 Aug 28. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY-GUIDED RANIBIZUMAB INJECTION FOR CYSTOID MACULAR EDEMA IN WELL-CONTROLLED UVEITIS: Twelve-Month Outcomes.

Reddy AK, Cabrera M, Yeh S, Davis JL, Albini TA.

PURPOSE: To determine whether serial ranibizumab injections are effective in the treatment of cystoid macular edema in patients with chronic controlled noninfectious uveitis.

METHODS: Five eyes of 5 patients were included in a prospective noncomparative therapeutic trial. They received intravitreal injections of ranibizumab at Day 0 and were followed monthly for 1 year. Injections were repeated monthly if persistent or new cystic edema manifested on optical coherence tomography. The primary outcome measure was the mean change in best-corrected visual acuity from baseline at 12 months. Secondary outcome measures included mean percentage change in central subfield retinal thickness (CST) and incidence of adverse events through Month 24.

RESULTS: Thirty-two injections were performed over the study period. At 1 year, the mean increase in acuity was 12.2 Early Treatment for Diabetic Retinopathy Study letters ($P = 0.015$). There was a statistically significant increase in visual acuity over time ($P = 0.002$). The CST decreased by 31.4%, 46.0%, 37.6%, and 45.4% relative to baseline at 3, 6, 9, and 12 months, respectively ($P = 0.003$). One patient experienced recurrence of uveitis with subsequent cataract and glaucoma progression.

CONCLUSION: Optical coherence tomography-guided monthly intravitreal ranibizumab injections delivered over the course of 1 year resulted in improved vision and reduced central retinal thickness.

PMID: 25170857 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Aug 28. [Epub ahead of print]

Structures affecting recovery of macular function in patients with age-related macular degeneration after intravitreal ranibizumab.

Nishimura T, Machida S, Hashizume K, Kurosaka D.

PURPOSE: To determine the retinal structures affecting the recovery of macular function in patients with exudative age-related macular degeneration (AMD) treated with intravitreal ranibizumab (IVR).

METHOD: Thirty eyes of 30 patients with exudative AMD who were treated with IVR at monthly intervals for 3 months were studied. Focal macular electroretinograms (fmERGs) and spectral-domain optical coherence tomography (SD-OCT) were performed before and 3 months after beginning the IVR injections. The fmERGs were elicited by a 15° white stimulus spot centered on the fovea. The thickness of different retinal layers, presence of a serous retinal detachment (SRD), and presence of a pigment epithelial detachment (PED) at the fovea was determined in the SD-OCT images. Measurements were made of the inner, middle, and outer layers of the retina and also of the SRD and PED in the horizontal and vertical meridians at 1.2 mm from the fovea (parafoveal regions). The significance of the correlations between these structural parameters and the a-wave amplitude of the fmERG was determined.

RESULTS: There was no significant correlation between the structural parameters of the fovea and the a-wave amplitude. In the parafoveal regions, the thickness of the outer retinal layer was significantly correlated with an increase of the a-wave amplitude ($R = 0.56$, $P = 0.001$). In addition, the SRD thickness was negatively and significantly correlated with the a-wave amplitude ($R = -0.54$, $P = 0.002$). The change in the parafoveal SRD thickness after IVRs was the only independent determinant of recovery of the a-wave amplitude after the treatments ($P < 0.05$).

CONCLUSIONS: The macular function measured by the fmERGs was determined by the parafoveal outer layer and SRD thickness in patients with exudative AMD. Of these, changes in the SRD thickness by IVRs most strongly affected the recovery of macular function.

PMID: 25163415 [PubMed - as supplied by publisher]

Mol Pharm. 2014 Aug 27. [Epub ahead of print]

Comparison of Binding Characteristics and In Vitro Activities of Three Inhibitors of Vascular Endothelial Growth Factor A.

Yang J, Wang X, Fuh G, Yu L, Wakshull E, Khosraviani M, Day ES, Demeule B, Liu J, Shire SJ, Ferrara N, Yadav S.

Abstract: The objectives of this study were to evaluate the relative binding and potencies of three inhibitors of vascular endothelial growth factor A (VEGF), used to treat neovascular age-related macular degeneration, and assess their relevance in the context of clinical outcome. Ranibizumab is a 48 kDa antigen binding fragment, which lacks a fragment crystallizable (Fc) region and is rapidly cleared from the systemic circulation. Aflibercept, a 110 kDa fusion protein and bevacizumab, a 150 kDa monoclonal antibody, each contain an Fc region. Binding affinities were determined using Biacore analysis. Competitive binding by sedimentation velocity analytical ultracentrifugation (SV-AUC) was used to support the binding affinities determined by Biacore of ranibizumab and aflibercept to VEGF. A bovine retinal microvascular endothelial cell (BREC) proliferation assay was used to measure potency. Biacore measurements were format dependent, especially for aflibercept, suggesting that biologically relevant, true affinities of recombinant VEGF (rhVEGF) and its inhibitors are yet to be determined. Despite this assay format dependency, ranibizumab appeared to be a very tight VEGF binder in all three formats. The results are also very comparable to those reported previously¹⁻³. At equivalent molar ratios ranibizumab was able to displace aflibercept from preformed aflibercept-VEGF complexes in solution as assessed by SV-AUC, whereas aflibercept was not able to significantly displace ranibizumab from preformed ranibizumab-VEGF complexes. Ranibizumab, aflibercept, and bevacizumab showed dose-dependent inhibition of BREC proliferation induced by 6 ng/ml VEGF, with average IC₅₀ values of 0.088 ± 0.032 nM, 0.090 ± 0.009 nM, and 0.500 ± 0.091 nM, respectively. Similar results were obtained with 3ng/mL VEGF. In summary Biacore studies and SV-AUC solution studies show that aflibercept does not bind with higher affinity than ranibizumab to VEGF as recently reported⁴ and both inhibitors appeared to be equipotent with respect to their ability to inhibit VEGF function.

PMID: 25162961 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2014 Aug 27. [Epub ahead of print]

2-Year Outcome of Intravitreal Injections of Ranibizumab for Myopic Choroidal Neovascularization.

Wu TT, Kung YH.

Purpose: To evaluate the 2-year outcome, efficacy, and safety of intravitreal ranibizumab injections for myopic choroidal neovascularization (CNV).

Methods: We retrospectively reviewed the medical records of 28 consecutive eyes that received intravitreal injections of ranibizumab for myopic CNV with a 24-month follow-up. Retreatment was performed as needed in eyes with persistent or recurrent CNV. Patient demographic data, best-corrected visual acuity (BCVA), CNV findings on fluorescent angiography, central macular thickness on optical coherence tomography, total number of treatments, and complications were recorded.

Results: Mean baseline BCVA was 0.53±0.32 logMAR [Snellen equivalent (SE), 6/20], and improved significantly to 0.28±0.32 logMAR (SE, 6/11) at 1 year and 0.29±0.28 logMAR (SE, 6/12) at 2 years (both P<0.01, Wilcoxon signed-rank test). The average number of total injections over 2 years was 3.32 (SD 2.13). A mean of 2.82 injections were performed in the first year, and 0.50 in the second year. Twenty-three eyes (82.1%) had no need for treatment during the second year of follow-up. Mean improvement from the baseline was 2.57 Snellen lines (SD 2.35) at 1 year, and 2.29 lines (SD 2.69) at 2 years. At 2 years, 11 eyes (39.3%) showed a gain of at least 3 lines after treatment. No complications were noted after treatment.

Conclusions: Intravitreal ranibizumab injection was safe and effective in treating myopic CNV, with visual improvement maintained over 2 years.

PMID: 25162313 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2014 Aug 18;7(4):681-5. doi: 10.3980/j.issn.2222-3959.2014.04.18. eCollection 2014.

Spontaneous or secondary to intravitreal injections of anti-angiogenic agents retinal pigment epithelial tears in age-related macular degeneration.

Leon PE, Saviano S, Zanei A, Pastore MR, Guaglione E, Mangogna A, Tognetto D.

AIM: To evaluate the visual function evolution of retinal pigment epithelial (RPE) tears in patients with age-related macular degeneration (AMD) according to type of occurrence [spontaneous or secondary to anti-vascular endothelial growth factor (anti-VEGF) injection] and the topographic location of the tear after a two-year follow-up period.

METHODS: A total of 15 eyes of 14 patients with RPE tears in exudative AMD were analyzed retrospectively at the University Eye Clinic of Trieste. Inclusion criteria were: patient age of 50 or older with AMD and RPE tears both spontaneous occurring or post anti-VEGF treatment. Screening included: careful medical history, complete ophthalmological examination, fluorescein angiography (FA), indocyanine green angiography (ICG), autofluorescence and infrared imaging and optical coherence tomography (OCT). Patients were evaluated every month for visual acuity (VA), fundus examination and OCT. Other data reported were: presence of PED, number of injections before the tear, location of the lesion.

RESULTS: Mean follow-up was 24wk (SD±4wk). A total of 15 eyes were studied for RPE tear. In 6 cases (40%), the RPE tears occurred within two years of anti-VEGF injections the others occurred spontaneously. In 13 cases (86.6%), the RPE tear was associated with pigment epithelial detachment (PED). In 7 cases (46.6%), the RPE tear occurred in the central area of the retina and involved the fovea. Two lesions were found in the parafoveal region, six in the extra-macular area. In all cases visual acuity decreased at the end of the follow-up period ($P<0.01$) independently of the type or the topographical location of the lesion.

CONCLUSION: RPE tear occurs in exudative AMD as a spontaneous complication or in relation to anti-VEGF injections. Visual acuity decreased significantly and gradually in the follow-up period in all cases. No correlation was found between visual loss and the type of onset or the topographic location of the tears.

PMID: 25161943 [PubMed] PMCID: PMC4137207

Acta Ophthalmol. 2014 Aug 27. doi: 10.1111/aos.12540. [Epub ahead of print]

A randomized trial to compare the safety and efficacy of two ranibizumab dosing regimens in a Turkish cohort of patients with choroidal neovascularization secondary to AMD.

Eldem BM, Muftuoglu G, Topbaş S, Cakir M, Kadayifcilar S, Ozmert E, Bahçecioğlu H, Sahin F, Sevgi S; the SALUTE study group.

PURPOSE: To compare visual outcomes, number of visits and ranibizumab injections in patients treated with a Wait & Extend (W&E) or Treat & Observe (T&O) regimen.

METHODS: This 12-month, randomized, multicentre, open-label study enrolled patients aged ≥50 years with choroidal neovascularization (CNV) secondary to AMD who had not received anti-VEGF agents. Patients received three monthly injections of ranibizumab before randomization (1:1): (i) T&O patients were examined monthly and retreated if needed, (ii) W&E patients had a follow-up visit 1 month later. If no lesions were active, the interval to the next visit was extended by 2 weeks to a maximum of 8 weeks. Active lesions were re-treated and the follow-up schedule restarted. Primary end-point was change in BCVA at

Month 12.

RESULTS: Of the 104 screened patients, 99 were eligible and received ≥ 1 ranibizumab injection; 93 were randomized (T&O: 45, W&E: 48). The median (interquartile range [IQR]) change in BCVA (logMAR) from baseline at Month 12 was similar between groups (T&O: -0.12 [0.38]; W&E: -0.18 [0.32], $p = 0.267$). Median (IQR) number of visits at study end (including screening, baseline and control visit after 1st injection) was 15.0 (1.0) for T&O, and 12.0 (2.0) for W&E ($p < 0.001$). Injection numbers were similar between groups (median [IQR]: 6.0 [3.0] and 5.0 [4.0], respectively, $p = 0.215$). Adverse events were similar between groups.

CONCLUSION: W&E regimen resulted in a similar efficacy and safety profile to the labelled T&O regimen in patients with CNV secondary to AMD, and may help reduce the burden of follow-up visits.

PMID: 25160859 [PubMed - as supplied by publisher]

Retina. 2014 Aug 25. [Epub ahead of print]

CHANGES IN FLARE AFTER INTRAVITREAL INJECTION OF THREE DIFFERENT ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR MEDICATIONS.

Blaha GR, Brooks NO, Mackel CE, Pani A, Stewart AP, Price LL, Barouch FC, Chang J, Marx JL.

PURPOSE: To compare the change in anterior chamber flare after intravitreal injection of the anti-vascular endothelial growth factor agents bevacizumab, aflibercept, and ranibizumab.

METHODS: Sixty-one eyes of 53 patients underwent intravitreal injection with anti-vascular endothelial growth factor medications for exudative age-related macular degeneration, diabetic macular edema, or retinal vein occlusion. There were a total of 26 eyes injected with bevacizumab, 14 eyes injected with aflibercept, and 21 eyes injected with ranibizumab. Anterior segment flare was measured with a laser flare meter (Kowa) before intravitreal injection and 1 day after injection. The change in flare was analyzed.

RESULTS: The mean change in flare after 1 day was +2.5 photons per millisecond in patients who received bevacizumab, 0.0 photons per millisecond for aflibercept, and -0.2 photons per millisecond for ranibizumab. There was a statistically significant difference between the 3 medications ($P = 0.006$). Pairwise analysis of the change in flare showed a statistically significant difference between bevacizumab and ranibizumab ($P = 0.002$). The change in flare in patients who received aflibercept was not different from that in those who received bevacizumab ($P = 0.08$) or ranibizumab ($P = 0.99$).

CONCLUSION: There was a statistically significant increase in flare after bevacizumab injection compared with ranibizumab. This difference was small and is not believed to be clinically significant. There was no statistical difference in the change in flare between aflibercept and the other medications, although the number of eyes in the aflibercept group was small.

PMID: 25158942 [PubMed - as supplied by publisher]

Ophthalmic Epidemiol. 2014 Aug 26:1-9. [Epub ahead of print]

Predicting Non-response to Ranibizumab in Patients with Neovascular Age-related Macular Degeneration.

van Asten F, Rovers MM, Lechanteur YT, Smailhodzic D, Muether PS, Chen J, den Hollander AI, Fauser S, Hoyng CB, van der Wilt GJ, Klevering BJ.

Purpose: To validate known and determine new predictors of non-response to ranibizumab in patients with neovascular age-related macular degeneration (AMD) and to incorporate these factors into a prediction

rule.

Methods: This multicenter, observational cohort study included 391 patients treated with ranibizumab for neovascular AMD. We performed genetic analysis for single nucleotide polymorphisms in AMD-associated genes and collected questionnaires regarding environmental factors and disease history. The primary outcome was non-response to treatment, defined as a loss of visual acuity $\geq 30\%$ of letters.

Results: Of the 391 patients, 47 were classified as non-responsive. Independent predictors for non-response were age, baseline visual acuity, diabetes mellitus and accumulation of risk alleles in the CFH, ARMS2 and VEGF-A genes. The area under the receiver operating characteristic curve was 0.77 (95% confidence interval 0.70-0.84). We derived a clinical prediction rule, with possible total risk scores ranging from 0-19 points. The absolute risk of non-response varied from 3-52% between risk score groups.

Conclusion: This is an important step towards a clinical prediction rule that can aid clinicians in identifying AMD patients with increased likelihood of non-response, and consequently contribute to making shared treatment decisions.

PMID: 25157998 [PubMed - as supplied by publisher]

Pol Merkur Lekarski. 2014 Jul;37(217):56-60.

[Neovascular form of age-related macular degeneration --current management in Poland and in Europe]. [Article in Polish]

Teper S, Nowińska A, Lyssek-Boroń A, Wylegała E.

Abstract: Currently in Poland neovascular form of age-related macular degeneration (AMD) is treated with vascular endothelial growth factor (VEGF) inhibitors--ranibizumab, aflibercept and bevacizumab. Photodynamic therapy is still refunded, although it is very rarely used. It can be estimated that only small minority (about 5-10%) of cases are properly treated due to mainly refunding restrictions in Poland. In countries with wider access to treatment 50% reduction in AMD-related blindness incidence was noted. Low-cost off-label anti-VEGF agent bevacizumab is almost inaccessible in Polish public health system because of law regulations. In order to increase availability of anti-VEGF injections vials of all mentioned drugs are divided which raises safety concerns. Despite new potent drug in the market aflibercept, cost of treatment remains very high. The optimal treatment regimen includes three monthly injections, after which is usually used pro re nata therapy based primarily on the outcome of macular optical coherence tomography. Routinely recommended antibiotic prophylaxis of injection-related endophthalmitis probably has no meaning apart from the generation of resistance.

PMID: 25154202 [PubMed - in process]

Eye (Lond). 2014 Aug 22. doi: 10.1038/eye.2014.186. [Epub ahead of print]

Association of retinal vessel calibre and visual outcome in eyes with diabetic macular oedema treated with ranibizumab.

Moradi A, Sepah YJ, Ibrahim MA, Sophie R, Moazez C, Bittencourt MG, Annam RE, Hanout M, Liu H, Ferraz D, Do DV, Nguyen QD.

Purpose: The study aims to identify the association between the baseline retinal vascular calibre and visual outcome of patients with diabetic macular oedema (DMO) treated with intravitreal ranibizumab.

Methods: The 1-M field (as defined in the ETDRS study) of the digital colour fundus photographs of DMO patients who had been treated primarily with ranibizumab in a clinical trial was assessed. Of the 84 patients, 25 had gradable retinal photographs that could be subjected to analyses by the Interactive Vessel

Analysis (IVAN) software at baseline. The average retinal vascular calibre of the six largest venules (CRVE) and the six largest arterioles (CRAE) in the peripapillary area (0.5 and 1 disc diameter from the optic disc margin) was measured. The relationship between CRVE and CRAE at baseline and the change in visual acuity at month 12 was assessed using the Mann-Whitney U test.

Results: Ten eyes from 10 patients who had shown an improvement of ≥ 2 lines of best corrected visual acuity (BCVA) at month 12 had a wider baseline CRVE ($248.3 \pm 24.5 \mu\text{m}$) compared with the 15 eyes from 15 patients who did not show the improvement of ≥ 2 lines ($226.6 \pm 44.8 \mu\text{m}$, $P < 0.05$). The baseline CRAE did not differ significantly in these patients (156.1 ± 22.7 vs $142 \pm 17.5 \mu\text{m}$, $P = 0.17$).

Conclusions: A wider baseline retinal venular calibre may be a predictor of better visual outcome in DMO eyes treated with ranibizumab. Further prospective studies with a larger sample size and a broader range of disease severity and visual acuity are needed to confirm this finding. Eye advance online publication, 22 August 2014; doi:10.1038/eye.2014.186.

PMID: 25145456 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2014 Aug 26. pii: IOVS-14-14407. doi: 10.1167/iov.14-14407. [Epub ahead of print]

Comparison of Multifocal Electroretinography and Microperimetry in Age-related Macular Degeneration.

Wu Z, Ayton LN, Guymer RH, Luu CD.

Purpose: To correlate and compare retinal function measured using multifocal electroretinography (mfERG) and microperimetry in intermediate age-related macular degeneration (AMD).

Methods: Sixty AMD participants underwent mfERG and microperimetry testing in one eye, and 44 control participants were included to provide normative values for each test. Thirteen hexagons in the central three rings of a 103 hexagon stimulus grid on mfERG and retinotopically-matched points on microperimetry were chosen and converted into standard deviations (SDs) away from the normal participants (Z-score) to represent the magnitude of measured functional deficit and allow a comparison of the two measures.

Results: For the average of all points on mfERG and microperimetry, mfERG N1-P1 response amplitude and microperimetric retinal sensitivity was significantly lower ($P = 0.013$ and $P < 0.001$ respectively) and mfERG P1 implicit time was significantly increased ($P < 0.001$) in the AMD participants compared to the control participants. Considering retinotopically-matched points, there was no significant correlation between the average Z-scores of the microperimetric retinal sensitivity and mfERG implicit time ($R = 0.254$, $P = 0.051$), nor response amplitudes ($R = 0.006$, $P = 0.965$), and the measured functional deficit on microperimetry was consistently greater than both mfERG parameters ($P < 0.001$).

Conclusions: The measured functional deficit on microperimetry was greater than mfERG parameters in eyes with intermediate AMD. The absence of correlations between these two measures suggests that mfERG may be capturing unique aspects of retinal dysfunction. These findings are important when considering the use of these functional measures in intermediate AMD.

PMID: 25159206 [PubMed - as supplied by publisher]

Ophthalmic Physiol Opt. 2014 Sep;34(5):592-613. doi: 10.1111/opo.12150.

A survey of current and anticipated use of standard and specialist equipment by UK optometrists.

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Dabasia PL, Edgar DF, Garway-Heath DF, Lawrenson JG.

PURPOSE: To investigate current and anticipated use of equipment and information technology (IT) in community optometric practice in the UK, and to elicit optometrists' views on adoption of specialist equipment and IT.

METHODS: An anonymous online questionnaire was developed, covering use of standard and specialist diagnostic equipment, and IT. The survey was distributed to a random sample of 1300 UK College of Optometrists members.

RESULTS: Four hundred and thirty-two responses were received (response rate = 35%). Enhanced (locally commissioned) or additional/separately contracted services were provided by 73% of respondents. Services included glaucoma repeat measures (30% of respondents), glaucoma referral refinement (22%), fast-track referral for wet age-related macular degeneration (48%), and direct cataract referral (40%). Most respondents (88%) reported using non-contact/pneumo tonometry for intra-ocular pressure measurement, with 81% using Goldmann or Perkins tonometry. The most widely used item of specialist equipment was the fundus camera (74% of respondents). Optical Coherence Tomography (OCT) was used by 15% of respondents, up from 2% in 2007. Notably, 43% of those anticipating purchasing specialist equipment in the next 12 months planned to buy an OCT. 'Paperless' records were used by 39% of respondents, and almost 80% of practices used an electronic patient record/practice management system. Variations in responses between parts of the UK reflect differences in the provision of the General Ophthalmic Services contract or community enhanced services. There was general agreement that specialised equipment enhances clinical care, permits increased involvement in enhanced services, promotes the practice and can be used as a defence in clinico-legal cases, but initial costs and ongoing maintenance can be a financial burden. Respondents generally agreed that IT facilitates administrative flow and secure exchange of health information, and promotes a state-of-the-art practice image. However, use of IT may not save examination time; its dynamic nature necessitates frequent updates and technical support; the need for adequate training is an issue; and security of data is also a concern.

CONCLUSION: UK optometrists increasingly employ modern equipment and IT services to enhance patient care and for practice management. While the clinical benefits of specialist equipment and IT are appreciated, questions remain as to whether the investment is cost-effective, and how specialist equipment and IT may be used to best advantage in community optometric practice.

PMID: 25160893 [PubMed - in process]

Ophthalmic Physiol Opt. 2014 Sep;34(5):540-51. doi: 10.1111/opo.12152.

Prediction of higher visual function in macular degeneration with multifocal electroretinogram and multifocal visual evoked potential.

Herbik A, Geringswald F, Thieme H, Pollmann S, Hoffmann MB.

OBJECTIVE: Visual search can be guided by past experience of regularities in our visual environment. This search guidance by contextual memory cues is impaired by foveal vision loss. Here we compared retinal and cortical visually evoked responses in their predictive value for contextual cueing impairment and visual acuity.

METHODS: Multifocal electroretinograms to flash stimulation (mfERGs; 103 locations; 55.8° diameter) and visual evoked potentials to pattern-reversal stimulation (mfVEPs; 60 locations; 48.6° diameter) were recorded monocularly in participants with age-related macular degeneration (n = 14 and 16, respectively). Response magnitudes were calculated as the respective signal-to-noise ratios for each eccentricity. Visual acuities (logMAR, range: 0.0-1.2) and contextual cueing effects on visual search (reaction time gain, range: -0.14-0.15) were correlated with the signal-to-noise ratios. A step-wise regression analysis was applied separately to the mfERG- and mfVEP-dataset to determine the eccentricity range and the processing stage

that is critical for these visual functions.

RESULTS: Central mfERGs (1.0-3.2°) were the sole predictor of contextual cueing of visual search ($p = 0.006$), but they were not significant predictors of visual acuity. In contrast, central mfVEPs (1.3-3.2°) were the sole predictor of visual acuity ($p < 0.001$), but they were not significant predictors of contextual cueing.

CONCLUSIONS: Contextual cueing is more dependent on parafoveal mfERG magnitude while visual acuity is more dependent on parafoveal mfVEP magnitude. The relation of contextual cueing to parafoveal mfERG magnitudes indicates the predictive value of retinal bipolar cell activity for this advanced level of visual function.

PMID: 25160891 [PubMed - in process]

Ophthalmic Physiol Opt. 2014 Sep;34(5):509-18. doi: 10.1111/opo.12148.

Cognitive speed of processing training in older adults with visual impairments.

Elliott AF, O'Connor ML, Edwards JD.

PURPOSE: To examine whether older adults with vision impairment differentially benefit from cognitive speed of processing training (SPT) relative to healthy older adults.

METHODS: Secondary data analyses were conducted from a randomised trial on the effects of SPT among older adults. The effects of vision impairment as indicated by (1) near visual acuity, (2) contrast sensitivity, (3) self-reported cataracts and (4) self-reported other eye conditions (e.g., glaucoma, macular degeneration, diabetic retinopathy, optic neuritis, and retinopathy) among participants randomised to either SPT or a social- and computer-contact control group was assessed. The primary outcome was Useful Field of View Test (UFOV) performance.

RESULTS: Mixed repeated-measures ancovas demonstrated that those randomized to SPT experienced greater baseline to post-test improvements in UFOV performance relative to controls (p 's < 0.001), regardless of impairments in near visual acuity, contrast sensitivity or presence of cataracts. Those with other eye conditions significantly benefitted from training ($p = 0.044$), but to a lesser degree than those without such conditions. Covariates included age and baseline measures of balance and depressive symptoms, which were significantly correlated with baseline UFOV performance.

CONCLUSIONS: Among a community-based sample of older adults with and without visual impairment and eye disease, the SPT intervention was effective in enhancing participants' UFOV performance. The analyses presented here indicate the potential for SPT to enhance UFOV performance among a community-based sample of older adults with visual impairment and potentially for some with self-reported eye disease; further research to explore this area is warranted, particularly to determine the effects of eye diseases on SPT benefits.

PMID: 25160890 [PubMed - in process]

Retina. 2014 Aug 25. [Epub ahead of print]

PACHYCHOROID NEOVASCULOPATHY.

Pang CE, Freund KB.

PURPOSE: To report 3 cases of pachychoroid neovascularization, a form of Type 1 (sub-retinal pigment epithelium) neovascularization, occurring over areas of increased choroidal thickness and dilated choroidal vessels.

METHODS: A retrospective observational case series of three patients who underwent comprehensive ophthalmic examination and multimodal imaging with fundus photography, fundus autofluorescence, spectral domain optical coherence tomography, enhanced depth imaging optical coherence tomography, fluorescein angiography, and indocyanine green angiography.

RESULTS: In all 3 eyes of 3 patients, aged 55 years to 63 years, there was Type 1 neovascularization overlying a localized area of choroidal thickening and dilated choroidal vessels seen with enhanced depth imaging optical coherence tomography. With indocyanine green angiography, there were large choroidal veins and choroidal hyperpermeability seen beneath the area of the neovascular tissue in all three eyes. No eyes had evidence of submacular exudative detachment or autofluorescence changes to suggest antecedent acute or chronic central serous chorioretinopathy. No eyes had drusen or degenerative changes to suggest age-related macular degeneration or other degenerative diseases. In one patient, the fellow unaffected eye demonstrated retinal pigment epithelium abnormalities, best seen with fundus autofluorescence, overlying focal dilated choroidal vessels seen with enhanced depth imaging optical coherence tomography and associated choroidal hyperpermeability seen with indocyanine green angiography, consistent with the diagnosis of pachychoroid pigment epitheliopathy. All three eyes showed the appearance of polypoidal structures within the neovascular tissue.

CONCLUSION: Pachychoroid neovasculopathy falls within a spectrum of diseases associated with choroidal thickening that includes pachychoroid pigment epitheliopathy, central serous chorioretinopathy, and polypoidal choroidal vasculopathy and should be considered as a possible diagnosis in eyes with features of Type 1 neovascularization and choroidal thickening in the absence of characteristic age-related macular degeneration or degenerative changes. Pachychoroid neovasculopathy may occur as a focal abnormality within the macula, even in myopic eyes with normal subfoveal choroidal thickness. Pachychoroid neovasculopathy can ultimately progress to the development of polypoidal choroidal vasculopathy.

PMID: 25158945 [PubMed - as supplied by publisher]

Healthc Inform Res. 2014 Jul;20(3):191-8. doi: 10.4258/hir.2014.20.3.191. Epub 2014 Jul 31.

New parametric imaging method with fluorescein angiograms for detecting areas of capillary nonperfusion.

Kim YJ, Jeong CB, Hwang JM, Yang HK, Lee SH, Kim KG.

OBJECTIVES: Fluorescein angiography (FAG) is currently the most useful diagnostic modality for examining retinal circulation, and it is frequently used for the evaluation of patients with diabetic retinopathy, occlusive diseases, such as retinal venous and arterial occlusions, and wet macular degeneration. This paper presents a method for objectively evaluating retinal circulation by quantifying circulation-related parameters.

METHODS: This method allows the semiautomatic preprocessing and registering of FAG images. The arterial input function is estimated from the registered set of FAG images using gamma-variate fitting. Then, the parameters can be computed by deconvolution on the basis of truncated singular value decomposition, and they can finally be presented as parametric color images in a combination of three colors, red, green, and blue.

RESULTS: After the estimation of arterial input function, the parameters of relative blood flow and mean transit time were computed using deconvolution analysis based on truncated singular value decomposition.

CONCLUSIONS: The parametric color image is helpful to interpret the status of retinal blood circulation and provides quantitative data on retina ischemia without interobserver variability. This system easily provides the status of retinal blood circulation both qualitatively and quantitatively. It also helps to standardize FAG interpretation and may contribute to network-based telemedicine systems in the future.

PMID: 25152832 [PubMed] PMCID: PMC4141133

Stem Cell Res Ther. 2014 Apr 22;5(2):56. [Epub ahead of print]

Ocular stem cells: a status update!

Dhamodaran K, Subramani M, Ponnalagu M, Shetty R, Das D.

Abstract: Stem cells are unspecialized cells that have been a major focus of the field of regenerative medicine, opening new frontiers and regarded as the future of medicine. The ophthalmology branch of the medical sciences was the first to directly benefit from stem cells for regenerative treatment. The success stories of regenerative medicine in ophthalmology can be attributed to its accessibility, ease of follow-up and the eye being an immune-privileged organ. Cell-based therapies using stem cells from the ciliary body, iris and sclera are still in animal experimental stages but show potential for replacing degenerated photoreceptors. Limbal, corneal and conjunctival stem cells are still limited for use only for surface reconstruction, although they might have potential beyond this. Iris pigment epithelial, ciliary body epithelial and choroidal epithelial stem cells in laboratory studies have shown some promise for retinal or neural tissue replacement. Trabecular meshwork, orbital and sclera stem cells have properties identical to cells of mesenchymal origin but their potential has yet to be experimentally determined and validated. Retinal and retinal pigment epithelium stem cells remain the most sought out stem cells for curing retinal degenerative disorders, although treatments using them have resulted in variable outcomes. The functional aspects of the therapeutic application of lenticular stem cells are not known and need further attention. Recently, embryonic stem cell-derived retinal pigment epithelium has been used for treating patients with Stargardts disease and age-related macular degeneration. Overall, the different stem cells residing in different components of the eye have shown some success in clinical and animal studies in the field of regenerative medicine.

PMID: 25158127 [PubMed - as supplied by publisher] PMCID: PMC4055087

Regen Med. 2014 Jul;9(4):479-95. doi: 10.2217/rme.14.16.

Deciphering the therapeutic stem cell strategies of large and midsize pharmaceutical firms.

Vertès AA.

Abstract: The slow adoption of cytotherapeutics remains a vexing hurdle given clinical progress achieved to date with a variety of stem cell lineages. Big and midsize pharmaceutical companies as an asset class still delay large-scale investments in this arena until technological and market risks will have been further reduced. Nonetheless, a handful of stem cell strategic alliance and licensing transactions have already been implemented, indicating that progress is actively monitored, although most of these involve midsize firms. The greatest difficulty is, perhaps, that the regenerative medicine industry is currently only approaching the point of inflexion of the technology development S-curve, as many more clinical trials read out. A path to accelerating technology adoption is to focus on innovation outliers among healthcare actors. These can be identified by analyzing systemic factors (e.g., national science policies and industry fragmentation) and intrinsic factors (corporate culture, e.g., nimble decision-making structures; corporate finance, e.g., opportunity costs and ownership structure; and operations, e.g., portfolio management strategies, threats on existing businesses and patent expirations). Another path is to accelerate the full clinical translation and commercialization of an allogeneic cytotherapeutic product in any indication to demonstrate the disease-modifying potential of the new products for treatment and prophylaxis, ideally for a large unmet medical need such as dry age-related macular degeneration, or for an orphan disease such as biologics-refractory acute graft-versus-host disease. In times of decreased industry average research productivities, regenerative medicine products provide important prospects for creating new franchises with a market potential that could very well mirror that achieved with the technology of monoclonal antibodies.

PMID: 25159065 [PubMed - in process]

J Biomater Appl. 2014 Aug 20. pii: 0885328214547751. [Epub ahead of print]

Hybrid vitronectin-mimicking polycaprolactone scaffolds for human retinal progenitor cell differentiation and transplantation.

Lawley E, Baranov P, Young M.

Abstract: Many advances have been made in an attempt to treat retinal degenerative diseases, such as age-related macular degeneration and retinitis pigmentosa. The irreversible loss of photoreceptors is common to both, and currently no restorative clinical treatment exists. It has been shown that retinal progenitor and photoreceptor precursor cell transplantation can rescue the retinal structure and function. Importantly, retinal progenitor cells can be collected from the developing neural retina with further expansion and additional modification in vitro, and the delivery into the degenerative host can be performed as a single-cell suspension injection or as a complex graft transplantation. Previously, we have described several polymer scaffolds for culture and transplantation of retinal progenitor cells of both mouse and human origin. This tissue engineering strategy increases donor cell survival and integration. We have also shown that biodegradable poly(ϵ -caprolactone) induces mature photoreceptor differentiation from human retinal progenitor cells. However, poor adhesive properties limit its use, and therefore it requires additional surface modification. The aim of this work was to study vitronectin-mimicking oligopeptides (Synthemax II-SC) poly(ϵ -caprolactone) films and their effects on human retinal progenitor cell adhesion, proliferation, and differentiation. Here, we show that the incorporation of vitronectin-mimicking oligopeptide into poly(ϵ -caprolactone) leads to dose-dependent increases in cell adhesion; the optimum dose identified as 30 μ g/ml. Inhibition of human retinal progenitor cells proliferation was seen on poly(ϵ -caprolactone) and was maintained with the hybrid scaffold. This has been shown to be beneficial for driving cell differentiation. Additionally, we observed equal expression of Nrl, rhodopsin, recoverin, and rod outer membrane 1 after differentiation on the hybrid scaffold as compared to the standard fibronectin coating of poly(ϵ -caprolactone). After transplantation into rd1 retina degenerative mice, human retinal progenitor cells were able to migrate to the outer nuclear layer and survive for three weeks. We conclude that Synthemax II-SC can be incorporated into poly(ϵ -caprolactone) to create a hybrid chemically defined scaffold for clinical application.

PMID: 25145988 [PubMed - as supplied by publisher]

Pathogenesis

Bull Acad Natl Med. 2013 Mar;197(3):661-74; discussion 674-5.

[Iron and regulatory proteins in the normal and pathological retina].[Article in French]

Jeanny JC, Picard E, Sergeant C, Jonet L, Yefimova M, Courtois Y.

Abstract: Iron is necessary for cell metabolism, but excess iron can be toxic. Iron can generate oxygen free radicals through the Fenton reaction. Iron accumulation has been observed in the retina of patients with age-related macular degeneration (AMD). We have shown its accumulation in photoreceptor segments in two animal models of genetic retinal degeneration (RCS rats and Rd10 mice). In these rodents, hTf, injected intraperitoneally or expressed by genetic modification, delayed photoreceptor degeneration. Our studies highlight the therapeutic potential of Tf in degenerative processes such as retinitis pigmentosa and AMD.

PMID: 25163348 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2014 Aug 26. pii: IOVS-14-15091. doi: 10.1167/iovs.14-15091. [Epub ahead of print]

Deletion of aryl hydrocarbon receptor AHR in mice leads to subretinal accumulation of microglia and RPE atrophy.

Kim SY, Yang HJ, Chang YS, Kim JW, Brooks M, Chew EY, Wong WT, Fariss R, Rachel R, Cogliati T, Qian H, Swaroop A.

PURPOSE: The aryl hydrocarbon receptor (AHR) is a ligand-activated nuclear receptor that regulates cellular response to environmental signals, including UV and blue wavelength light. This study was undertaken to elucidate AHR function in retinal homeostasis.

METHODS: RNA-seq datasets were examined for Ahr expression in the mouse retina and rod photoreceptors. The Ahr^{-/-} mice were evaluated by fundus imaging, optical coherence tomography, histology, immunohistochemistry and electroretinogram (ERG). For light damage experiments, adult mice were exposed to 14,000-15,000 lux of diffuse white light for 2 hr.

RESULTS: In mouse retina, Ahr transcripts were up-regulated during development, with continued increase in aging rod photoreceptors. Fundus examination of 3 month-old Ahr^{-/-} mice revealed subretinal autofluorescent spots, which increased in number with age and following acute light exposure. Ahr^{-/-} retina also showed subretinal microglia accumulation that correlated with autofluorescence changes, RPE abnormalities, and reactivity against immunoglobulin, complement factor H and glial fibrillary acidic protein. Functionally, Ahr^{-/-} mice displayed reduced ERG c-wave amplitudes.

CONCLUSIONS: The Ahr^{-/-} mice exhibited subretinal accumulation of microglia and focal RPE atrophy, phenotypes observed in age-related macular degeneration (AMD). Together with a recently published report on another Ahr^{-/-} mouse model, our study suggests that AHR has a protective role in the retina as an environmental stress sensor. As such, its altered function may contribute to human AMD progression and provide a target for pharmacological intervention.

PMID: 25159211 [PubMed - as supplied by publisher]

Drug Discov Today Ther Strateg. 2013;10(1):e11-e20.

Pharmacological inhibition of lipofuscin accumulation in the retina as a therapeutic strategy for dry AMD treatment.

Petrukhin K.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the western world. There is no FDA-approved treatment for the most prevalent dry (atrophic) form of AMD. Photoreceptor degeneration in dry AMD is triggered by abnormalities in the retinal pigment epithelium (RPE). It has been suggested that excessive accumulation of fluorescent lipofuscin pigment in the RPE represents an important pathogenic factor in etiology and progression of dry AMD. Cytotoxic lipofuscin bisretinoids, such as A2E, are formed in the retina in a non-enzymatic way from visual cycle retinoids. Inhibition of toxic bisretinoid production in the retina seems to be a sound treatment strategy for dry AMD. In this review we discuss the following classes of pharmacological treatments inhibiting lipofuscin bisretinoid formation in the retina: direct inhibitors of key visual cycle enzymes, RBP4 antagonists, primary amine-containing aldehyde traps, and deuterated analogs of vitamin A.

PMID: 25152755 [PubMed] PMCID: PMC4140438

Exp Eye Res. 2014 Sep;126:68-76. doi: 10.1016/j.exer.2014.05.013.

Approaches for detecting lysosomal alkalization and impaired degradation in fresh and cultured RPE cells: Evidence for a role in retinal degenerations.

Guha S, Coffey EE, Lu W, Lim JC, Beckel JM, Laties AM, Boesze-Battaglia K, Mitchell CH.

Abstract: Lysosomes contribute to a multitude of cellular processes, and the pH of the lysosomal lumen plays a central mechanistic role in many of these functions. In addition to controlling the rate of enzymatic degradation for material delivered through autophagic or phagocytotic pathways, lysosomal pH regulates events such as lysosomal fusion with autophagosomes and the release of lysosomal calcium into the cytoplasm. Disruption of either the steady state lysosomal pH or of the regulated manipulations to lysosomal pH may be pathological. For example, chloroquine elevates the lysosomal pH of retinal pigmented epithelial (RPE) cells and triggers a retinopathy characterized by the accumulation of lipofuscin-like material in both humans and animals. Compensatory responses to restore lysosomal pH are observed; new data illustrate that chronic chloroquine treatment increases mRNA expression of the lysosomal/autophagy master transcription factor TcFEB and of the vesicular proton pump vHATPase in the RPE/choroid of mice. An elevated lysosomal pH with upregulation of TcFEB and vHATPase resembles the pathology in fibroblasts of patients with mutant presenilin 1 (PS1), suggesting a common link between age-related macular degeneration (AMD) and Alzheimer's disease. While the absolute rise in pH is often small in these disorders, elevations of only a few tenths of a pH unit can have a major impact on both lysosomal function and the accumulation of waste over decades. Accurate measurement of lysosomal pH can be complex, and imprecise measurements have clouded the field. Protocols to optimize pH measurement from fresh and cultured cells are discussed, and indirect measurements to confirm changes in lysosomal pH and degradative capacity are addressed. The ability of reacidifying treatments to restore degradative function confirms the central role of lysosomal pH in these disorders and identifies potential approaches to treat diseases of lysosomal accumulation like AMD and Alzheimer's disease. In summary, various approaches to determine lysosomal pH in fresh and cultured cells, as well as the potential to restore pH levels to an optimal range, can help identify and repair pathologies associated with lysosomal defects in RPE cells and perhaps also suggest new approaches to treat lysosomal storage diseases throughout the body.

PMID: 25152362 [PubMed - in process] PMCID: PMC4143779

Cell Mol Life Sci. 2014 Aug 26. [Epub ahead of print]

Emerging roles for nuclear receptors in the pathogenesis of age-related macular degeneration.

Malek G, Lad EM.

Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in the elderly in the Western world. Over the last 30 years, our understanding of the pathogenesis of the disease has grown exponentially thanks to the results of countless epidemiology, genetic, histological, and biochemical studies. This information, in turn, has led to the identification of multiple biologic pathways potentially involved in development and progression of AMD, including but not limited to inflammation, lipid and extracellular matrix dysregulation, and angiogenesis. Nuclear receptors are a superfamily of transcription factors that have been shown to regulate many of the pathogenic pathways linked with AMD and as such they are emerging as promising targets for therapeutic intervention. In this review, we will present the fundamental phenotypic features of AMD and discuss our current understanding of the pathobiological disease mechanisms. We will introduce the nuclear receptor superfamily and discuss the current literature on their effects on AMD-related pathophysiology.

PMID: 25156067 [PubMed - as supplied by publisher]

Epidemiology

J Ophthalmol. 2014;2014:139826. doi: 10.1155/2014/139826. Epub 2014 Jun 17.

The frequency of exfoliation syndrome in the central anatolia region of Turkey.

Kılıç R, Sezer H, Comçalı SÜ, Bayraktar S, Göktolga G, Cakmak Y, Cetin AB, Cumurcu T.

Aim: The aim of this study was to investigate the frequency of exfoliation syndrome in the Central Anatolia region of Turkey and to evaluate its relationship with cardiovascular and ocular diseases.

Methods: Patients over the age of 45 years who presented to the clinic were included in the study. All cases underwent a comprehensive ophthalmology examination. Exfoliation syndrome was diagnosed with the presence of exfoliative material on the lens anterior capsule or iris on slit lamp examination. The patients were divided into two groups as the exfoliation syndrome group and nonexfoliation syndrome group according to the presence of exfoliative material.

Results: Exfoliative material was found in one or both eyes of 212 of the 2103 patients (10.1%) evaluated within the scope of the study. A significant relationship was found between exfoliation syndrome and increasing age and male gender. A significant relationship was found between exfoliation syndrome and glaucoma, cataracts, age-related macular degeneration, and phacodonesis. While no relationship was found between exfoliation syndrome and hypertension or diabetes mellitus, a significant relationship was found with coronary artery disease.

Conclusion: The unilateral or bilateral exfoliation syndrome frequency was 10.1% in this hospital-based study. A statistically significant relationship was found between exfoliation syndrome and advancing age, gender, and coronary artery disease.

PMID: 25165574 [PubMed]

Biomark Res. 2014 Aug 18;2:15. doi: 10.1186/2050-7771-2-15. eCollection 2014.

Vascular endothelial growth factor genetic polymorphisms and susceptibility to age-related macular degeneration in Tunisian population.

Habibi I, Sfar I, Chebil A, Kort F, Bouraoui R, Jendoubi-Ayed S, Makhoul M, Abdallah TB, El Matri L, Gorgi Y.

PURPOSE: Three VEGF SNPs (-2578) C/A, (+405) G/C and (+936) C/T were investigated in Tunisian exudative AMD patients in order to determine their association with the disease susceptibility and their influence to intravitreal bevacizumab therapy response.

METHODS: 145 AMD patients and 207 age-matched controls were included. 68 patients were treated with intravitreal bevacizumab. SNPs genotyping were performed using direct sequencing. The serum VEGF was assayed by ELISA (R&D).

RESULTS: The (+405) CC and (+936) TT genotypes were higher in AMD patients than in controls ($p = 5 \times 10^{-6}$) and $p = 0.021$, respectively). The mean plasma levels of VEGF were statistically higher in AMD patients (84.22 pg/ml) than in controls (15 pg/ml). Three months after bevacizumab treatment, 52 patients (85.6%) were classified as good responders (GR) and 16 (14.4%) as poor responders (PR). The mean plasmatic-VEGF levels in GR patients was higher (86.61 ± 80.30 pg/ml) than in PR patients (47.12 ± 45.74 pg/ml) ($p = 0.086$). The patients with genotype homozygous TT (+936) would be PR compared to those carrying CT and CC genotypes. Whereas, those with AA (-2578) genotype would be GR compared with others genotypes ($p = 0.014$; $p = 0.042$ respectively).

CONCLUSIONS: Our results show that VEGF genetic variants may contribute to the susceptibility to

neovascular AMD in Tunisian patients.

PMID: 25165559 [PubMed]

Genetics

Invest Ophthalmol Vis Sci. 2014 Aug 21. pii: IOVS-14-15142. doi: 10.1167/iovs.14-15142. [Epub ahead of print]

Direct-to-Consumer Personal Genome Testing for Age-related Macular Degeneration.

Buitendijk GH, Amin N, Hofman A, van Duijn CM, Vingerling JR, Klaver CC.

Purpose: Genetic testing may be the next step in clinical medicine for a more personalized approach in determining risk of disease. Direct-to-consumer (DTC) personal genome tests may fulfill this role. We explored the practicability and predictive value of DTC-tests from four companies (23andMe, deCODEme, Easy DNA, Genetic testing laboratories) for age-related macular degeneration (AMD)

Methods: Body specimens of three individuals were collected and sent to four companies for DNA genotyping and disease risk estimation. In addition, DNA was also genotyped using Illumina HumanOmniExpress 12v1 array in the Rotterdam Study laboratory, and risk estimates of AMD were calculated using the validated prediction model from the population-based Three Continent AMD Consortium.

Results: Genotyped results of the four DTC-tests matched genotyping performed by the Rotterdam Study laboratory. The estimated risks provided by the companies varied considerably in the tested individuals, from a 1.6-fold difference for overall relative risk to an up to 12-fold difference for lifetime risk. The lifetime risks for the individuals ranged from 1.4-16.1% in the DTC-tests, while they varied from 0.5-4.2% in the validated prediction model. Most important reasons for the differences in risks were the testing of only a limited set of genetic markers, the choice of the reference population, and the methodology applied for risk calculation.

Conclusions: Direct-to-consumer personal genome tests are not suitable for clinical application as yet. More comprehensive genetic testing and inclusion of environmental risk factors may improve risk prediction of AMD.

PMID: 25146986 [PubMed - as supplied by publisher]

Cold Spring Harb Perspect Med. 2014 Aug 28. [Epub ahead of print]

Gene Therapy for PRPH2-Associated Ocular Disease: Challenges and Prospects.

Conley SM, Naash MI.

Abstract: The peripherin-2 (PRPH2) gene encodes a photoreceptor-specific tetraspanin protein called peripherin-2/retinal degeneration slow (RDS), which is critical for the formation and maintenance of rod and cone outer segments. Over 90 different disease-causing mutations in PRPH2 have been identified, which cause a variety of forms of retinitis pigmentosa and macular degeneration. Given the disease burden associated with PRPH2 mutations, the gene has long been a focus for preclinical gene therapy studies. Adeno-associated viruses and compacted DNA nanoparticles carrying PRPH2 have been successfully used to mediate improvement in the rds^{-/-} and rds^{+/-} mouse models. However, complexities in the pathogenic mechanism for PRPH2-associated macular disease coupled with the need for a precise dose of peripherin-2 to combat a severe haploinsufficiency phenotype have delayed the development of clinically viable genetic treatments. Here we discuss the progress and prospects for PRPH2-associated gene

therapy.

PMID: 25167981 [PubMed - as supplied by publisher]

Biomed Res Int. 2014;2014:450386. doi: 10.1155/2014/450386. Epub 2014 Aug 6.

Gene Ontology and KEGG Enrichment Analyses of Genes Related to Age-Related Macular Degeneration.

Zhang J, Xing Z, Ma M, Wang N, Cai YD, Chen L, Xu X.

Abstract: Identifying disease genes is one of the most important topics in biomedicine and may facilitate studies on the mechanisms underlying disease. Age-related macular degeneration (AMD) is a serious eye disease; it typically affects older adults and results in a loss of vision due to retina damage. In this study, we attempt to develop an effective method for distinguishing AMD-related genes. Gene ontology and KEGG enrichment analyses of known AMD-related genes were performed, and a classification system was established. In detail, each gene was encoded into a vector by extracting enrichment scores of the gene set, including it and its direct neighbors in STRING, and gene ontology terms or KEGG pathways. Then certain feature-selection methods, including minimum redundancy maximum relevance and incremental feature selection, were adopted to extract key features for the classification system. As a result, 720 GO terms and 11 KEGG pathways were deemed the most important factors for predicting AMD-related genes.

PMID: 25165703 [PubMed - in process]

Eye (Lond). 2014 Aug 29. doi: 10.1038/eye.2014.196. [Epub ahead of print]

A novel deletion mutation in RS1 gene caused X-linked juvenile retinoschisis in a Chinese family.

Huang Y, Mei L, Gui B, Su W, Liang D, Wu L, Pan Q.

Purpose: X-linked juvenile retinoschisis (XLRS), a leading cause of juvenile macular degeneration, is characterized by a spoke-wheel pattern in the macular region of the retina and splitting of the neurosensory retina. This study aimed to identify the underlying genetic defect in a Chinese family with XLRS.

Methods: The proband underwent complete ophthalmic examinations, including fundus examination, fundus autofluorescence, and optical coherence tomography. DNA extracted from proband and his younger brother was screened for mutations in RS1 gene. The detected RS1 mutation was tested in all available family members and 200 healthy controls.

Results: Reduced visual acuity, spoke-wheel pattern at the fovea, and split retina were observed in the proband. A novel frameshift mutation c.206-207delTG in the RS1 gene, leading to a truncated protein (p.L69fs16X), was identified in the proband and his younger brother. This mutation was not found in any unaffected member or in the healthy controls. The mother of the proband was hemizygous for this mutant allele.

Conclusions: We identified a novel causative mutation of RS1 in a Chinese family with XLRS. This finding expands the mutation spectrum of RS1 and provides evidence for a phenotype-genotype study in XLRS.

PMID: 25168411 [PubMed - as supplied by publisher]

Ophthalmic Genet. 2014 Aug 27:1-6. [Epub ahead of print]

MMP9 Gene Polymorphism is not Associated with Polypoidal Choroidal Vasculopathy and Neovascular Age-related Macular Degeneration in a Chinese Han Population.

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Zeng R, Zhang X, Wu K, Su Y, Wen F.

Background: Recently, one of our studies has revealed that the serum matrix metalloproteinase 9 (MMP9) level is elevated in polypoidal choroidal vasculopathy (PCV) but not in age-related macular degeneration (AMD). Previous studies have demonstrated that abnormal extracellular matrix (ECM) metabolism plays an important role in the pathogenesis of AMD and PCV. MMP9 is an important regulating enzyme in ECM metabolism, and the MMP9 gene may be a candidate gene for the susceptibility of PCV and AMD. In this study, we aimed to investigate whether the MMP9 gene polymorphism is associated with PCV and neovascular AMD (nAMD) in a Chinese Han population.

Methods: We performed a case-control study in a Chinese Han population. Three tag single nucleotide polymorphisms (SNPs) (rs17576, rs3787268 and rs2274755) of the MMP9 gene were genotyped in 251 patients with PCV, 157 patients with nAMD, and 204 control individuals using the Multiplex SNaPshot system and the direct DNA sequencing technique. The three SNPs genotypes and allele frequencies in the PCV, nAMD and control groups were evaluated using PLINK software and binary logistic regression analysis.

Results: In the PCV, nAMD, and control groups, the minor allele frequencies were 0.2099, 0.2070 and 0.2108 for the rs17576 variant; 0.4442, 0.4522 and 0.4461 for the rs3787268 variant; and 0.1036, 0.1338 and 0.1225 for the rs2274755 variant, respectively. The three tag SNPs were not significantly associated with susceptibility to PCV ($p = 0.9524$, 0.9553 , and 0.3672 , respectively) or nAMD ($p = 0.9015$, 0.8692 , and 0.6543 , respectively). None of the p values for the additive, dominant, or recessive models were statistically significant in the PCV or nAMD group.

Conclusions: No evidence was found to support an association between the MMP9 gene variants and susceptibility to either nAMD or PCV in a Chinese Han population.

PMID: 25162123 [PubMed - as supplied by publisher]

Diet & lifestyle

Acta Ophthalmol. 2014 Aug 27. doi: 10.1111/aos.12535. [Epub ahead of print]

Lutein supplementation leads to decreased soluble complement membrane attack complex sC5b-9 plasma levels.

Tian Y, Kijlstra A, van der Veen RL, Makridaki M, Murray IJ, Berendschot TT.

PURPOSE: The purpose of this study was to investigate the effect of lutein on systemic complement activation in elderly individuals.

METHODS: Seventy patients with signs of early age-related macular degeneration (AMD) were included in this study. All subjects were randomly assigned to receive a 10 mg daily dose of lutein or a placebo for a time period of 1 year. EDTA blood was collected before and at various time-points during the study (0, 4, 8 and 12 months). The plasma level of the soluble complement membrane attack complex sC5b-9 was measured by ELISA.

RESULTS: We found a significant 1.1 ng/ml monthly decrease in the plasma sC5b-9 concentration in the lutein group ($p < 0.001$), resulting in a decrease from 60.3 ng/ml at baseline to 46.3 ng/ml at 12 months. For the placebo group, we found a significant 0.6 ng/ml monthly increase in plasma sC5b-9 concentration ($p = 0.001$), resulting in an increase from 51.6 ng/ml at baseline to 58.4 ng/ml at 12 months.

CONCLUSIONS: Lutein supplementation inhibits the systemic activation of the complement system, which provides further functional evidence for the reported beneficial effects of this carotenoid in the management of AMD.

PMID: 25160533 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Aug 21. pii: IOVS-14-15025. doi: 10.1167/iov.14-15025. [Epub ahead of print]

Systemic administration of the antioxidant/iron chelator alpha lipoic acid protects against light-induced photoreceptor degeneration in the mouse retina.

Zhao L, Wang C, Song D, Li Y, Song Y, Su GF, Dunaief JL.

Purpose: Oxidative stress and inflammation play key roles in the light damage (LD) model of retinal degeneration as well as in age-related macular degeneration (AMD). We sought to determine if lipoic acid (LA), an antioxidant and iron chelator, protects the retina against LD.

Methods: Balb/c mice were treated with LA or control saline via intraperitoneal injection, and then were placed in constant cool white LED light (10,000 lux) for 4 hours. Retinas were evaluated at several time points after LD. Photoreceptor apoptosis was assessed using the TUNEL assay. Retinal function was analyzed via electroretinography (ERG). Retinal degeneration was assessed after LD by optical coherence tomography (OCT), TUNEL analysis and histology. The mRNAs of several oxidative stress, inflammation and iron related genes were quantified by qPCR.

Results: LD resulted in substantial photoreceptor-specific cell death. Dosing with LA protected photoreceptors, decreasing the numbers of TUNEL-positive photoreceptors and increasing the number of surviving photoreceptors. The retinal mRNA levels of genes indicating oxidative stress, inflammation and iron accumulation were lower following LD in mice treated with LA than in control mice. ERG analysis demonstrated functional protection by LA.

Conclusions: Systemic LA is protective against light-induced retinal degeneration. Since this agent has already proven protective in other retinal degeneration models and is safe and protective against diabetic neuropathy in patients, it is worthy of consideration for a human clinical trial against retinal degeneration or age-related macular degeneration.

PMID: 25146987 [PubMed - as supplied by publisher]

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