

Issue 261

Tuesday 12 January, 2016

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Retina. 2016 Jan 5. [Epub ahead of print]

RETINAL LAYER RESPONSE TO RANIBIZUMAB DURING TREATMENT OF DIABETIC MACULAR EDEMA: Thinner is Not Always Better.

Ebneter A, Wolf S, Abhishek J, Zinkernagel MS.

PURPOSE: To identify individual retinal layer thickness changes associated with visual acuity gain in diabetic macular edema treated with ranibizumab using layer segmentation on high-resolution optical coherence tomography scans.

METHODS: Retrospective observational case series. Thirty-three treatment-naïve eyes with diabetic macular edema were imaged by spectral domain optical coherence tomography at monthly visits while receiving intravitreal ranibizumab treatment as needed, guided by visual acuity. Thickness changes of individual layers after 1 year were quantitatively analyzed and correlated with visual acuity gain.

RESULTS: The mean best-corrected visual acuity improvement at 1 year was 6.2 (SEM $\pm$ 1.5) Early Treatment Diabetic Retinopathy Study letters, and central retinal thickness decreased by 66 ± 18 μ m. In the central subfield, there was a significant decrease of thickness for all layers ($P < 0.05$) except the outer nuclear layer. Multiple linear regression analysis revealed that thickness decrease of the inner retina was associated with better visual acuity, whereas for the outer retina the opposite was true. The best estimate of final visual acuity ($R = 0.817$, $P < 0.001$) was obtained, by including baseline visual acuity and thickness change of the inner and outer plexiform layers in the model.

CONCLUSION: Whereas thickness decrease of the inner retina was positively associated with visual acuity gain, the opposite was found for the outer retina. This might be indirect evidence for recovery of the outer retina during ranibizumab treatment.

PMID: 26735563 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Dec 14. [Epub ahead of print]

Risk of Myocardial Infarction and Stroke with Single or Repeated Doses of Intravitreal Bevacizumab in Age-Related Macular Degeneration.

Etminan M, Maberley DA, Babiuk DW, Carleton BC.

PURPOSE: To examine the risk of myocardial infarction and stroke with single and repeated doses of intravitreal bevacizumab in wet age related macular degeneration (AMD).

DESIGN: Nested case-control study and retrospective cohort study **METHODS:** Setting: Two patient cohorts from British Columbia, Canada.

STUDY POPULATION: Patients with wet AMD.

INTERVENTION: for the cohort study, patients who received the first intravitreal bevacizumab; for the nested case-control study, repeated injections of intravitreal bevacizumab.

MAIN OUTCOME MEASURES: myocardial infarction for the retrospective cohort study; myocardial infarction and stroke for the nested case-control study.

RESULTS: In the cohort analysis, there were 2,564 AMD subjects not on a vascular endothelial growth factor (VEGF) inhibitor and 5,644 subjects receiving intravitreal bevacizumab. The rate of myocardial infarction (MI) among bevacizumab users was 11/1000 person-years compared to 14.9/1000 person-years in non-users. The adjusted rate ratio (RR) for MI was 0.70 (95% CI: 0.50-1.00) and 0.74 (0.46-1.20) for the propensity score-adjusted analysis. In the nested case-control analysis there were 7,452 new users of VEGF inhibitors within which there were 313 cases of MI with 3,130 matched controls. The adjusted RR for MI among those receiving three or more injections compared to those receiving less than three was 0.71 (95% CI: 0.41-1.22). Also in nested the case-control analysis, the adjusted RR for stroke was 0.81 (95% CI: 0.39-1.65) for those receiving ≥ 4 injections vs. those receiving less than 4 injections.

CONCLUSION: Single or repeated doses of intravitreal bevacizumab were not shown to increase the risk of myocardial infarction or stroke in patients with wet AMD.

PMID: 26701272 [PubMed - as supplied by publisher]

Asia Pac J Ophthalmol (Phila). 2015 Dec 18. [Epub ahead of print]

A Review of Randomized Trials of Approved Pharmaceutical Agents for Macular Edema Secondary to Retinal Vein Occlusion.

Wang JK.

Abstract: There are 3 approved pharmaceutical agents for treating macular edema secondary to retinal vein occlusion (RVO): dexamethasone (a corticosteroid) implant and ranibizumab and aflibercept (both antivascular endothelial growth factor agents). All show a superior ability to improve vision and reduce macular thickness in comparison with sham injections or macular grid laser treatment. Prompt treatment with these agents may lead to a better outcome. A review of randomized trials of injected aflibercept or ranibizumab reveals protocol variations. They include "as needed" injections until functional and anatomical changes are achieved, preceded by either 1 injection or 3 to 6 monthly injections as loading doses. Ocular and systemic adverse effects of vascular endothelial growth factor antagonists for macular edema secondary to RVO are rarely severe. The antiedematous response to a single intravitreal dexamethasone implant is maximal 1 to 3 months after the injection. Intraocular pressure elevation and cataract aggravation should be monitored after the use of intravitreal dexamethasone implants. Intravitreal dexamethasone implants and ranibizumab injections reduce not only macular edema, but also the risk of retinal ischemia and neovascularization in patients with RVO.

PMID: 26692257 [PubMed - as supplied by publisher]

Asia Pac J Ophthalmol (Phila). 2015 Dec 21. [Epub ahead of print]

Ranibizumab Versus Bevacizumab for Neovascular Age-Related Macular Degeneration With an Incomplete Posterior Vitreous Detachment.

Rush RB, Rush SW.

PURPOSE: The aim of this study was to compare the effects of ranibizumab to those of bevacizumab during the treatment of neovascular age-related macular degeneration (AMD) with an incomplete posterior vitreous detachment.

METHODS: A retrospective chart review was performed on treatment-naïve neovascular AMD subjects with an incomplete posterior vitreous detachment treated with either ranibizumab or bevacizumab over a 12-month period.

RESULTS: One hundred thirty subjects were analyzed. There were 49 subjects determined to have vitreous attachment to the fovea. Subjects with vitreous attachment to the fovea required a significantly greater number of injections during the study interval compared with those without (10.2 ± 0.75 vs 7.8 ± 0.62) ($P < 0.0001$). In subjects with vitreous attachment to the fovea, the ranibizumab cohort had a greater improvement in visual acuity (0.18 ± 0.1 vs 0.04 ± 0.11 logMAR) ($P = 0.0176$) and a greater reduction in macular thickness (93.4 ± 32.2 μ m vs 30.3 ± 28.3 μ m) ($P = 0.0064$) compared with the bevacizumab cohort.

CONCLUSIONS: Neovascular AMD patients with vitreous attachment to the fovea may have better visual and anatomic outcomes when treated with ranibizumab compared with bevacizumab.

PMID: 26692256 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Dec 21;15(1):182.

One year results of intravitreal ranibizumab monotherapy for retinal angiomatous proliferation: a comparative analysis based on disease stages.

Park YG, Roh YJ.

BACKGROUND: Retinal angiomatous proliferation (RAP) has been known as a variant of exudative age-related macular degeneration (AMD) with a unfavorable prognosis. To evaluate the effect of ranibizumab administered initially as three loading doses for patients with various stages of RAP.

METHODS: A retrospective chart review of 40 patients (41 eyes) with RAP was conducted. The study divided patients into three groups of Group I (8 eyes in stage I), Group II (17eyes in stage II), and Group III (16 eyes in stage III). All patients received three initial monthly intravitreal injections (0.5 mg) of ranibizumab and were monitored monthly for 12 months. Reinjection of ranibizumab after three initial monthly doses was administered on as-needed basis. The main outcome measures were the change in the mean of best-corrected Snellen visual acuity (BCVA) and central macular thickness (CMT), and the total number of injections received during the 12 months.

RESULTS: The mean change in BCVA at 12 months was -0.286, -0.165, and -0.151 (logMAR) in Group I, II, and III, respectively. CMT was also reduced by a mean of 32.72 ± 56.75 , 57.45 ± 56.48 and 148.37 ± 98.59 μ m. The mean number of injections in Group I was significant lower than those in Group II and III ($P < 0.001$, $P < 0.001$, and $P = 0.15$ for Group I versus Group II, Group I versus Group III, and Group II versus Group III, respectively).

CONCLUSIONS: The 12-month follow-up outcomes suggest that three consecutive loading doses of intravitreal ranibizumab is an effective treatment on early stage (stage I) of RAP. Patients in stage I showed a significantly lower recurrence rate than patients in later stages.

PMID: 26691185 [PubMed - in process] PMCID: PMC4685625 Free PMC Article

Ophthalmology. 2015 Dec 11. [Epub ahead of print]

Subfoveal Choroidal Thickness during Aflibercept Therapy for Neovascular Age-Related Macular Degeneration: Twelve-Month Results.

Koizumi H, Kano M, Yamamoto A, Saito M, Maruko I, Sekiryu T, Okada AA, Iida T.

PURPOSE: To investigate changes in subfoveal choroidal thickness after intravitreal aflibercept injections

(IAIs) for neovascular age-related macular degeneration (AMD) at 12 months.

DESIGN: Retrospective, consecutive, interventional case series.

PARTICIPANTS: One hundred forty-four patients with treatment-naïve neovascular AMD examined at 3 university hospitals.

METHODS: After a loading phase of 3 monthly 2.0-mg IAIs, the patients were injected bimonthly with additional rescue injections performed for worsening. Subfoveal choroidal thickness in IAI-treated eyes was evaluated using enhanced depth imaging optical coherence tomography (OCT) or swept-source OCT.

MAIN OUTCOME MEASURES: Changes in subfoveal choroidal thickness over a 12-month period.

RESULTS: Of the 144 treated eyes, 58 (40.3%) had typical neovascular AMD and 86 (59.7%) had polypoidal choroidal vasculopathy (PCV). The mean subfoveal choroidal thickness of treated eyes decreased from $268.1 \pm 101.3 \mu\text{m}$ at baseline to $233.0 \pm 99.7 \mu\text{m}$ at 3 months and remained unchanged at $232.4 \pm 99.6 \mu\text{m}$ at 12 months (percentage decrease, 13.3% at 12 months compared with baseline; $P < 0.0001$), although there was some fluctuation in between treatments. This decrease in subfoveal choroidal thickness was associated significantly with gain in visual acuity for PCV eyes ($P = 0.0087$; $R = 0.28$), but not for eyes with typical neovascular AMD ($P = 0.17$; $R = 0.18$). Eyes without persistent or recurrent retinal fluid after the loading phase showed greater decrease in subfoveal choroidal thickness compared with those with persistent or recurrent retinal fluid, in both typical neovascular AMD ($P = 0.042$) and PCV ($P = 0.038$) eyes.

CONCLUSIONS:

Subfoveal choroidal thickness decreased over 12 months with IAI therapy in eyes with neovascular AMD. Changes in subfoveal choroidal thickness after IAIs seem to be related to visual and anatomic outcomes.

PMID: 26686967 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Dec 31. [Epub ahead of print]

Conversion to aflibercept after prior anti-VEGF therapy for persistent diabetic macular edema.

Rahimy E, Shahlaee A, Khan MA, Ying GS, Maguire JI, Ho AC, Regillo CD, Hsu J.

PURPOSE: To evaluate the short-term functional and anatomic outcomes of patients with persistent diabetic macular edema (DME) who were converted from bevacizumab and/or ranibizumab to aflibercept.

DESIGN: Retrospective, interventional, non-comparative, consecutive case series.

METHODS: Only eyes treated with at least 4 consecutive injections of ranibizumab/bevacizumab spaced 4-6 weeks apart prior to conversion and with at least 2 aflibercept injections afterwards were considered for inclusion. Pertinent patient demographic, examination, and treatment data were extracted from clinical charts and tabulated for analysis.

RESULTS: Fifty eyes of 37 patients were included. Eyes received a mean of 13.7 bevacizumab/ranibizumab injections prior to conversion, followed by 4.1 aflibercept injections over 4.6 months of subsequent follow-up. The mean logMAR visual acuity at the pre-switch visit was 0.60 ± 0.43 (Snellen equivalent, 20/80). This improved to 0.55 ± 0.48 (Snellen equivalent, 20/70) by the second visit after conversion, corresponding to a mean logMAR change of -0.05 ± 0.22 ($P=0.12$). The average central macular thickness from the pre-switch spectral-domain optical coherence tomography scan was $459.2 \pm 139.2 \mu\text{m}$. This significantly improved to $348.7 \pm 107.8 \mu\text{m}$ by the second visit following conversion, reflecting a mean decrease of $112 \pm 141 \mu\text{m}$ ($P<0.0001$). The mean intraocular pressure (IOP) recorded at the pre-switch visit was $15.1 \pm 3.3 \text{ mmHg}$. At the second follow-up after converting to aflibercept, the IOP averaged $14.9 \pm 3.2 \text{ mmHg}$, with a mean decrease of $0.2 \pm 3.0 \text{ mmHg}$ ($P=0.63$).

CONCLUSIONS: Conversion to aflibercept for persistent DME resulted in significant anatomical improvements. While trends towards improved visual acuity and reduction in IOP were observed, these were not statistically significant.

PMID: 26748058 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Dec 17;9:2355-71. eCollection 2015.

Aflibercept: a review of its use in the treatment of choroidal neovascularization due to age-related macular degeneration.

Balaratnasingam C, Dhrami-Gavazi E, McCann JT, Ghadiali Q, Freund KB.

Abstract: Choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) is an important cause of visual morbidity globally. Modern treatment strategies for neovascular AMD achieve regression of CNV by suppressing the activity of key growth factors that mediate angiogenesis. Vascular endothelial growth factor (VEGF) has been the major target of neovascular AMD therapy for almost two decades, and there have been several intravitreally-administered agents that have enabled anatomical restitution and improvement in visual function with continual dosing. Aflibercept (EYLEA®), initially named VEGF Trap-eye, is the most recent anti-VEGF agent to be granted US Food and Drug Administration approval for the treatment of neovascular AMD. Biologic advantages of aflibercept include its greater binding affinity for VEGF, a longer intravitreal half-life relative to other anti-VEGF agents, and the capacity to antagonize growth factors other than VEGF. This paper provides an up-to-date summary of the molecular mechanisms mediating CNV. The structural, pharmacodynamic, and pharmacokinetic advantages of aflibercept are also reviewed to rationalize the utility of this agent for treating CNV. Results of landmark clinical investigations, including VIEW 1 and 2 trials, and other important studies are then summarized and used to illustrate the efficacy of aflibercept for managing treatment-naïve CNV, recalcitrant CNV, and CNV due to polypoidal choroidal vasculopathy. Safety profile, patient tolerability, and quality of life measures related to aflibercept are also provided. The evidence provided in this paper suggests aflibercept to be a promising agent that can be used to reduce the treatment burden of neovascular AMD.

PMID: 26719668 [PubMed] PMCID: PMC4689264

Br J Ophthalmol. 2015 Dec 30. [Epub ahead of print]

Retina specialists treating cystoid macular oedema secondary to retinal vein occlusion recommend different treatments for patients than they would choose for themselves.

Wang MD, Jeng-Miller KW, Feng HL, Prenner JL, Fine HF, Shah SP.

AIMS: To evaluate the presence of cognitive bias among retinal specialists when recommending treatment options for cystoid macular oedema (CMO) secondary to retinal vein occlusion (RVO).

METHODS: Two randomly chosen samples of retina specialists were surveyed regarding their treatment and dosing regimen choices among three anti-vascular endothelial growth factor (anti-VEGF) biologics (aflibercept, bevacizumab and ranibizumab), intravitreal steroid, focal laser and observation for the treatment of CMO secondary to RVO. The first group was asked to make recommendations for two hypothetical patients: one with CMO secondary to branch RVO (BRVO) and the second with CMO secondary to central RVO (CRVO). The second group was asked to make recommendations as if they themselves were the hypothetical patient with the same disease processes.

RESULTS: The survey was completed by 492 respondents (20.1%). When comparing anti-VEGF agents for patients with BRVO, a majority of physicians recommended bevacizumab (60.5%) over ranibizumab (37.8%) and aflibercept (1.7%; $p < 0.0001$). For themselves, physicians were more likely to recommend ranibizumab (44.9%) over bevacizumab (39.2%) and aflibercept (15.9%; $p < 0.0001$). When comparing among the anti-VEGF agents chosen for patients with CRVO, a majority of physicians recommended

bevacizumab (56.7%) over ranibizumab (28.2%) and aflibercept (15.1%; $p < 0.0001$), but when choosing for themselves, retina specialists were equally divided among the three biologics (aflibercept 30.6%, bevacizumab 36.5% and ranibizumab 32.9%; $p = 0.559$). The results were influenced by geographical location but not by the gender, the length of practice or the type of practice.

CONCLUSIONS: Physicians should be aware that cognitive biases exist and take this into consideration when making treatment recommendations for their patients.

PMID: 26719492 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2016 Jan 5;16(1):3.

Use of flucinolone acetonide for patients with diabetic macular oedema: patient selection criteria and early outcomes in real world setting.

Elaraoud I, Andreatta W, Kidess A, Bhatnagar A, Tsaloumas M, Quhill F, Yang Y.

INTRODUCTION: Fluocinolone acetonide slow release implant (Iluvien®) was approved in December 2013 in UK for treatment of eyes which are pseudophakic with DMO that is unresponsive to other available therapies. This approval was based on evidence from FAME trials which were conducted at a time when ranibizumab was not available. There is a paucity of data on implementation of guidance on selecting patients for this treatment modality and also on the real world outcome of fluocinolone therapy especially in those patients that have been unresponsive to ranibizumab therapy.

METHOD: Retrospective study of consecutive patients treated with fluocinolone between January and August 2014 at three sites were included to evaluate selection criteria used, baseline characteristics and clinical outcomes at 3-month time point.

RESULTS: Twenty two pseudophakic eyes of 22 consecutive patients were included. Majority of patients had prior therapy with multiple intravitreal anti-VEGF injections. Four eyes had controlled glaucoma. At baseline mean VA and CRT were 50.7 letters and 631 μm respectively. After 3 months, 18 patients had improved CRT of which 15 of them also had improved VA. No adverse effects were noted. One additional patient required IOP lowering medication. Despite being unresponsive to multiple prior therapies including laser and anti-VEGF injections, switching to fluocinolone achieved treatment benefit.

CONCLUSION: The patient level selection criteria proposed by NICE guidance on fluocinolone appeared to be implemented. This data from this study provides new evidence on early outcomes following fluocinolone therapy in eyes with DMO which had not responded to laser and other intravitreal agents.

PMID: 26728265 [PubMed - in process] PMCID: PMC4700741

Adv Ther. 2016 Jan 8. [Epub ahead of print]

Cost-Effectiveness of Ranibizumab Versus Aflibercept for Macular Edema Secondary to Branch Retinal Vein Occlusion: A UK Healthcare Perspective.

Adedokun L, Burke C.

INTRODUCTION: Ranibizumab and aflibercept are anti-vascular endothelial growth factor agents licensed for the treatment of visual impairment due to macular edema secondary to branch retinal vein occlusion (BRVO). The aim of this study was to estimate, from a UK healthcare payer's perspective, the cost-effectiveness of ranibizumab versus aflibercept in this indication.

METHODS: A Markov model was used to simulate the outcomes and costs of treating BRVO. Patient baseline characteristics and efficacy data for ranibizumab were obtained from the BRAVO trial. The relative efficacy of aflibercept was derived from a published network meta-analysis. Injection frequencies were

derived from ranibizumab and aflibercept studies included in the network meta-analysis. Health states were defined by increments of 10 letters in best corrected visual acuity (BCVA). Patients could gain or lose a maximum of two health states between cycles. The first cycle was 6 months, followed by monthly cycles. Different utility values were assigned to the better-seeing and worse-seeing eyes based on BCVA. A 2-year treatment time frame and a lifetime time horizon were used. Future costs and health outcomes were discounted at 3.5% per annum. Sensitivity analyses were used to test the robustness of the model.

RESULTS: The lifetime cost per patient treated was £15,273 with ranibizumab and £17,347 with aflibercept. Ranibizumab was dominant over aflibercept, producing incremental health gains of 0.0120 quality-adjusted life-years (QALYs) and cost savings of £2074. Net monetary benefit for ranibizumab at a willingness-to-pay threshold of £20,000/QALY was £2314. Sensitivity analyses showed that the results were robust to variations in model parameters.

CONCLUSIONS: Ranibizumab provides greater health gains at a lower overall cost than aflibercept in the treatment of visual impairment due to macular edema secondary to BRVO. Ranibizumab is therefore cost-effective from a UK healthcare payer's perspective.

PMID: 26747252 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Jan 7:1-8. [Epub ahead of print]

Persistent Macular Thickening After Ranibizumab Treatment for Diabetic Macular Edema With Vision Impairment.

Bressler SB, Ayala AR, Bressler NM, Melia M, Qin H, Ferris FL 3rd, Flaxel CJ, Friedman SM, Glassman AR, Jampol LM, Rauser ME; Diabetic Retinopathy Clinical Research Network.

IMPORTANCE: The prevalence of persistent diabetic macular edema (DME) after months of anti-vascular endothelial growth factor therapy and its effect on visual acuity are unknown.

OBJECTIVE: To assess subsequent outcomes of eyes with DME persisting for 24 weeks after initiating treatment with 0.5 mg of ranibizumab.

DESIGN, SETTING, AND PARTICIPANTS: We performed post hoc, exploratory analyses of a randomized clinical trial from March 20, 2007, through January 29, 2014, from 117 of 296 eyes (39.5%) randomly assigned to receive ranibizumab with persistent DME (central subfield thickness ≥ 250 μ m on time domain optical coherence tomography) through the 24-week visit.

INTERVENTIONS: Four monthly intravitreal injections of ranibizumab and then as needed per protocol.

MAIN OUTCOMES AND MEASURES: Cumulative 3-year probabilities of chronic persistent DME (failure to achieve a central subfield thickness < 250 μ m and at least a 10% reduction from the 24-week visit on at least 2 consecutive study visits) determined by life-table analyses, and at least 10 letter (≥ 2 line) gain or loss of visual acuity among those eyes.

RESULTS: The probability of chronic persistent DME among eyes with persistent DME at the 24-week visit decreased from 100% at the 32-week visit to 81.1% (99% CI, 69.6%-88.6%), 55.8% (99% CI, 42.9%-66.9%), and 40.1% (99% CI, 27.4%-52.4%) at the 1-, 2-, and 3-year visits, respectively. At 3 years, visual acuity improved in eyes with and without chronic persistent DME through the follow-up period, respectively, by a mean of 7 letters and 13 letters from baseline. Among 40 eyes with chronic persistent edema through 3 years, 17 (42.5%) (99% CI, 23.1%-63.7%) gained 10 letters or more from baseline, whereas 5 (12.5%) (99% CI, 2.8%-31.5%) lost 10 letters or more from baseline.

CONCLUSIONS AND RELEVANCE: These data suggest less than half of eyes treated for DME with intravitreal ranibizumab have persistent central-involved DME through 24 weeks after initiating treatment. Among the 40% that then have chronic persistent central-involved DME through 3 years, longer-term visual acuity outcomes appear to be slightly worse than in the 60% in which DME does not persist. Nevertheless, when following the treatment protocol used in this trial among eyes with vision impairment from DME, long-

term improvement in visual acuity from baseline is typical and substantial (≥ 2 -line) loss of visual acuity is likely uncommon through 3 years, even when central-involved DME chronically persists.

PMID: 26746868 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Jan 8. [Epub ahead of print]

Gas-mediated vitreomacular adhesion release with intravitreal ranibizumab injections for exudative age-related macular degeneration.

Kang HM, Lee SJ, Kim CG, Chung EJ, Koh HJ.

PURPOSE: To evaluate the efficiency of gas-assisted vitreomacular adhesion (VMA) release combined with intravitreal ranibizumab injections for exudative age-related macular degeneration (AMD) patients.

MATERIALS AND METHODS: This prospective, interventional case series included a total of 23 eyes of 22 patients. The eyes were treated with intravitreal injection of 0.3 mL of perfluoropropane (C₃F₈) gas and concomitant intravitreal ranibizumab injection to stimulate VMA release. After three initial loading injections, additional intravitreal ranibizumab injections were performed pro re nata. Over a 12-month period, monthly examinations were performed for best-corrected visual acuity (BCVA, logMAR; logarithm of the minimum angle resolution), optical coherence tomography, and dilated fundus examinations.

RESULTS: After gas injection, 22 eyes (95.7 %) showed complete VMA release at 1 week. Complete VMA was achieved in all eyes at 2 months after VMA release, without serious ocular adverse events except one patient who developed a retinal tear. Mean BCVA was 0.61 ± 0.37 logMAR (20/81 Snellen equivalents) at baseline and 0.46 ± 0.30 logMAR (20/57 Snellen equivalents) at 12 months ($P = 0.135$). Mean central macular thickness was 357.9 ± 128.6 μ m at baseline and 245.6 ± 60.0 μ m at 12 months ($P = 0.188$). Mean numbers of intravitreal ranibizumab injections were 4.8 ± 2.4 times during 12 months (4 to 8 injections).

CONCLUSION: Gas-assisted VMA release can be used as an efficient alternative for exudative AMD patients with obvious VMA.

PMID: 26743753 [PubMed - as supplied by publisher]

Mol Pharm. 2016 Jan 4. [Epub ahead of print]

A Mechanistic Model of the Intravitreal Pharmacokinetics of Large Molecules and the Pharmacodynamic Suppression of Ocular VEGF Levels by Ranibizumab in Patients with Neovascular Age-related Macular Degeneration.

Hutton-Smith L, Gaffney E, Byrne H, Maini PK, Schwab D, Mazer N.

Abstract: Intravitreal injection of anti-VEGF antibodies or antibody fragments has been shown to be a highly effective treatment for neovascular age-related macular degeneration (wet AMD). The ocular half-life ($t_{1/2}$) of these large molecules, determined in ocular fluids or derived from serum levels, varies with molecular size and is larger in humans than in pre-clinical animal species. The high affinity binding of VEGF to these molecules lowers the free concentration of VEGF and reduces its occupancy on VEGF receptors in ocular tissues. To understand the biophysical determinants of $t_{1/2}$ for anti-VEGF antibodies and the time-course of VEGF in ocular fluids we developed a mechanistic model of intravitreal pharmacokinetics (IVT PK) for anti-VEGF antibodies and combined it with a mechanistic model of the pharmacodynamics (RVR PD) of VEGF suppression by ranibizumab, an anti-VEGF recombinant, humanized monoclonal antibody fragment (Fab). Our IVT PK model predicts that the ocular $t_{1/2}$ of a large molecule will be approximately 4 times the calculated value of its vitreous diffusion time (T_{diff}), defined as $r_{vit}^2/6D$ where r_{vit} is the radius of the vitreous chamber in that species (modeled as a sphere) and D is the diffusion coefficient of the molecule in physiological saline at 37 °C obtained from the Stokes-Einstein relation. This prediction is verified from a compilation of data and calculations on various large molecules in the human, monkey, rabbit and rat and is

consistent with the reported $t_{1/2}$ values of ranibizumab in humans (mean value 7.9 days) and the calculated T_{diff} of 1.52 days. Our RVR PD model is based on the recent publication of Saunders et al. (Br. J. Ophthalmol. 2015, 1-6. doi:10.1136/bjophthalmol-2015-306771) who reported data on the time-course of VEGF levels in aqueous humor samples obtained from 31 patients receiving ranibizumab treatment for wet AMD and developed a compartmental mathematical model to describe the VEGF suppression profiles. We modified Saunders' model with the known 2:1 stoichiometry of ranibizumab-VEGF binding and included the association and dissociation kinetics of the binding reactions. Using the RVR PD model we re-analyzed Saunders' data to estimate the in vivo dissociation constant (KD) between ranibizumab and VEGF. Our analysis demonstrates the delicate interrelationship between the in vivo KD value and the intravitreal half-life, and yields an in vivo KD estimate that is appreciably larger than the in vitro KD estimates reported in the literature. Potential explanations for the difference between the in vivo and in vitro KD values, which appear to reflect the different methodologies and experimental conditions, are discussed. We conclude that the combined mechanistic model of IVT PK and RVR PD provides a useful framework for simulating the effects of dose, KD and the molecular weight of VEGF-binding molecules on the duration of VEGF suppression.

PMID: 26726925 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Dec 29. [Epub ahead of print]

Choroidal Thickness Changes in Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy: A 12-month Prospective Study.

Ting DS, Ng WY, Ng SR, Tan SP, Yeo IY, Mathur R, Chan CM, Tan AC, Tan GS, Wong TY, Cheung CM.

PURPOSE: To describe 12-month changes in choroidal thickness after anti-vascular endothelial growth factor (anti-VEGF) therapy for typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV) **DESIGN:** Prospective, consecutive, non-interventional, longitudinal case series **METHODS:** This study included patients with typical AMD and PCV who received anti-VEGF therapy over a 12-month period. We utilized spectral domain optical coherence tomography with enhanced depth imaging mode to measure choroidal thickness.

RESULTS: Of the 163 patients, 77 had typical AMD and 86 had PCV. Patients with PCV were younger (67.6 vs 72.5 years, $p < 0.01$) and received fewer anti-VEGF injections (3.9 vs 5.6, $p = 0.02$) than patients with typical AMD. Baseline subfoveal choroidal thickness was not significantly different between PCV and to typical AMD eyes, and was thicker in the study eye compared to fellow eye in the typical AMD group (223.1 vs 208.8 μm , $p < 0.01$). Subfoveal choroidal thickness decreased significantly in both typical AMD (213.7 to 190.3 μm , $p < 0.001$) and PCV (240.8 vs 213.4 μm , $p < 0.01$) eyes, but no significant change was noted in fellow unaffected eyes. Reduction in choroidal thickness was associated with elevated C-reactive protein (odds ratio [OR]: 1.4, $p = 0.04$) and smoking (OR: 7.6, $p = 0.03$) at baseline, but not with age, refractive error, diagnosis of typical AMD or PCV, number or type of anti-VEGF injections, PDT therapy or baseline choroidal thickness.

CONCLUSIONS: A significant reduction in subfoveal choroidal thickness was noted after anti-VEGF therapy in typical AMD and PCV. Choroidal thickness changes were similar despite differences in number of anti-VEGF treatment.

PMID: 26743619 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Dec 15. [Epub ahead of print]

Predictors of Response to Intravitreal Anti-Vascular Endothelial Growth Factor Treatment of Age-Related Macular Degeneration.

Shah AR, Williams S, Bauman CR, Rosner B, Duker JS, Seddon JM.

PURPOSE: To identify factors that influence visual and anatomic response to treatment with intravitreal anti-vascular endothelial growth factor (VEGF) for neovascular age-related macular degeneration (AMD).

DESIGN: Observational cohort study.

METHODS: Seventy-two patients were included in this study. Best corrected Snellen visual acuity (VA) and central foveal thickness measured on optical coherence tomography (OCT) at time of treatment and post-treatment follow-up visits were recorded. Associations between demographic, behavioral, and genetic risk factors and the two outcomes were analyzed using mixed effects linear regression models. Two loci in complement factor H (CFH) were included in a risk score to determine the association between CFH risk and improvement in VA and central foveal thickness.

RESULTS: There was a minimal but not statistically significant improvement in VA in the overall study population following anti-VEGF treatment (mean: 3.7 ± 3.0 letters). Significant improvement in VA was observed for the non-risk CFH Y402H genotype ($P < 0.001$) and for a low CFH risk score ($P = 0.019$). Regarding the outcome of change in central foveal thickness, improvement was noted in all genotype groups, but reduction after treatment was significantly higher in the low CFH risk score group ($P = 0.033$). A significant improvement in mean VA was observed for smokers ($P < 0.001$), but this relationship was not observed for central foveal thickness.

CONCLUSION: After anti-VEGF therapy, significant improvement in VA was observed for low risk CFH genotypes and subjects with a low risk score. There was a statistically significant reduction in central foveal thickness overall, and subjects with a low CFH risk score improved more than the high risk group.

PMID: 26705092 [PubMed - as supplied by publisher]

Optom Vis Sci. 2015 Dec 22. [Epub ahead of print]

Anti-Vascular Endothelial Growth Factor with Gas for Submacular Hemorrhage.

Shin JY, Choi HJ, Chung B, Choi M, Lee J, Byeon SH.

PURPOSE: To investigate the treatment outcome of pneumatic displacement and intravitreal anti-vascular endothelial growth factor (VEGF) for submacular hemorrhage (SMH) from exudative age-related macular degeneration (AMD).

METHODS: Best-corrected visual acuity (BCVA) and central foveal thickness (CFT) were measured at baseline and at 1, 3, and 6 months after initial treatment in 72 eyes of 72 patients treated with a combination of pneumatic displacement and anti-VEGF injection for SMH from exudative AMD.

RESULTS: Best-corrected visual acuity and CFT showed significant improvement from baseline during the 6-month follow-up period (logarithm of the minimum angle of resolution BCVA from 1.80 to 1.00, CFT from 886 to 383 μm , $p < 0.001$, respectively). The decrease in subretinal hemorrhage was greater than that in subretinal pigment epithelial hemorrhage at 1 month after initial treatment ($p < 0.001$). In eyes with symptoms for less than 30 days, higher reflectivity of hemorrhage on optical coherence tomography and higher CFT were associated with lower BCVA after 6 months of treatment (reflectivity $B = 0.335$, $p = 0.007$; CFT $B = 0.001$, $p = 0.003$).

CONCLUSIONS: The combination of pneumatic displacement and intravitreal anti-VEGF is a useful treatment option for SMH secondary to AMD. Higher baseline CFT and higher reflectivity of hemorrhage were associated with lower BCVA 6 months after initial treatment.

PMID: 26704146 [PubMed - as supplied by publisher]

Other treatment & diagnosis

J Cataract Refract Surg. 2015 Oct;41(10):2125-35.

Injectable intraocular telescope: Pilot study.

Qureshi MA, Robbie SJ, Tabernero J, Artal P.

PURPOSE: To assess the feasibility of a new injectable telescopic intraocular lens (IOL).

SETTING: London Eye Hospital, London, United Kingdom.

DESIGN: Prospective interventional pilot study.

METHOD: Eyes with bilateral, intermediate, or advanced dry age-related macular degeneration (AMD); preoperative decimal corrected distance visual acuity (CDVA) of 0.25 or less; and improvement with extraocular simulation of the intervention had implantation of 2 IOLs designed for use together in a Galilean telescope configuration (iolAMD). Patients were followed for 4 months. Safety was assessed by monitoring visual acuity, intraocular pressure, specular microscopy, and anterior segment and macular optical coherence tomographies. Fixation stability and macular sensitivity were determined using microperimetry in some eyes.

RESULTS: There were no significant intraoperative or postoperative complications. In 1 eye, an anterior sulcus IOL was replaced; there were no sequelae. The mean endothelial cell density was reduced by 18%. The mean decimal CDVA improved from 0.12 preoperatively to 0.20 at 4 months, a 67% gain. The mean change in spherical equivalent after implantation was -1.5 diopters (D) with 0.5 D of induced astigmatism. Microperimetric testing indicated a magnification effect and a deviation of the retinal image by up to 5 degrees, with improved fixation stability.

CONCLUSIONS: This injectable intraocular miniature telescope appears safe in the short to medium term and capable of improving visual function. No significant issues were encountered regarding candidate eye selection or patient retention and cooperation. Further work is needed to evaluate the safety and efficacy of the device, particularly with respect to daily-living activities and the range of indications.

FINANCIAL DISCLOSURE:

Dr. Qureshi has a financial interest in London Eye Hospital Pharma. No other author has a financial or proprietary interest in any material or method mentioned.

PMID: 26703288 [PubMed - in process]

Biomed Opt Express. 2015 Nov 2;6(12):4661-75. eCollection 2015.

Advanced image processing for optical coherence tomographic angiography of macular diseases.

Zhang M, Wang J, Pechauer AD, Hwang TS, Gao SS, Liu L, Liu L, Bailey ST, Wilson DJ, Huang D, Jia Y.

Abstract: This article provides an overview of advanced image processing for three dimensional (3D) optical coherence tomographic (OCT) angiography of macular diseases, including age-related macular degeneration (AMD) and diabetic retinopathy (DR). A fast automated retinal layers segmentation algorithm using directional graph search was introduced to separate 3D flow data into different layers in the presence of pathologies. Intelligent manual correction methods are also systematically addressed which can be done rapidly on a single frame and then automatically propagated to full 3D volume with accuracy better than 1 pixel. Methods to visualize and analyze the abnormalities including retinal and choroidal neovascularization, retinal ischemia, and macular edema were presented to facilitate the clinical use of OCT angiography.

PMID: 26713185 [PubMed] PMCID: PMC4679245

Ophthalmologe. 2015 Dec 22. [Epub ahead of print]

[Clinical applications of OCT angiography]. [Article in German]

Fang PP, Lindner M, Steinberg JS, Müller PL, Gliem M, Charbel Issa P, Krohne TU, Holz FG.

BACKGROUND: Optical coherence tomography angiography (OCT-A) allows noninvasive, depth-selective visualization of retinal and choroidal vascular networks by detecting the endoluminal blood flow. This results in three-dimensional high-resolution images which are not possible by regular fluorescein angiography in this spatial resolution. Thus, OCT-A can be used to visualize the microperfusion of retinal and choroidal vessels and their alterations due to diverse pathologies and during the course of therapy. Based on several clinical case reports this article gives an overview of the wide range of applications of OCT-A.

METHODS: The OCT-A images were obtained with the Spectralis OCT-2 prototype (Heidelberg Engineering, Heidelberg, Germany). This device provides an increased A scan rate of 70 kHz, which allows the generation of high-resolution OCT volume scans.

RESULTS: The areas of application are manifold and include neovascular age-related macular degeneration, diabetic retinopathy, retinal vascular occlusion, inflammatory diseases and telangiectasia of various etiologies. The resulting images and their interpretation differ significantly from regular fluorescein angiography. Knowledge of these differences and of the limitations of this novel diagnostic device are of importance for its clinical application. For certain indications, OCT-A may be used as a substitute for invasive fluorescein angiography and provides more detailed information, particularly due to the absence of blockage phenomena, such as pooling or staining.

CONCLUSION: The use of OCT-A allows visualization of the microperfusion of the retinal and choroidal vascular networks and their alterations due to diverse diseases in high resolution and with segmentation of different anatomical layers. The exact interpretation of the three-dimensional OCT-A images and their clinical application are currently under clinical evaluation.

PMID: 26694492 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8207-14.

Concordance of Macular Pigment Measurement Using Customized Heterochromatic Flicker Photometry and Fundus Autofluorescence in Age-Related Macular Degeneration.

Akuffo KO, Beatty S, Stack J, Peto T, Leung I, Corcoran L, Power R, Nolan JM.

PURPOSE: We compared macular pigment (MP) measurements using customized heterochromatic flicker photometry (Macular Metrics Densitometer) and dual-wavelength fundus autofluorescence (Heidelberg Spectralis HRA + OCT MultiColor) in subjects with early age-related macular degeneration (AMD).

METHODS: Macular pigment was measured in 117 subjects with early AMD (age, 44-88 years) using the Densitometer and Spectralis, as part of the Central Retinal Enrichment Supplementation Trial (CREST; ISRCTN13894787). Baseline and 6-month study visits data were used for the analyses. Agreement was investigated at four different retinal eccentricities, graphically and using indices of agreement, including Pearson correlation coefficient (precision), accuracy coefficient, and concordance correlation coefficient (ccc).

RESULTS: Agreement was poor between the Densitometer and Spectralis at all eccentricities, at baseline (e.g., at 0.25° eccentricity, accuracy = 0.63, precision = 0.35, ccc = 0.22) and at 6 months (e.g., at 0.25° eccentricity, accuracy = 0.52, precision = 0.43, ccc = 0.22). Agreement between the two devices was significantly greater for males at 0.5° and 1.0° of eccentricity. At all eccentricities, agreement was unaffected by cataract grade.

CONCLUSIONS: In subjects with early AMD, MP measurements obtained using the Densitometer and Spectralis are not statistically comparable and should not be used interchangeably in either the clinical or

research setting. Despite this lack of agreement, statistically significant increases in MP, following 6 months of supplementation with macular carotenoids, were detected with each device, confirming that these devices are capable of measuring change in MP within subjects over time. (<http://www.controlled-trials.com> number, ISRCTN13894787.).

PMID: 26720473 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8120-4.

En Face Optical Coherence Tomography to Detect and Measure Geographic Atrophy.

Pilotto E, Guidolin F, Convento E, Antonini R, Stefanon FG, Parrozzani R, Midena E.

PURPOSE: To detect and quantify geographic atrophy (GA) secondary to age-related macular degeneration using en face optical coherence tomography (OCT) and to correlate it to GA measured with fundus autofluorescence (FAF).

METHODS: Twenty-four consecutive patients (27 eyes) were studied with both standard (STD)- and enhanced depth imaging (EDI)-OCT. En face OCT images were obtained at the outer retinal layer (OR) and at the choroidal layer (CH) level for both STD- and EDI-OCT. Areas of GA were measured on the en face OCT images and were correlated with the GA areas measured on blue (B)- and near infrared (NIR)-wavelength FAF images.

RESULTS: The intraoperator agreement in GA measurement was excellent with en face OCT at both OR and CH levels (intraclass correlation coefficient [ICC] = 0.99 in EDI and 0.98 in STD at OR level; 0.99 in EDI and 0.99 in STD at CH level). The interoperator agreement was excellent at OR level (ICC = 0.97 in EDI and 0.98 in STD), good at CH level (ICC = 0.95 in EDI, 0.90 in STD). The geographic atrophy area, at both B-FAF and NIR-FAF, was significantly equivalent to the GA area at OR level (B-FAF versus STD-OR and EDI-OR: $P = 0.0057$ and 0.0090 , respectively; NIR-FAF versus STD-OR and EDI-OR: $P = 0.0131$ and 0.0036 , respectively), but not at CH level.

CONCLUSIONS: En face OCT is a reliable method to detect and quantify GA, particularly when analyzed at the OR level, where the photoreceptors' loss creates an abrupt transition in OCT reflectivity.

PMID: 26720464 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8325-8330.

Predictive Value of Outer Retina En Face OCT Imaging for Geographic Atrophy Progression.

Giocanti-Auregan A, Tadayoni R, Fajnkuchen F, Dourmad P, Magazzeni S, Cohen SY.

PURPOSE: We determined if the ellipsoid zone (EZ) disruption pattern could be predictive of the geographic atrophy (GA) pattern at 1 year in dry age-related macular degeneration (AMD).

METHODS: A retrospective study was done of dry eyes in patients with AMD and GA from July to November 2013. Eyes with previous choroidal neovascularization were excluded. Based on spectral domain optical coherence tomography (SD-OCT), the GA was assessed at each timepoint, using a sub-RPE slab derived from the Cirrus Advanced RPE Analysis software encompassing the RPE (sub-RPE slab). Disruption of the EZ also was assessed at baseline, using en face extraction of a 20- μ m-thick slab, 20 μ m above the RPE (EZ slab) encompassing the EZ band using two different algorithms (RPE and RPE-fit). The EZ disruption area surrounding GA at baseline was quantified using ImageJ software. Primary endpoint was to identify en face pattern similarities between the baseline EZ disruption and the 1-year GA. Secondary endpoint was to correlate the baseline EZ disruption area surrounding GA with the GA enlargement over 1 year. Statistical analysis was performed using a correlation test (Pearson) and a t-test.

RESULTS: We included 37 eyes of 31 patients with dry AMD. En face EZ disruption pattern correlated in two-thirds of cases with the 1-year GA pattern using both algorithms. The EZ disruption area surrounding GA at baseline and GA enlargement over 1 year were poorly correlated when RPE-fit algorithm ($R = 0.17$) was used. The correlation was still poor using an RPE algorithm ($R = 0.38$), but increased after selection of eyes without reticular pseudodrusen ($R = 0.79$).

CONCLUSIONS: The EZ disruption pattern could be an indicator for GA pattern progression, but is not a good quantitative tool to predict the size of GA in the overall population over a 1-year period except for patients without reticular pseudodrusen. The results in this specific population must be confirmed by further studies.

PMID: 26747761 [PubMed - as supplied by publisher]

Int Ophthalmol. 2015 Dec 23. [Epub ahead of print]

Clinically detectable drusen domains in fibulin-5-associated age-related macular degeneration (AMD): Drusen subdomains in fibulin-5 AMD.

Kucukevcilioglu M, Patel CB, Stone EM, Russell SR.

Abstract: To evaluate whether drusen of subjects with fibulin-5 mutation-associated age-related macular degeneration (AMD) have clinically demonstrable drusen domains as evidenced by differences between color and fluorescein angiographic profiles. Of seven patients we identified with AMD due to mutations in the fibulin-5 gene (Fib-5 AMD), five had color fundus photography and fluorescein angiography (FA). One had bilateral choroidal neovascularization and no drusen. For each eye, the green channel (GC) of the digital RGB (Red-Green-Blue) color image and hyperfluorescent domain (HD) intensity of the FA image were registered and drusen were manually segmented and measured. Totally 75 small ($\leq 62 \mu\text{m}$), 110 intermediate ($63\text{--}125 \mu\text{m}$), and 30 large ($>125 \mu\text{m}$) drusen were measured in four patients within the 6×6 mm central macular areas. All four subjects demonstrated central or paracentral HDs within each drusen perimeter. HDs were found in association with each druse, with a HD/GC ratio of 0.82, 0.76, and 0.72 respectively for small, intermediate, and large drusen (Student T Test: $P < 0.01$, $P < 0.01$, $P < 0.01$). A statistical difference was found for the HD/GC ratios between small- and intermediate-sized drusen and small- and large-sized drusen but not between intermediate-sized and large-sized drusen ($P = 0.001$, $P < 0.001$, $P > 0.05$, respectively). AMD patients with mutations in fibulin-5 share drusen phenotypic structure and have HD/GC ratios that are similar to individuals with cuticular or basal laminar drusen. Drusen substructure may reflect similarities in drusen stage and/or genesis and appear to vary among AMD genotypes.

PMID: 26694911 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Jan 4. [Epub ahead of print]

Frosted branch angiitis complicated by retinal vein occlusion: clinical course and long-term visual outcome.

Greifner G, Neri P, Amer R.

PURPOSE: Frosted branch angiitis (FBA) is a rare entity characterized by acute panuveitis in the form of a florid translucent retinal perivascular sheathing of both arterioles and venules, with variable uveitis, retinal edema and visual loss. Primary and secondary cases have been described in association with infectious, inflammatory and malignant etiologies. We aim to describe the clinical course and long-term visual outcome of three patients who developed retinal vein occlusion (RVO) and macular edema as a complication of FBA.

METHODS: Descriptive case series.

RESULTS: Three young healthy patients aged 22, 37 and 45 years presented with sudden visual

disturbance secondary to unilateral primary FBA, which improved significantly following high-dose steroid therapy. Several weeks later, RVO developed, with marked cystoid macular edema. Visual improvement was achieved and maintained with anti-VEGF therapy over a follow-up period ranging from 14 to 44 months.

CONCLUSION: FBA may be considered a risk factor for the development of secondary RVO because of the severe retinal vasculitis that eventually leads to activation of the coagulation system and retinal thrombosis. It remains to be determined whether antiplatelet therapy needs to be administered prophylactically in such a scenario in order to reduce the risk or prevent the development of RVO.

PMID: 26728758 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Jan 8. [Epub ahead of print]

Photodynamic therapy: current role in the treatment of chorioretinal conditions.

Newman DK.

Abstract: Verteporfin photodynamic therapy (vPDT) is a selective vaso-occlusive treatment that targets choroidal vascular abnormalities. It was initially developed to treat neovascular age-related macular degeneration using the 'standard' vPDT protocol (verteporfin 6 mg/m², vPDT laser fluence 50 J/cm²). vPDT therapy has subsequently evolved as an important treatment modality for a range of other chorioretinal conditions including choroidal haemangioma, central serous chorioretinopathy, polypoidal choroidal vasculopathy, and peripapillary choroidal neovascularisation. Various 'safety-enhanced' vPDT protocols have been devised to optimise treatment outcomes, typically using reduced dose verteporfin (verteporfin 3 mg/m²) or reduced fluence vPDT (vPDT laser fluence 25 J/cm²). This paper reviews the current role of vPDT therapy in the treatment of chorioretinal conditions.

PMID: 26742867 [PubMed - as supplied by publisher]

Retina. 2015 Dec 29. [Epub ahead of print]

DEVELOPMENT OF INTRARETINAL CYSTOID LESIONS IN EYES WITH INTERMEDIATE AGE-RELATED MACULAR DEGENERATION.

Steinberg JS, Göbel AP, Thiele S, Fleckenstein M, Holz FG, Schmitz-Valckenberg S.

PURPOSE: To evaluate the development of intraretinal cystoid lesions (ICLs) in eyes with intermediate age-related macular degeneration.

METHODS: Serial multimodal retinal imaging data of 105 eyes from 87 age-related macular degeneration subjects (median age of 75.0 years) with no late age-related macular degeneration at baseline from the prospective longitudinal natural history "molecular diagnostic of age-related macular degeneration-study" were included. The presence of ICLs-defined as lacunar hyporeflective areas within the neurosensory retina-was determined by spectral-domain optical coherence tomography at Month 24. Both baseline and further follow-up data were additionally evaluated.

RESULTS: At Month 24, ICLs were identified in 12 of 105 (11.7%) eyes of which 4 had developed signs of choroidal neovascularization since baseline. Intraretinal cystoid lesions in these four eyes with choroidal neovascularization were mostly found at the level of the outer nuclear layer. Intraretinal cystoid lesions in the remaining 8 eyes occurred mainly at the level of the inner nuclear layer, showed smaller horizontal and vertical dimensions, and were not spatially confined to an increase in retinal thickness.

CONCLUSION: The results indicate that ICLs may develop also in the absence of active neovascularization. Distinctive morphologic features and localization of ICLs may be indicative of different underlying pathogenetic mechanisms. If no manifest choroidal neovascularization can be established in the

presence of ICLs, close monitoring as well as awareness and self-monitoring seem to be advisable.

PMID: 26716957 [PubMed - as supplied by publisher]

Ophthalmologe. 2016 Jan 7. [Epub ahead of print]

[OCT angiography for exudative age-related macular degeneration : Initial experiences]. [Article in German]

Lommatzsch A, Farecki ML, Book B, Heimes B, Pauleikhoff D.

Abstract: The new technique of optical coherence tomography (OCT) angiography allows a non-invasive reconstruction of the three-dimensional structure of the total retinal and choroidal vascularization within seconds. There are still limitations caused by movement artefacts, superimposition of superficial retinal vessels at the retinal pigment epithelium (RPE) level and insufficient three-dimensional imaging modalities. Initial experiences with this new method and especially the correlation with the current standard diagnostic procedure of fluorescein angiography show that new information can be obtained regarding specific vascular and neovascular changes. For three-dimensional neovascular changes, such as those found in exudative age-related macular degeneration (AMD,) a more sophisticated diagnostic analysis strategy must be specifically developed. Initial experiences demonstrate that the differentiation into the various types of choroidal neovascularization (CNV) by fluorescein angiography, specifically for type 1 (occult) and type 2 (classical) can also be visualized by OCT angiography. Furthermore, the new technology provides additional information on the choroidal and outer retinal changes associated with this disease, which may result in a better understanding of the underlying pathology.

PMID: 26743785 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Jan 8. [Epub ahead of print]

Ultraviolet or blue-filtering intraocular lenses: what is the evidence?

Downes SM.

Abstract: Cataract surgery was revolutionised by the introduction of modern intraocular lenses in the late 1940's. By the late 1960's to 1970's evidence had emerged that short-wavelength light caused phototoxicity at the retina and retinal pigment epithelium. By the early 1980's ultraviolet filters had been incorporated into intraocular lenses. This caused intense controversy, as there was concern that the UV-filtering chromophore might leach out into the eye causing toxicity. With the arrival of blue-filtering intraocular lenses (BFIOLs) in 1990's, a further debate was ignited as to their safety and potential disadvantages. Selecting the optimal performing intraocular lens to obtain the best visual performance with the fewest potential drawbacks has become complex and challenging for cataract surgeons and their patients with the wide choice of lenses available. Choosing a personalised lens to address astigmatism, presbyopia, spherical aberration, chromatic aberration, and potentially to shield the retina from short-wavelength light is now possible. The potential benefits and possible side effects of these different innovations emphasise the importance of assessing the evidence for their clinical utility, allowing the surgeon and the patient to weigh-up the risk benefit ratio and make an informed decision. The BFIOLs were developed to reduce cyanopsia, address chromatic aberration, and improve contrast sensitivity in different lighting conditions, as well as to prevent short-wavelength light reaching the retina thus potentially reducing the risk of developing age-related macular degeneration. Further design development of the BFIOLs was to mimic the natural crystalline lens absorption and transmittance properties in adulthood. Multiple publications have reported on the potential benefits and pitfalls of implanting a blue-filtering lens. The potential disadvantages raised in the literature over the last 25 years since their introduction, regarding compromise of visual function and disruption of the circadian system, have been largely dispelled. The clear benefits of protecting the retina from short-wavelength light make a BFIOLs a sensible choice. The purpose of this article presented at the Cambridge symposium 2015 is to review the literature on this subject.

PMID: 26742866 [PubMed - as supplied by publisher]

Curr Med Chem. 2015 Dec 21. [Epub ahead of print]

Ozone: a multifaceted molecule with unexpected therapeutic activity.

Zanardi I, Borrelli E, Valacchi G, Travagli V, Bocci V1.

Abstract: A comprehensive outline for understanding and recommending the therapeutic use of ozone in combination with established therapy in diseases characterized by a chronic oxidative stress is currently available. The view of the absolute ozone toxicity is wrong, because it has been based either on lung or on studies performed in artificial environments that do not correspond to the real antioxidant capacity of body compartments. In fact, ozone exerts either a potent toxic activity or it can stimulate biological responses of vital importance, analogously to gases with prospective therapeutic value such as NO, CO, H₂S, H₂, as well as O₂ itself. Such a crucial difference has increasingly become evident during the last decade. The purpose of this review is to explain the aspects still poorly understood, highlighting the divergent activity of ozone on the various biological districts. It will be clarified that such a dual effect does not depend only upon the final gas concentration, but also on the particular biological system where ozone acts. The real significance of ozone as adjuvant therapeutic treatment concerns severe chronic pathologies among which cardiovascular diseases, chronic obstructive pulmonary diseases, multiple sclerosis, and the dry form of age-related macular degeneration. It is time for a full insertion of ozone therapy within pharmaceutical sciences, responding to all the requirements of Quality, efficacy and safety, rather than as either an alternative or an esoteric approach.

PMID: 26687830 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2016 Jan 8. [Epub ahead of print]

Functional and morphological evaluation of blue light-emitting diode-induced retinal degeneration in mice.

Kim GH, Kim HI, Paik SS, Jung SW, Kang S, Kim IB.

PURPOSE: The purpose of this study was to evaluate a retinal degeneration (RD) model induced by exposing mice to a blue light-emitting diode (LED), which led to photoreceptor cell death.

METHODS: RD was induced in BALB/c mice by exposure to a blue LED (460 nm) for 2 hours. Retinal function was examined using scotopic electroretinography (ERG). Histopathological changes were assessed by hematoxylin and eosin (H&E) staining and electron microscopy. Apoptotic cell death was evaluated by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay. In addition, retinal inflammation and oxidative stress were evaluated by immunohistochemistry with anti-glial fibrillary acidic protein (GFAP) and anti-8-hydroxy-2'-deoxyguanosine (8-OHdG), respectively.

RESULTS: Scotopic ERG showed that blue LED exposure resulted in a decrease in both a-waves and b-waves in mice retinas in an illuminance-dependent manner. H&E, TUNEL assay, and electron microscopy revealed massive photoreceptor cell death by apoptosis in the central region of the retina. Retinal stress and inflammation were detected by increased expression of GFAP and by electron microscopy findings demonstrating microglia infiltration in the outer nuclear layer and subretinal space. In addition, increased labeling of 8-OHdG was observed in the retinas from blue LED exposure.

CONCLUSIONS: These results suggest that blue LED-induced RD may be a useful animal model in which to study the pathogenesis of RD, including age-related macular degeneration, and to evaluate the effects of new therapeutic agents prior to clinical trials, where oxidative stress and inflammation are the underlying RD mechanisms.

PMID: 26743754 [PubMed - as supplied by publisher]

Conf Proc IEEE Eng Med Biol Soc. 2015 Aug;2015:8127-30.

Analyzing OCT images of age-related macular degeneration patients to identify spatial health correlations.

Go S, Chundi P, Subramaniam M, Margalit E.

Abstract: An approach to automatically group age-related macular degeneration (AMD) patients having similar retinal health profiles by clustering Optical Coherence Tomography (OCT) images is described. Spatial health patterns within and across profiles are discovered by identifying segments of images that have similar levels of health in a given retina region. Segmentations of various sizes are considered and the segmentation where the segment similarity most closely matches the discovered health profiles is used to identify health patterns. Our experiments with OCT images of 10 AMD patients show that - i) health profiles generated by clustering closely correspond to those identified by a physician expert, ii) a rich set of spatial patterns can be discovered within and across profiles using regular image segmentation, and iii) new images can be successfully classified into existing profiles so that physicians can provide effective profile-based treatments.

PMID: 26738180 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2015 Aug;2015:5260-3.

Multiple ocular diseases detection based on joint sparse multi-task learning.

Xiangyu Chen, Yanwu Xu, Fengshou Yin, Zhuo Zhang, Wong DW, Tien Yin Wong, Jiang Liu.

Abstract: In this paper, we present a multiple ocular diseases detection scheme based on joint sparse multi-task learning. Glaucoma, Pathological Myopia (PM), and Age-related Macular Degeneration (AMD) are three major causes of vision impairment and blindness worldwide. The proposed joint sparse multitask learning framework aims to reconstruct a test fundus image with multiple features from as few training subjects as possible. The linear version of this problem could be casted into a multi-task joint covariate selection model, which can be very efficiently optimized via kernelizable accelerated proximal gradient method. Extensive experiments are conducted in order to validate the proposed framework on the SiMES dataset. From the Area Under Curve (AUC) results in multiple ocular diseases classification, our method is shown to outperform the state-of-the-art algorithms.

PMID: 26737478 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2015 Aug;2015:4351-4. doi: 10.1109/EMBC.2015.7319358.

Reducing the artifacts in the identification of outer retinal boundary in the SD-OCT image with inherit retinal dystrophies.

Min Zhang, Sekiguchi H, Uji A, Yakami M, Togashi K.

Abstract: This paper presents a new SD-OCT outer retinal boundary identification method based on the improved graph-theoretic approach in SD-OCT retinal image, which is robust to the image quality degradation and the pathological morphology variability. The performance of the proposed method was verified using the SD-OCT image database with inherit retinal dystrophies, which suffer from the artifacts most among different macular degeneration diseases. The experimental results of the subjective evaluation indicated that the identification results using the proposed method was substantially improved compared with the current built-in software in the SD-OCT devices.

PMID: 26737258 [PubMed - in process]

Conf Proc IEEE Eng Med Biol Soc. 2015 Aug;2015:2952-5.

Sparse high order potentials for extending multi-surface segmentation of OCT images with drusen.

Oliveira J, Pereira S, Goncalves L, Ferreira M, Silva CA.

Abstract: Drusen quantification is important for evaluating age-related macular degeneration (AMD) progress. Most methods for retinal layers segmentation in optical coherence tomography (OCT) depend heavily on prior information. This improves robustness, but also has the downside of increasing surface rigidity. Hence, those algorithms normally smooth drusen borders, as significant local variations are not expected. In this work, we propose to integrate sparse higher order potentials (SHOPs) into a multi-surface segmentation framework to cope with local boundary variations caused by drusen. The algorithm was evaluated in a database of 20 patients with AMD. The mean unsigned error for the inner retinal pigment epithelium (IRPE) and Bruch's membrane (BM) was 5.65 ± 6.26 and 4.37 ± 5.25 μm , respectively. These results are relative to the average of two experts, whose inter-observer variability was 7.30 ± 6.87 μm for IRPE and 5.03 ± 4.37 μm for BM. The use SHOPs resulted in a successful segmentation of the IRPE. The remaining boundaries were also successfully segmented.

PMID: 26736911 [PubMed - in process]

Clin Ophthalmol. 2015 Dec 17;9:2345-53. eCollection 2015.

Microcurrent stimulation in the treatment of dry and wet macular degeneration.

Chaikin L, Kashiwa K, Bennet M, Papastergiou G, Gregory W.

PURPOSE: To determine the safety and efficacy of the application of transcutaneous (transpalpebral) microcurrent stimulation to slow progression of dry and wet macular degeneration or improve vision in dry and wet macular degeneration.

METHODS: Seventeen patients aged between 67 and 95 years with an average age of 83 years were selected to participate in the study over a period of 3 months in two eye care centers. There were 25 eyes with dry age-related macular degeneration (DAMD) and six eyes with wet age-related macular degeneration (WAMD). Frequency-specific microcurrent stimulation was applied in a transpalpebral manner, using two programmable dual channel microcurrent units delivering pulsed microcurrent at 150 μA for 35 minutes once a week. The frequency pairs selected were based on targeting tissues, which are typically affected by the disease combined with frequencies that target disease processes. Early Treatment Diabetic Retinopathy Study or Snellen visual acuity (VA) was measured before and after each treatment session. All treatment was administered in a clinical setting.

RESULTS: Significant increases were seen in VA in DAMD ($P=0.012$, Wilcoxon one-sample test), but in WAMD, improvements did not reach statistical significance ($P=0.059$). In DAMD eyes, twice as many patients showed increase in VA (52%) compared to those showing deterioration (26%), with improvements being often sizeable, whereas deteriorations were usually very slight. In WAMD eyes, five of six (83%) patients showed an increase and none showed deterioration.

CONCLUSION: The substantial changes observed over this period, combined with continued improvement for patients who continued treatment once a month, are encouraging for future studies. The changes observed indicate the potential efficacy of microcurrent to delay degeneration and possibly improve age-related macular degeneration, both wet and dry. However, this study has no control arm, so results should be treated with caution. Randomized double-blind controlled studies are needed to determine long-term effects.

PMID: 26719667 [PubMed] PMCID: PMC4689270

Graefes Arch Clin Exp Ophthalmol. 2016 Jan 4. [Epub ahead of print]

Identity of pigmented subretinal cells in age-related macular degeneration.

Lad EM, Cousins SW, Proia AD.

PMID: 26728757 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 Dec 17. [Epub ahead of print]

Assessment of Choroidal Topographic Changes by Swept-Source Optical Coherence Tomography After Intravitreal Ranibizumab for Exudative Age-Related Macular Degeneration.

Takkar B, Azad S.

PMID: 26706269 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2015 Dec 22;10(12):e0145305. eCollection 2015.

PBN (Phenyl-N-Tert-Butylnitron)-Derivatives Are Effective in Slowing the Visual Cycle and Rhodopsin Regeneration and in Protecting the Retina from Light-Induced Damage.

Stiles M, Moiseyev GP, Budda ML, Linens A, Brush RS, Qi H, White GL, Wolf RF, Ma JX, Floyd R, Anderson RE, Mandal NA.

Abstract: A2E and related toxic molecules are part of lipofuscin found in the retinal pigment epithelial (RPE) cells in eyes affected by Stargardt's disease, age-related macular degeneration (AMD), and other retinal degenerations. A novel therapeutic approach for treating such degenerations involves slowing down the visual cycle, which could reduce the amount of A2E in the RPE. This can be accomplished by inhibiting RPE65, which produces 11-cis-retinol from all-trans-retinyl esters. We recently showed that phenyl-N-tert-butyl nitron (PBN) inhibits RPE65 enzyme activity in RPE cells. In this study we show that like PBN, certain PBN-derivatives (PBNs) such as 4-F-PBN, 4-CF₃-PBN, 3,4-di-F-PBN, and 4-CH₃-PBN can inhibit RPE65 and synthesis of 11-cis-retinol in in vitro assays using bovine RPE microsomes. We further demonstrate that systemic (intraperitoneal, IP) administration of these PBNs protect the rat retina from light damage. Electroretinography (ERG) and histological analysis showed that rats treated with PBNs retained ~90% of their photoreceptor cells compared to a complete loss of function and 90% loss of photoreceptors in the central retina in rats treated with vehicle/control injections. Topically applied PBN and PBNs also significantly slowed the rate of the visual cycle in mouse and baboon eyes. One hour dark adaptation resulted in 75-80% recovery of bleachable rhodopsin in control/vehicle treated mice. Eye drops of 5% 4-CH₃-PBN were most effective, inhibiting the regeneration of bleachable rhodopsin significantly (60% compared to vehicle control). In addition, a 10% concentration of PBN and 5% concentration of 4-CH₃-PBN in baboon eyes inhibited the visual cycle by 60% and by 30%, respectively. We have identified a group of PBN related nitrones that can reach the target tissue (RPE) by systemic and topical application and slow the rate of rhodopsin regeneration and therefore the visual cycle in mouse and baboon eyes. PBNs can also protect the rat retina from light damage. There is potential in developing these compounds as preventative therapeutics for the treatment of human retinal degenerations in which the accumulation of lipofuscin may be pathogenic.

PMID: 26694648 [PubMed - in process] PMCID: PMC4687940

Biomed Res Int. 2015;2015:863845. doi: 10.1155/2015/863845. Epub 2015 Dec 1.

Antiangiogenic and Neurogenic Activities of Sleeping Beauty-Mediated PEDF-Transfected RPE

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Cells In Vitro and In Vivo.

Johnen S, Djalali-Talab Y, Kazanskaya O, Möller T, Harmening N, Kropp M, Izsvák Z, Walter P, Thumann G.

Abstract: Pigment epithelium-derived factor (PEDF) is a potent multifunctional protein that inhibits angiogenesis and has neurogenic and neuroprotective properties. Since the wet form of age-related macular degeneration is characterized by choroidal neovascularization (CNV), PEDF would be an ideal candidate to inhibit CNV and support retinal pigment epithelial (RPE) cells. However, its short half-life has precluded its clinical use. To deliver PEDF to the subretinal space, we transfected RPE cells with the PEDF gene using the Sleeping Beauty transposon system. Transfected cells expressed and secreted biologically active recombinant PEDF (rPEDF). In cultures of human umbilical vein endothelial cells, rPEDF reduced VEGF-induced cumulative sprouting by $\geq 47\%$, decreased migration by 77%, and increased rate of apoptosis at least 3.4 times. rPEDF induced neurite outgrowth in neuroblastoma cells and protected ganglion and photoreceptor cells in organotypic retinal cultures. In a rat model of CNV, subretinal transplantation of PEDF-transfected cells led to a reduction of the CNV area by 48% 14 days after transplantation and decreased clinical significant lesions by 55% and 40% after 7 and 14 days, respectively. We showed that transplantation of pigment epithelial cells overexpressing PEDF can restore a permissive subretinal environment for RPE and photoreceptor maintenance, while inhibiting choroidal blood vessel growth.

PMID: 26697494 [PubMed - in process] PMCID: PMC4678073

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8314-24. doi: 10.1167/iovs.15-18359.

Wnt/ β -Catenin Signaling Mediates Regeneration of Retinal Pigment Epithelium After Laser Photocoagulation in Mouse Eye.

Han JW, Lyu J, Park YJ, Jang SY, Park TK.

PURPOSE: Laser photocoagulation of retinal pigment epithelium (RPE) is used to stimulate the regenerative processes of the RPE. However, the molecular mechanisms that control RPE proliferation and the epithelial-mesenchymal transition (EMT) during regeneration remain poorly understood. We investigated the role of Wnt/ β -catenin signaling in the regeneration of mouse RPE after laser photocoagulation.

METHODS: C57BL/6J mice were photocoagulated unilaterally. To determine the β -catenin-dependent Wnt signal transduction in the photocoagulated RPE, the expression levels of Wnts, β -catenin, and their target genes were analyzed using real time-PCR and Western blotting. Retinal pigment epithelium proliferation and EMT were determined by 5-ethynyl-2'-deoxyuridine (EdU) incorporation assay and by profiling expression of EMT markers, respectively, in eyes injected intravitreally with a Wnt/ β -catenin signaling antagonist, Dkk-1, after laser photocoagulation.

RESULTS: Expression of several of the 19 Wnt genes was significantly increased in laser-treated RPE. The expression levels of β -catenin signaling target genes cyclin D1, Otx2, and Mitf were higher in laser-treated RPE than in control RPE. The number of EdU-positive cells in the laser-treated area was significantly lower in the Dkk-1-injected group than in the laser-treated group or laser-treated + vehicle-injected group. There were more Otx2- and Mitf-positive cells after laser photocoagulation and markedly fewer in the Dkk-1-injected group. Otx2- and Mitf-positive cells were colocalized with EdU-positive cells. The EMT markers vimentin and α -smooth muscle actin (α -SMA) were upregulated in the laser-treated area and significantly downregulated in the Dkk-1-injected group.

CONCLUSIONS: Laser photocoagulation activates a Wnt/ β -catenin signal transduction pathway, promoting both RPE proliferation and EMT. Wnt/ β -catenin signaling also upregulates the expression of Otx2 and Mitf, key transcription factors in RPE formation. Our results demonstrate an important role for Wnt/ β -catenin signaling in RPE proliferation and EMT, and suggest that manipulating Wnt/ β -catenin signaling may have

therapeutic potential for RPE regeneration.

PMID: 26720485 [PubMed - in process]

PLoS One. 2015 Dec 30;10(12):e0145323. eCollection 2015.

Circulating Autoantibodies in Age-Related Macular Degeneration Recognize Human Macular Tissue Antigens Implicated in Autophagy, Immunomodulation, and Protection from Oxidative Stress and Apoptosis.

Iannaccone A, Giorgianni F, New DD, et al; Health ABC study.

BACKGROUND: We investigated sera from elderly subjects with and without age-related macular degeneration (AMD) for presence of autoantibodies (AABs) against human macular antigens and characterized their identity.

METHODS: Sera were collected from participants in the Age-Related Maculopathy Ancillary (ARMA) Study, a cross-sectional investigation ancillary to the Health ABC Study, enriched with participants from the general population. The resulting sample (mean age: 79.2±3.9 years old) included subjects with early to advanced AMD (n = 131) and controls (n = 231). Sera were tested by Western blots for immunoreactive bands against human donor macular tissue homogenates. Immunoreactive bands were identified and graded, and odds ratios (OR) calculated. Based on these findings, sera were immunoprecipitated, and subjected to 2D gel electrophoresis (GE). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to identify the targets recognized by circulating AABs seen on 2D-GE, followed by ELISAs with recombinant proteins to confirm LC-MS/MS results, and quantify autoreactivities.

RESULTS: In AMD, 11 immunoreactive bands were significantly more frequent and 13 were significantly stronger than in controls. Nine of the more frequent bands also showed stronger reactivity. OR estimates ranged between 4.06 and 1.93, and all clearly excluded the null value. Following immunoprecipitation, 2D-GE and LC-MS/MS, five of the possible autoreactivity targets were conclusively identified: two members of the heat shock protein 70 (HSP70) family, HSPA8 and HSPA9; another member of the HSP family, HSPB4, also known as alpha-crystallin A chain (CRYAA); Annexin A5 (ANXA5); and Protein S100-A9, also known as calgranulin B that, when complexed with S100A8, forms calprotectin. ELISA testing with recombinant proteins confirmed, on average, significantly higher reactivities against all targets in AMD samples compared to controls.

CONCLUSIONS: Consistent with other evidence supporting the role of inflammation and the immune system in AMD pathogenesis, AABs were identified in AMD sera, including early-stage disease. Identified targets may be mechanistically linked to AMD pathogenesis because the identified proteins are implicated in autophagy, immunomodulation, and protection from oxidative stress and apoptosis. In particular, a role in autophagy activation is shared by all five autoantigens, raising the possibility that the detected AABs may play a role in AMD via autophagy compromise and downstream activation of the inflammasome. Thus, we propose that the detected AABs provide further insight into AMD pathogenesis and have the potential to contribute to disease biogenesis and progression.

PMID: 26717306 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8403-8418.

Modulating the Transport Characteristics of Bruch's Membrane With Steroidal Glycosides and its Relevance to Age-Related Macular Degeneration (AMD).

Lee Y, Hussain AA, Seok JH, Kim SH, Marshall J.

PURPOSE: Beneficial expectations of supplement therapies to increase the transport of nutrients, vitamins, and antioxidants across Bruch's membrane in AMD, by mass action alone, remain inconclusive. Therefore,

the potential for targeting the transport pathways themselves to improve bidirectional exchange using amphipathic steroidal glycosides (ginsenosides) has been investigated.

METHODS: Bruch's choroid preparations were mounted in modified Ussing chambers and basal levels of hydraulic conductivity (23 donors, age range, 12-89 years) and diffusional transport of FITC-albumin (21 donors, age range, 12-92 years) quantified. Then, following a 24-hour incubation with ginsenoside preparations, the transport parameters were re-evaluated and the resulting data analyzed with respect to aging and modulation by ginsenosides.

RESULTS: Basal hydraulic conductivity of Bruch's showed an age-related exponential decline with a half-life of 19 years. Incubation with ginsenosides improved hydraulic conductivity with levels equivalent to donors 19 years younger. Across the age range examined, hydraulic conductivities were increased to 2.05-fold $\pm$ 0.38 ($P < 0.001$) of basal values. Diffusional transport of albumin across Bruch's also showed an age-related exponential decline with a half-life of 18 years. The decay curves were elevated on incubation with ginsenosides and diffusional rates were equivalent to donors 15 years younger. Diffusional rates were elevated 2.01-fold $\pm$ 0.49 over basal values ($P < 0.001$).

CONCLUSIONS: Transport characteristics of human Bruch's can be improved by ginsenosides, facilitating the bidirectional exchange of nutrients and waste products across the membrane. With improved transport pathways, the need for supplement therapies becomes redundant. Slowed aging of Bruch's is expected to delay the onset and/or progression of AMD.

PMID: 26747771 [PubMed - as supplied by publisher]

J Biol Chem. 2016 Jan 4. [Epub ahead of print]

Mutations in complement factor H impair alternative pathway regulation on mouse glomerular endothelial cells in vitro.

Loeven MA, Rops AL, Lehtinen MJ, van Kuppevelt TH, Daha MR, Smith RJ, Bakker M, Berden JH, Rabelink TJ, Jokiranta TS, van der Vlag J.

Abstract: Complement factor H (FH) inhibits complement activation and interacts with glomerular endothelium via its complement control protein (CCP) domains 19-20, which also recognize heparan sulfate (HS). Abnormalities in FH are associated with the renal diseases atypical hemolytic uremic syndrome (aHUS) and dense deposit disease, and the ocular disease age-related macular degeneration. Although FH systemically controls complement activation, clinical phenotypes selectively manifest in kidneys and eyes, suggesting the presence of tissue-specific determinants of disease development. Recent results imply the importance of tissue-specifically expressed, sulfated glycosaminoglycans (GAGs), like HS, in determining FH binding to and activity on host tissues. Therefore, we investigated which GAGs mediate human FH and recombinant human FH CCP19-20 (FH19-20) binding to mouse glomerular endothelial cells (mGEnCs) in ELISA. Furthermore, we evaluated the functional defects of FH19-20 mutants during complement activation by measuring C3b deposition on mGEnCs using flow cytometry. FH and FH19-20 bound dose-dependently to mGEnCs and TNF- α treatment increased binding of both proteins, while heparinase digestion and competition with heparin/HS inhibited binding. Furthermore, 2-O-, and 6-O-, but not N-desulfation of heparin significantly increased the inhibitory effect on FH19-20 binding to mGEnCs. Compared to wild type FH19-20, aHUS-associated mutants were less able to compete with FH in normal human serum during complement activation on mGEnCs, confirming their potential glomerular pathogenicity. In conclusion, our study shows that FH and FH19-20 binding to glomerular endothelial cells is differentially mediated by HS, but not other GAGs. Furthermore, we describe a novel, patient serum-independent competition assay for pathogenicity screening of FH19-20 mutants.

PMID: 26728463 [PubMed - as supplied by publisher]

BMC Ophthalmol. 2015 Dec 29;15(1):187.

Matrix metalloproteinases in the mouse retina: a comparative study of expression patterns and MMP antibodies.

De Groef L, Andries L, Lemmens K, Van Hove I, Moons L.

BACKGROUND: Matrix metalloproteinases (MMPs), a family of Zn(2+)-dependent endoproteases, have been shown to act as fine regulators of both health and disease. Limited research revealed that they are essential to maintaining ocular physiology and inordinate MMP activities have been linked to several neurodegenerative disorders of the retina, including age-related macular degeneration, proliferative diabetic retinopathy and glaucomatous optic neuropathies (GONs). Nevertheless, a clear definition of their pathology-exacerbating and/or -resolving actions is lacking, especially in the context of GONs, as most studies thus far merely focused on expression profiling in human patients. Therefore, in an initial step towards an improved understanding of MMP functions in the retina, we studied the spatial expression pattern of MMP-2, -3, -9 and MT1-MMP in the healthy mouse retina.

METHODS: The spatial expression pattern of MMP-2, -3, -9 and MT1-MMP was studied in the healthy mouse retina via immunohistochemical stainings, and immunoreactivity profiles were compared to existing literature. Moreover, we considered sensitivity and specificity issues with commercially available MMP antibodies via Western blot.

RESULTS: Basal expression of MMP-2,-3, -9 and MT1-MMP was found in the retina of healthy, adult mice. MMP-2 expression was seen in Müller glia, predominantly in their end feet, which is in line with available literature. MMP-3 expression was described for the first time in the retina, and was observed in vesicle-like structures along the radial fibers of Müller glia. MMP-9 expression, about which still discords exists, was seen in microglia and in a sparse subset of (apoptosing) RGCs. MT1-MMP localization was for the first time studied in adult mice and was found in RGC axons and Müller glia, mimicking the MT1-MMP expression pattern seen in rabbits and neonatal mice. Moreover, one antibody was selected for each MMP, based on its staining pattern in Western blot.

CONCLUSIONS: The present MMP immunoreactivity profiles in the mouse retina and validation of MMP antibodies, can be instrumental to study MMP expression in mouse models of ocular pathologies and to compare these expression profiles to observations from clinical studies, which would be a first step in the disentanglement of the exact role MMPs in ocular/retinal diseases.

PMID: 26714639 [PubMed - in process] PMCID: PMC4696081

Br J Ophthalmol. 2016 Jan 8. [Epub ahead of print]

CFH Y402H polymorphism and the complement activation product C5a: effects on NF-κB activation and inflammasome gene regulation.

Cao S, Wang JC, Gao J, Wong M, To E, White VA, Cui JZ, Matsubara JA.

BACKGROUND/AIMS: The Y402H polymorphism in the complement factor H (CFH) gene is an important risk factor for age-related macular degeneration (AMD). Complement activation products and proinflammatory cytokines are associated with this polymorphism at the systemic level, but less is known of the associations in the outer retina of the genotyped eye. Here we investigate complement activation products and their role in nuclear factor (NF)-κB activation and gene expression of the NLRP3 inflammasome pathway.

METHODS: Postmortem donor eyes were genotyped for the CFH Y402H polymorphism and assessed for complement C3a, C5a, interleukin (IL)-18 and tumour necrosis factor (TNF)-α. ARPE19 cells were stimulated basolaterally with C5a or TNF-α in polarised cultures. NF-κB activation was assessed with a reporter cell line. Gene expression of inflammasome-related (NLRP3, caspase-1, IL-1β and IL-18) and classic inflammatory (IL-6 and IL-8) genes was studied. The distribution of inflammasome products, IL-1β

and IL-18, was studied in postmortem donor eyes with AMD pathologies.

RESULTS: Eyes with the homozygous at-risk variant demonstrated higher levels of C5a, IL-18 and TNF- α in Bruch's membrane and choroid. C5a promoted NF- κ B activation and upregulation of IL-18 in polarised ARPE19. TNF- α promoted NF- κ B activation and gene expression of caspase-1, IL-1 β , IL-18, IL-6 and IL-8, but downregulated NLRP3. In eyes with geographic atrophy, strong immunoreactivity was observed for inflammasome products IL-1 β and IL-18 compared with age-matched controls.

CONCLUSION: The at-risk polymorphism of the CFH Y402H may contribute to AMD disease process through increased complement and NF- κ B activation, and the upregulation of IL-18, a product of inflammasome activation.

PMID: 26746578 [PubMed - as supplied by publisher]

Immunobiology. 2015 Dec 19. [Epub ahead of print]

Age-related macular degeneration: Complement in action.

van Lookeren Campagne M, Strauss EC, Yaspan BL.

Abstract: The complement system plays a key role in host-defense against common pathogens but must be tightly controlled to avoid inflammation and tissue damage. Polymorphisms in genes encoding two important negative regulators of the alternative complement pathway, complement factor H (CFH) and complement factor I (CFI), are associated with the risk for Age-Related Macular Degeneration (AMD), a leading cause of vision impairment in the ageing population. In this review, we will discuss the genetic basis of AMD and the potential impact of complement de-regulation on disease pathogenesis. Finally, we will highlight recent therapeutic approaches aimed at controlling complement activation in patients with AMD.

PMID: 26742632 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2016 Jan 7. [Epub ahead of print]

Pigmentation and Macular Degeneration: Is There a Role for GPR143?

McKay BS, Schwartz SG.

PMID: 26741053 [PubMed - as supplied by publisher]

Iran J Public Health. 2015 Nov;44(11):1570-1.

Retinoic Acid Receptor Beta in Pathophysiology of Age-Related Macular Degeneration.

Tavakolifar S, Lasemi S, Mohammadgholiha S, Soheili ZS.

PMID: 26744723 [PubMed]

Epidemiology

Turk J Med Sci. 2015;45(5):1115-21.

Is Alzheimer disease related to age-related macular degeneration?

Seden D, Alime G, Kadir D, Serpil D, Levent T, Özlem T.

BACKGROUND/AIM: To compare the cognitive functions and define the frequency of Alzheimer disease (AD) between participants with and without age-related macular degeneration (AMD).

MATERIALS AND METHODS: Fifty-nine patients with late-stage AMD (74.3 ± 7.3 years) and 49 age-, sex-, and education-matched control subjects were compared for the presence of AD according to the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Detailed neuropsychological tests were performed for all subjects.

RESULTS: Neuropsychiatric tests scores were lower in the AMD group than the control group. The frequency of AD was higher in patients with AMD (40.7% in AMD and 20.4% in control group, $P = 0.03$), and particularly higher in late dry (nonvascular) AMD (d-AMD) patients (71.4% in d-AMD and 31.1% in late wet (vascular) AMD, $P = 0.007$). d-AMD patients performed worse than controls on all tests. There was also an association between age, sex, and low education and neuropsychiatric tests scores ($P < 0.01$). However, there was no association between visual acuity and neuropsychiatric tests scores.

CONCLUSION: The increased frequency of AD in patients with AMD is significant. This study demonstrated the importance of cognitive assessment in patients with AMD, particularly in the d-AMD type.

PMID: 26738356 [PubMed - in process]

Turk J Med Sci. 2015;45(5):1004-9.

Age-related macular degeneration and Alzheimer disease.

Çerman E, Eraslan M, Çekiç O.

Abstract: This review highlight the similarities in the pathogenesis between Alzheimer disease and age-related macular degeneration. All studies published between 1990 and 2014 were reviewed to identify the common pathological pathways. Alzheimer disease and age-related macular degeneration share common features such as vitronectin and amyloid- β accumulation, increased oxidative stress, and apolipoprotein and complement activation pathways, which are reviewed as histologic and immunologic common features.

PMID: 26738339 [PubMed - in process]

BMC Res Notes. 2015 Dec 30;8(1):833.

Macular disease research in the United Kingdom 2011-2014: a bibliometric analysis of outputs, performance and coverage.

Royle P, Waugh N.

BACKGROUND: Bibliometric indicators, based on measuring patterns of publications and citations, are widely used by universities and research funders to assess research performance. Our aims were to: (1) perform a bibliometric analysis of UK macular disease research publications from 2011 to 2014 and compare this with the other countries producing major output in the area, and (2) compare the pattern of UK macular disease publication with the priorities for age-related macular degeneration (AMD) developed by the Sight Loss and Vision Priority Setting Partnership (SLV-PSP).

METHODS: We used the Scopus database to retrieve macular disease articles published from 2011 to 2014. Citations to articles from 2011 to 2013 and journal impact factors (JIFs) for 2014 articles were obtained. Articles with UK authors were allocated to the 10 SLV-PSP priorities for age-related macular degeneration (AMD), where possible.

RESULTS: The UK, USA, and Germany and China were the top four producers of macular disease research from 2011 to 2013. All except China had a higher proportion of citations than articles. There were 421 articles with UK authors published from 2011 to 2014, of which 49 % had international collaborators.

The UK produced 9.7 % of the world's output of macular disease articles from 2011 to 2013, but received 14.2 % of the world's share of citations. UK authors' share of the world's top 10 % of cited publications from 2011 to 2013 was 16.2 %. In 2014, 13.2 % of UK articles were in journals in the top 10 % when ranked by Journal Impact Factors (JIFs), while the overall UK article share for that year was 9.9 %. UK articles did not show a strong correlation between citations and JIFs. The SLV-PSP published a set of 10 priorities for research into age-related macular degeneration in October 2103. Only 8 % of the UK's 2011-2014 publications matched the SLV-PSP top priority (treatment to stop dry AMD progressing) and 34 % did not match any of the SLV-PSP priorities, mainly because the priorities did not include invasive treatment of wet AMD.

CONCLUSIONS: The UK is performing well in macular research, based on bibliometric indicators. The distribution of past research topics does not match the priorities set by the SLV-PSP.

PMID: 26715430 [PubMed - in process] PMCID: PMC4696132

BMC Ophthalmol. 2015 Dec 29;15(1):188.

Population awareness of diabetic eye disease and age related macular degeneration in Nepal: the Bhaktapur Retina Study.

Thapa R, Bajimaya S, Paudyal G, Khanal S, Tan S, Thapa SS, van Rens G.

BACKGROUND: Diabetic retinopathy (DR) and age-related macular degeneration (AMD) are among the leading causes of visual impairment and blindness in developing countries. This study aims to explore the awareness of these retinal diseases in Nepal.

METHOD: A population based cross-sectional study conducted among individuals 60 years and older from the Bhaktapur district of Nepal. One thousand consecutive subjects were enrolled and subjected to a structured questionnaire.

RESULT: Subject age ranged from 60 to 93 years with a mean of 69.5 years $\pm$ 7.1 (S.D.). Males and females comprised 45.1 and 55.9 % of the population, respectively. The majority was illiterate (78.2 %), and agriculture was the predominant occupation (79.8 %). 12.1 % were aware of the effect of diabetes on the eye, and among them, 99 % were aware that diabetes was a blinding disease caused by DR. 11.5 % of the subjects were aware of DR, and 10.1 % were aware that subjects with diabetes should undergo periodic eye examinations. Only 7.6 % of subjects were aware of AMD. 7.5 and 7.4 % were aware about its aggravation with smoking and sunlight exposure, respectively. Younger age group, males, literates, service holders, best corrected visual acuity >0.3 LogMAR, were each significantly associated with an increase in awareness of diabetic retinopathy. Smokers and those with agricultural occupations were less aware regarding AMD. Those with diabetes, with or without DR were significantly more aware than those not having the disease.

CONCLUSION: Among the Bhaktapur population, awareness of DR and AMD was only 11.5 and 7.6 % respectively. Older age groups, females, illiterates, farmers, and those with poor visual acuity were less aware of these blinding diseases. We recommend community-based eye health education programs targeted at raising awareness of these diseases and preventive measures.

PMID: 26714483 [PubMed - in process] PMCID: PMC4696239

J Ophthalmic Vis Res. 2015 Jul-Sep;10(3):279-85.

Prevalence and Causes of Visual Impairment and Blindness in Central Iran; The Yazd Eye Study.

Katibeh M, Pakravan M, Yaseri M, Pakbin M, Soleimanizad R.

PURPOSE: To determine the prevalence and causes of blindness and visual impairment (VI) in Yazd,

central Iran.

METHODS: This population-based, cross-sectional study was performed on adults aged 40-80 years, residing in Yazd district, in 2010-2011. Eligible subjects were selected using cluster random sampling. Each participant underwent an interview and complete ophthalmologic examination. Blindness and VI were defined as best-corrected visual acuity (VA) $<3/60$ and $<6/18$ in the better eye, respectively.

RESULTS: Out of 2,320 eligible individuals, 2,098 participated in the study (90.4% response rate), of whom, 2,023 subjects completed all evaluations. The standardized prevalence of blindness and VI were 0.7% (95% confidence interval [CI], 0.3-1.0%) and 4.4% (95% CI, 3.3-5.4%), respectively which was significantly associated with older age (odd ratio [OR] = 3.2, 95% CI: 1.9-5.2 and OR = 3.1, 95% CI: 2.3-4.2, respectively) and female sex (OR = 3.6, 95% CI: 1.1-12.3 and OR = 1.7, 95% CI: 1.2-2.5, respectively). The proportion of avoidable causes of blindness and VI were 92.9% (95% CI: 80.0-100.0%) and 76.6% (95% CI: 69.2-85.0%), respectively. Major causes of blindness were diabetic retinopathy (50.0%), glaucoma (21.4%) and cataracts (14.3%) whereas main causes of VI were cataracts (41.5%), diabetic retinopathy (17.0%) and age-related macular degeneration (13.8%).

CONCLUSIONS: Diabetic retinopathy, glaucoma, cataract and age-related macular degeneration were the leading causes of blindness and VI in Yazd, most of which are avoidable. Planning for prevention of blindness is highly recommended to decrease the proportion of avoidable blindness.

PMID: 26730314 [PubMed] PMCID: PMC4687262

Genetics

Nat Genet. 2015 Dec 21. [Epub ahead of print]

A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants.

Fritsche LG, Igl W, Bailey JN, et al

Abstract: Advanced age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, with limited therapeutic options. Here we report on a study of >12 million variants, including 163,714 directly genotyped, mostly rare, protein-altering variants. Analyzing 16,144 patients and 17,832 controls, we identify 52 independently associated common and rare variants ($P < 5 \times 10^{-8}$) distributed across 34 loci. Although wet and dry AMD subtypes exhibit predominantly shared genetics, we identify the first genetic association signal specific to wet AMD, near MMP9 (difference P value = 4.1×10^{-10}). Very rare coding variants (frequency $<0.1\%$) in CFH, CFI and TIMP3 suggest causal roles for these genes, as does a splice variant in SLC16A8. Our results support the hypothesis that rare coding variants can pinpoint causal genes within known genetic loci and illustrate that applying the approach systematically to detect new loci requires extremely large sample sizes.

PMID: 26691988 [PubMed - as supplied by publisher]

Hum Mol Genet. 2016 Jan 6. [Epub ahead of print]

A dominant mutation in MAPKAPK3, an actor of p38 signaling pathway, causes a new retinal dystrophy involving Bruch's membrane and retinal pigment epithelium.

Meunier I, Lenaers G, Bocquet B, et al

Abstract: Inherited retinal dystrophies are clinically and genetically heterogeneous with significant number of cases remaining genetically unresolved. We studied a large family from the West Indies islands with a peculiar retinal disease, the Martinique Crinkled Retinal Pigment Epitheliopathy that begins around the age of 30 with retinal pigment epithelium and Bruch's membrane changes resembling a dry desert land, and

ends with a retinitis pigmentosa. Whole-exome sequencing identified a heterozygous c.518T>C (p.Leu173Pro) mutation in MAPKAPK3 that segregates with the disease in 14 affected and 28 unaffected siblings from three generations. This unknown variant is predicted to be damaging by bioinformatic predictive tools, and the mutated protein to be nonfunctional by crystal structure analysis. MAPKAPK3 is a serine/threonine protein kinase of the p38 signaling pathway that is activated by a variety of stress stimuli, and is implicated in cellular responses and gene regulation. In contrast to other tissues, MAPKAPK3 is highly expressed in the retinal pigment epithelium, suggesting a crucial role for retinal physiology. Expression of the mutated allele in HEK cells revealed a mislocalization of the protein in the cytoplasm, leading to cytoskeleton alteration and cytodieresis inhibition. In Mapkapk3^{-/-} mice, Bruch's membrane is irregular with both abnormal thickened and thinned portions. In conclusion, we identified the first pathogenic mutation in MAPKAPK3 associated with a retinal disease. These findings shed new lights on Bruch's membrane/retinal pigment epithelium pathophysiology and will open studies of this signaling pathway in diseases with retinal pigment epithelium and Bruch's membrane alterations, such as age-related macular degeneration.

PMID: 26744326 [PubMed - as supplied by publisher]

Eur J Hum Genet. 2016 Jan 6. [Epub ahead of print]

Common coding variants in the HLA-DQB1 region confer susceptibility to age-related macular degeneration.

Jorgenson E, Melles RB, Hoffmann TJ, Jia X, Sakoda LC, Kvale MN, Banda Y, Schaefer C, Risch N, Shen L.

Abstract: Age-related macular degeneration (AMD) risk variants in the complement system point to the important role of immune response and inflammation in the pathogenesis of AMD. Although the human leukocyte antigen (HLA) region has a central role in regulating immune response, previous studies of genetic variation in HLA genes and AMD have been limited by sample size or incomplete coverage of the HLA region by first-generation genotyping arrays and imputation panels. Here, we conducted a large-scale HLA fine-mapping study with 4841 AMD cases and 23 790 controls of non-Hispanic white ancestry from the Kaiser Permanente Genetic Epidemiology Research on Adult Health and Aging cohort. Genotyping was conducted using custom Affymetrix Axiom arrays, with dense coverage of the HLA region. Classic HLA polymorphisms were imputed using SNP2HLA, which utilizes a large reference panel to provide improved imputation accuracy of variants in this region. We examined a total of 6937 SNPs and 172 classical HLA alleles, conditioning on established AMD risk variants, which revealed novel associations with two non-synonymous SNPs in perfect linkage disequilibrium, rs9274390 and rs41563814 (odds ratio (OR)=1.21; $P=1.4 \times 10^{-11}$) corresponding to amino-acid changes at position 66 and 67 in HLA-DQB1, respectively, and the DQB1*02 classical HLA allele (OR=1.22; $P=3.9 \times 10^{-10}$) with the risk of AMD. We confirmed these association signals, again conditioning on established risk variants, in the MMAP data set of subjects with advanced AMD (rs9274390/rs41563814: OR=1.28; $P=1.30 \times 10^{-3}$, DQB1*02: OR=1.32; $P=9.00 \times 10^{-4}$). These findings support a role of HLA class II alleles in the risk of AMD.

PMID: 26733291 [PubMed - as supplied by publisher]

Curr Eye Res. 2016 Jan 5:1-10. [Epub ahead of print]

Probable Chemical Hypoxia Effects on Progress of CNV Through Induction of Promoter CpG demethylation and Overexpression of IL17RC in Human RPE Cells.

Alivand MR, Sabouni F, Soheili ZS.

PURPOSE: To survey the changes of promoter CpG methylation status and mRNA expression of IL17RC (interleukin 17 receptor C) gene in retinal pigment epithelium (RPE) cells under chemical hypoxia condition for choroidal neovascularization (CNV) modeling in vitro.

MATERIALS AND METHODS: RPE cells were cultured in both untreated as a control group and treated by cobalt chloride media as a hypoxia group for various concentrations (100-150 μ M) and times (24-36 hrs.) To confirm chemical hypoxia condition, mRNA expression of HIF (Hypoxia Inducible Factor) -1 α , -2 α , and Vascular Endothelial Growth Factor (VEGF) was compared between two groups by Real-time PCR. Also, in normoxia and hypoxia conditions, IL17RC expression changes and promoter CpG methylation status were evaluated by Real-time PCR and methylation-specific PCR (MSP) techniques, respectively.

RESULTS: Overexpression of HIF-1 α , HIF-2 α , and VEGF was significant in hypoxia versus normoxia conditions. Our data showed overexpression of IL17RC (2.1- to 6.3-fold) and decreasing of its promoter methylation in comparison with hypoxia and normoxia conditions. It was found that there are significant association between promoter methylation status and expression of IL17RC in chemical hypoxia condition.

CONCLUSION: Therefore, methylation of IL17RC could play as a marker in CNV and degeneration of RPE cells in vitro. Additionally, HIF- α and methylation phenomena may be considered as critical targets for blocking in angiogenesis of age-related degeneration in future studies.

PMID: 26731132 [PubMed - as supplied by publisher]

Ophthalmic Res. 2016 Jan 5;55(3):135-144. [Epub ahead of print]

Association of Two Polymorphisms, rs1061170 and rs1410996, in Complement Factor H with Age-Related Macular Degeneration in an Asian Population: A Meta-Analysis.

Wu M, Guo Y, Ma Y, Zheng Z, Wang Q, Zhou X.

BACKGROUND: With the increasing number of studies indicating that two single-nucleotide polymorphisms (SNPs), rs1061170 and rs1410996, in complement factor H (CFH) might be associated with the susceptibility to age-related macular degeneration (AMD), the exact association still remains uncertain. Thus, we conducted a meta-analysis to systematically summarize and clarify the association between the two SNPs and the AMD risk particularly in an Asian population.

METHODS: A systematic search of studies on the association of two SNPs with the susceptibility to AMD was conducted in PubMed, Embase and Web of Science. Summary odds ratios (ORs) and 95% confidence intervals (CIs) of allele contrast and genotype contrast were estimated using the random or fixed effects model. The Q statistic test was used to identify heterogeneity, and the funnel plot was adopted to evaluate publication bias. A total of 19 case-control studies on rs1061170 and 8 studies on rs1410996 were included.

RESULTS: Clearly a significantly increased trend of AMD was observed with the rs1061170 (T vs. C: OR = 1.91, 95% CI = 1.71-2.13, pH = 0.029; TC vs. CC: OR = 2.11, 95% CI = 1.30-3.42, pH = 0.792; TT vs. CC: OR = 3.90, 95% CI = 2.45-6.22, pH = 0.774). Similarly, the rs1410996 polymorphism also showed a rising AMD tendency (T vs. C: OR = 1.48, 95% CI = 1.17-1.87, pH < 0.001; TC vs. CC: OR = 1.52, 95% CI = 1.13-2.04, pH = 0.002; TT vs. CC: OR = 2.10, 95% CI = 1.27-3.49, pH < 0.001). What is more, subgroup analysis revealed that both polymorphisms indicated a high risk of nAMD (neovascular AMD) in Asian populations.

CONCLUSIONS: This meta-analysis suggested that CFH rs1061170 and rs1410996 polymorphisms were associated with AMD risk, both of which demonstrated a higher susceptibility to AMD, especially to nAMD. However, the results of rs1410996 should be interpreted with caution due to the limited sample and heterogeneity. Large-scale and well-designed studies are needed to validate our findings.

PMID: 26727378 [PubMed - as supplied by publisher]

Stem cells

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8258-67.

Generating iPSC-Derived Choroidal Endothelial Cells to Study Age-Related Macular Degeneration.

Songstad AE, Wiley LA, Duong K, Kaalberg E, Flamme-Wiese MJ, Cranston CM, Riker MJ, Levasseur D, Stone EM, Mullins RF, Tucker BA.

PURPOSE: Age-related macular degeneration (AMD), the most common cause of incurable blindness in the western world, is characterized by the dysfunction and eventual death of choroidal endothelial (CECs), RPE, and photoreceptor cells. Stem cell-based treatment strategies designed to replace photoreceptor and RPE cells currently are a major scientific focus. However, the success of these approaches likely also will require replacement of the underlying, supportive choroidal vasculature. The purpose of this study was to generate stem cell-derived CECs to develop efficient differentiation and transplantation protocols.

METHODS: Dermal fibroblasts from the Tie2-GFP mouse were isolated and reprogrammed into two independent induced pluripotent stem cell (iPSC) lines via viral transduction of the transcription factors Oct4, Sox2, Klf4, and c-Myc. Tie2-GFP iPSCs were differentiated into CECs using a coculture method with either the RF6A CEC line or primary mouse CECs. Induced pluripotent stem cell-derived CECs were characterized via RT-PCR and immunocytochemistry for EC- and CEC-specific markers.

RESULTS: Induced pluripotent stem cells generated from mice expressing green fluorescent protein (GFP) under control of the endothelial Tie2 promoter display classic pluripotency markers and stem cell morphology. Induced pluripotent stem cell-derived CECs express carbonic anhydrase IV, eNOS, FOXA2, PLVAP, CD31, CD34, ICAM-1, Tie2, TTR, VE-cadherin, and vWF.

CONCLUSIONS: Induced pluripotent stem cell-derived CECs will be a valuable tool for modeling of choriocapillaris-specific insults in AMD and for use in future choroidal endothelial cell replacement approaches.

PMID: 26720480 [PubMed - in process]

Brain Res. 2015 Dec 17. [Epub ahead of print]

Looking into the future: Using induced pluripotent stem cells to build two and three dimensional ocular tissue for cell therapy and disease modeling.

Song MJ, Bharti K.

Abstract: Retinal degenerative diseases are the leading cause of irreversible vision loss in developed countries. In many cases the diseases originate in the homeostatic unit in the back of the eye that contains the retina, retinal pigment epithelium (RPE) and the choriocapillaris. RPE is a central and a critical component of this homeostatic unit, maintaining photoreceptor function and survival on the apical side and choriocapillaris health on the basal side. In diseases like age-related macular degeneration (AMD), it is thought that RPE dysfunctions cause disease-initiating events and as the RPE degenerates photoreceptors begin to die and patients start losing vision. Patient-specific induced pluripotent stem (iPS) cell-derived RPE provides direct access to a patient's genetics and allow the possibility of identifying the initiating events of RPE-associated degenerative diseases. Furthermore, iPS cell-derived RPE cells are being tested as a potential cell replacement in disease stages with RPE atrophy. In this article we summarize the recent progress in the field of iPS cell-derived RPE "disease modeling" and cell therapies and also discuss the possibilities of developing a model of the entire homeostatic unit to aid in studying disease processes in the future.

PMID: 26706569 [PubMed - as supplied by publisher]

Diet, lifestyle and low vision

Int J Mol Sci. 2015 Dec 16;16(12):29900-10.

Effect of Guibi-Tang, a Traditional Herbal Formula, on Retinal Neovascularization in a Mouse Model of Proliferative Retinopathy.

Lee YM, Lee YR, Kim CS, Jo K, Sohn E, Kim JS, Kim J.

Abstract: Ocular pathologic angiogenesis is an important causative risk factor of blindness in retinopathy of prematurity, proliferative diabetic retinopathy, and neovascular macular degeneration. Guibi-tang (GBT) is a frequently used oriental herbal formula in East Asian countries, and is also called Qui-pi-tang in Chinese and Kihi-To in Japanese. In the present study, we investigated the preventive effect of GBT on retinal pathogenic neovascularization in a mouse model of oxygen-induced retinopathy (OIR). C57BL/6 mice were exposed to 75% hyperoxia for five days on postnatal day 7 (P7). The mice were then exposed to room air from P12 to P17 to induce ischemic proliferative retinopathy. GBT (50 or 100 mg/kg/day) was intraperitoneally administered daily for five days (from P12 to P16). On P17, Retinal neovascularization was measured on P17, and the expression levels of 55 angiogenesis-related factors were analyzed using protein arrays. GBT significantly decreased retinal pathogenic angiogenesis in OIR mice, and protein arrays revealed that GBT decreased PAI-1 protein expression levels. Quantitative real-time PCR revealed that GBT reduced vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF2), and plasminogen activator inhibitor 1 (PAI-1) mRNA levels in OIR mice. GBT promotes potent inhibitory activity for retinal neovascularization by decreasing VEGF, FGF2, and PAI-1 levels.

PMID: 26694358 [PubMed - in process] Free full text

Invest Ophthalmol Vis Sci. 2015 Dec 1;56(13):8069-74.

Oral Lutein Supplementation Enhances Macular Pigment Density and Contrast Sensitivity but Not in Combination With Polyunsaturated Fatty Acids.

Wolf-Schnurbusch UE, Zinkernagel MS, Munk MR, Ebnetter A, Wolf S.

PURPOSE: It has been shown that lutein and zeaxanthin accumulate in the macula where they enhance contrast sensitivity and may reduce the risk of progression to advanced age-related macular degeneration (AMD). Furthermore, omega-3 long-chain polyunsaturated fatty acids (PUFA) might further reduce this risk. However, controversy exists regarding whether PUFA may reduce the bioavailability of lutein.

METHODS: This was a prospective 12-month, randomized, open label study evaluating the effect of supplementation with lutein, other antioxidants, and minerals on contrast sensitivity (CS) and macular pigment optical density (MPOD) in patients with age-related maculopathy. A total of 79 patients were randomized to either lutein (10 mg) and antioxidant supplement or lutein and antioxidant supplement in combination with PUFA. Patients received supplementation for a period of 6 months and were followed for a total of 12 months.

RESULTS: Serum lutein and zeaxanthin increased significantly by the first follow-up visit at 1 month, and remained elevated throughout the intervention period of 6 months in the lutein-only group but not in the lutein+PUFA group. Macular pigment optical density and CS increased significantly in the lutein-only group ($P < 0.005$) but not in the lutein+PUFA group ($P = 0.059$) compared to baseline. Best-corrected visual acuity remained unchanged during the entire study period in both groups.

CONCLUSIONS: Addition of PUFA may reduce the bioavailability of lutein and therefore lessen the beneficial effect on macular pigment and CS. This needs to be considered when prescribing lutein supplements to patients with low lutein levels. (ClinicalTrials.gov number, NCT00563979.).

PMID: 26720458 [PubMed - in process]

Molecules. 2015 Dec 14;20(12):22395-410.

Retinoprotective Effects of Bilberry Anthocyanins via Antioxidant, Anti-Inflammatory, and Anti-Apoptotic Mechanisms in a Visible Light-Induced Retinal Degeneration Model in Pigmented Rabbits.

Wang Y, Zhao L, Lu F, Yang X, Deng Q, Ji B, Huang F.

Abstract: Excessive visible light exposure can induce damage to retinal cells and contribute to the development or progression of age-related macular degeneration. In this study we created a model of phototoxicity in pigmented rabbits. Furthermore, we investigated the protective effect of bilberry anthocyanin extract (BAE, Table A1) and explored the possible mechanisms of action in this model. The model of light-induced retinal damage was established by the pigmented rabbits exposed to light at 18,000 lx for 2 h, and they were sacrificed on day 7. After administration of BAE at dosages of 250 and 500 mg/kg/day, retinal dysfunction was significantly inhibited in terms of electroretinograms, and the decreased thicknesses of retinal outer nuclear layer and lengths of the outer segments of the photoreceptor cells were suppressed in rabbits with retinal degeneration. BAE attenuated the changes caused by light to certain apoptotic proteins (Bax, Bcl-2, and caspase-3). The extract increased the levels of superoxide dismutase, glutathione peroxidase, and catalase, as well as the total antioxidant capacity, but decreased the malondialdehyde level in the retinal cells. BAE inhibited the light-induced elevation in the levels of proinflammatory cytokines and angiogenic parameters (IL-1 β and VEGF). Results showed that visible light-induced retinal degeneration model in pigmented rabbits was successfully established and BAE exhibited protective effects by increasing the antioxidant defense mechanisms, suppressing lipid peroxidation and proinflammatory cytokines, and inhibiting retinal cells apoptosis.

PMID: 26694327 [PubMed - in process]

Prim Care Companion CNS Disord. 2015 Aug 20;17(4). eCollection 2015.

Association of Ophthalmologic Disorders and Depression in the Elderly: A Review of the Literature.

McCusker S, Koola MM.

OBJECTIVE: To review the prevalence of depression in common ophthalmologic disorders in the elderly and provide insight into treatment.

DATA SOURCES: PubMed, Google Scholar, and DynaMed were searched using the terms depression and ophthalmology in combination with depression, mood disorders, cataracts, vision loss, age-related macular degeneration, primary open-angle glaucoma, and Fuchs corneal dystrophy. Articles were limited to those published in the English language between 1993 and 2013.

STUDY SELECTION AND DATA EXTRACTION: Twenty-eight articles that studied the prevalence of depression in ophthalmologic disorders were screened and summarized.

RESULTS: The strongest association between ophthalmologic disorders and psychiatry is depression. In the future, primary care physicians and psychiatrists should play a significant role in the assessment and treatment of depression in visually impaired patients.

CONCLUSION: Greater recognition and treatment of depression in individuals with impaired vision is warranted.

PMID: 26693037 [PubMed] PMCID: PMC4664565

Purinergic Signal. 2016 Jan 7. [Epub ahead of print]

Saffron reduces ATP-induced retinal cytotoxicity by targeting P2X7 receptors.

Corso L, Cavallero A, Baroni D, Garbati P, Prestipino G, Bisti S, Nobile M, Picco C.

Abstract: P2X7-type purinergic receptors are distributed throughout the nervous system where they contribute to physiological and pathological functions. In the retina, this receptor is found in both inner and outer cells including microglia modulating signaling and health of retinal cells. It is involved in retinal neurodegenerative disorders such as retinitis pigmentosa and age-related macular degeneration (AMD). Experimental studies demonstrated that saffron protects photoreceptors from light-induced damage preserving both retinal morphology and visual function and improves retinal flicker sensitivity in AMD patients. To evaluate a possible interaction between saffron and P2X7 receptors (P2X7Rs), different cellular models and experimental approaches were used. We found that saffron positively influences the viability of mouse primary retinal cells and photoreceptor-derived 661W cells exposed to ATP, and reduced the ATP-induced intracellular calcium increase in 661W cells. Similar results were obtained on HEK cells transfected with recombinant rat P2X7R but not on cells transfected with rat P2X2R. Finally, patch-clamp experiments showed that saffron inhibited cationic currents in HEK-P2X7R cells. These results point out a novel mechanism through which saffron may exert its protective role in neurodegeneration and support the idea that P2X7-mediated calcium signaling may be a crucial therapeutic target in the treatment of neurodegenerative diseases.

PMID: 26739703 [PubMed - as supplied by publisher]

Fitoterapia. 2015 Dec 17;109:58-66. [Epub ahead of print]

Zeaxanthin and ocular health, from bench to bedside.

Manikandan R, Thiagarajan R, Goutham G, Arumugam M, Beulaja M, Rastrelli L, Skalicka-Woźniak K, Habtemariam S, Orhan IE, Nabavi SF, Nabavi SM.

Abstract: Cataracts, glaucoma, and age-related macular degeneration are known as major ocular problems which cause blindness among the elderly population worldwide. Oxidative stress plays an important role in both the initiation and progression of ocular problems and with respect to this; dietary antioxidants can serve as a therapeutic strategy for the improvement of ocular health. Zeaxanthin is known as one of the most important and common xanthophyll carotenoids, possessing multiple therapeutic effects such as strong antioxidant and pro-oxidant behaviour as well as anti-inflammatory effects. A growing body of literature shows that zeaxanthin mitigates ocular problems and suppresses oxidative stress in the retinal tissues. This paper aims to critically review the available literature regarding the beneficial effects of zeaxanthin on ocular problems with emphasis on its chemistry, bioavailability, and sources.

PMID: 26705841 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2015 Dec 18. [Epub ahead of print]

Visual exploration of objects and scenes in patients with age-related macular degeneration.

Thibaut M, Delerue C, Boucart M, Tran TH.

OBJECTIVE: Studies on people with age-related macular degeneration (AMD) have shown that they are able to detect briefly displayed objects and scenes with high accuracy (above 80%). However, in everyday life we explore our environment to search and to recognize objects. We assessed visual exploration in people with AMD during the identification of objects and scenes.

METHOD: Twenty patients with AMD, fifteen age-matched and twelve young controls participated. We used colored photographs of isolated objects, natural scenes and objects in scenes, displayed centrally on a monitor. Participants were asked to name the objects and scenes. Ocular movements were recorded during the identification task. Scan paths, saccades, fixations, and accuracy were also recorded.

RESULTS: People with AMD exhibited lower accuracy (by about 30%). Eye movement parameters were impaired with a larger number of saccades, shorter fixation durations and a larger scan path than controls.

CONCLUSIONS: Our results are consistent with studies on artificial scotoma in normally sighted people showing that a central scotoma impairs oculomotricity. In contrast to detection tasks, people with central vision loss exhibit impaired performance in identification of objects and scenes (62 to 66%). Eye movement studies suggest that the lower accuracy in patients is likely due to the use of peripheral vision and instability of fixation.

PMID: 26707755 [PubMed - as supplied by publisher]

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