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MD Research News

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Drug treatment

Am J Ophthalmol. 2014 Nov 18. [Epub ahead of print]

One-Year Outcomes of Aflibercept in Recurrent or Persistent Neovascular Age-Related Macular Degeneration.

Arcinue CA, Ma F, Barteselli G, Sharpsten L, Gomez ML, Freeman WR.

PURPOSE: To evaluate 6-month and 1-year outcomes of every 8 weeks (Q8W) aflibercept in patients with resistant neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective, interventional, consecutive case series.

METHODS: Retrospective review of patients with resistance (multiple recurrences or persistent exudation) to every 4 weeks (Q4W) ranibizumab or bevacizumab that were switched to Q8W aflibercept.

RESULTS: Sixty-three eyes of 58 patients had a median of 13 (interquartile range (IQR), 7-22) previous anti Vascular Endothelial Growth Factor (anti-VEGF) injections. At 6-months after changing to aflibercept, 60.3% of eyes were completely dry, which was maintained up to one-year. The median maximum retinal thickness improved from 355 microns to 269 microns at 6 months ($p<0.0001$) and 248 microns at one year ($p<0.0001$). There was no significant improvement in ETDRS visual acuity at 6 months ($p=0.2559$) and one-year follow-up ($p=0.1081$) compared with baseline. The mean difference in ETDRS visual acuity compared to baseline at 6 months was -0.05 logMAR (+2.5 letters) and 0.04 logMAR at 1 year (-2 letters).

CONCLUSION: Sixty percent of eyes with resistant AMD while on Q4W ranibizumab or bevacizumab were completely dry after changing to Q8W aflibercept at the 6-month and 1-year follow-ups, but visual acuity did not significantly improve. Only a third of eyes needed to be switched from Q8W to Q4W aflibercept due to persistence of fluid; Q8W dosing of aflibercept without the initial 3 monthly loading doses may be a good alternative in a select group of patients who may have developed ranibizumab or bevacizumab resistance.

PMID: 25461263 [PubMed - as supplied by publisher]

Ophthalmologica. 2014 Nov 29. [Epub ahead of print]

Ranibizumab plus Verteporfin Photodynamic Therapy in Neovascular Age-Related Macular Degeneration: 12 Months of Retreatment and Vision Outcomes from a Randomized Study.

Hatz K, Schneider U, Henrich PB, Braun B, Sacu S, Prünte C.

Purpose: To investigate the injection frequency and visual acuity (VA) outcomes with combination therapy (ranibizumab plus verteporfin photodynamic therapy, PDT) versus monotherapy (ranibizumab).

Methods: A total of 40 patients with exudative age-related macular degeneration were randomized 1:1 to ranibizumab 0.3 mg plus single standard verteporfin PDT or ranibizumab 0.3 mg plus sham PDT. Ranibizumab was administered 3 times monthly followed by 'as needed' to month 12 based on predetermined vision/anatomical criteria. Retreatment rates, VA outcomes and safety were assessed.

Results: During months 3-12, combination therapy patients required fewer ranibizumab injections (mean 1.3) compared with monotherapy patients (2.8). Mean VA improved by 9.0 letters with combination therapy versus 7.5 letters in the monotherapy group at month 12. Both treatment regimens were well tolerated.

Conclusion: The need for ranibizumab retreatment might be reduced by administering a single verteporfin PDT on the same day as the first ranibizumab injection, without compromising VA outcomes or safety. © 2014 S. Karger AG, Basel.

PMID: 25471330 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2014 Nov 29:0. [Epub ahead of print]

Two week, OCT-based follow-up as guidance for retreatment with ranibizumab for CNV apparently refractory to therapy.

Manousaridis K, Talks J.

PURPOSE: To assess the value of 2-week optical coherence tomography (OCT) follow-up for re-treatment decision-making in patients receiving monthly ranibizumab injections for choroidal neovascular membrane (CNV), which was apparently refractory to treatment.

METHODS: A total of 25 eyes of 25 consecutive patients with refractory CNV were included. Patients were classified as having refractory disease if no visual acuity (VA) change and no change in the pattern of macular fluid was noticed on OCT after at least 3 consecutive monthly injections, excluding the loading doses. Repeat injection was given and reassessment with VA and OCT was undertaken at 2, 4, 8, and 12 weeks.

RESULTS: Complete resolution or marked reduction of macular fluid was noted in 19 patients at 2 weeks (responders). In 18 responders, the fluid increased on 4- and persisted on 8- and 12-week follow-ups, so that further injections were given at these time points. In 6 patients, no significant change was noted at 2 weeks (nonresponders). In all of them, VA and OCT were stable on 4-, 8-, and 12-week follow-ups, without further injections.

CONCLUSIONS: As some patients are responding for at least part of the month, injections may be worth continuing or possibly more frequent injections, tailored to the individual's response, may need to be considered. Alternative therapies such as aflibercept may also need to be considered. In nonresponding eyes, other cytokines except for vascular endothelial growth factor are probably involved in the pathogenesis or such cases may have structural damage that will not respond to therapy.

PMID: 25449645 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Nov 6. [Epub ahead of print]

Improvement in Vision-Related Function with Intravitreal Aflibercept: Data from Phase 3 Studies in Wet Age-Related Macular Degeneration.

Yuzawa M, Fujita K, Wittrup-Jensen KU, Norenberg C, Zeitz O, Adachi K, Wang EC, Heier J, Kaiser P, Chong V, Korobelnik JF.

PURPOSE: To evaluate the effect of intravitreal aflibercept injection on visual function in wet age-related macular degeneration (AMD).

DESIGN: Prospective, multicenter, double-masked, active-controlled, parallel-group, randomized phase 3 clinical studies (VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD [VIEW] 1 and 2 [clinicaltrials.gov identifiers, NCT00509795 and NCT00637377, respectively]).

PARTICIPANTS: Patients (n = 2419) with active, treatment-naïve, exudative AMD. This analysis included patients who received intravitreal aflibercept 2.0 mg every 8 weeks (2q8; n = 607) or ranibizumab 0.5 mg every 4 weeks (0.5q4; n = 595).

INTERVENTION: Patients were randomized 1:1:1:1 to receive intravitreal aflibercept 2q8 (after 3 initial monthly doses), intravitreal aflibercept 2q4, intravitreal aflibercept 0.5q4, or ranibizumab 0.5q4 in the study eye. Patients in the intravitreal aflibercept 2q8 group received a sham injection alternating with active treatment.

MAIN OUTCOME MEASURES: The 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) was administered at baseline and at weeks 12, 24, 36, and 52. The NEI VFQ-25 subscale scores were compared between intravitreal aflibercept 2q8 and ranibizumab 0.5q4 treatment arms, the approved dosing for each agent worldwide. Change in composite NEI VFQ-25 score was evaluated based on categorical change in visual acuity (worsened, unchanged, improved).

RESULTS: Baseline NEI VFQ-25 scores were similar for both treatments in both studies. Mean change from baseline to 52 weeks was similar for ranibizumab 0.5q4 and intravitreal aflibercept 2q8 across all 12 subscales, with the greatest improvements noted for mental health and general vision (9.0-11.6 points, both treatments, both studies). Improvement of 4 points or more (both treatments, both studies) also was observed for subscales near vision, distance vision, role difficulties, and dependency. Mean change from baseline to 52 weeks in NEI VFQ-25 composite score (pooled data) stratified by clinical response showed meaningful improvement only in patients who gained 5 Early Treatment Diabetic Retinopathy letters or more (7.3 and 7.8 points for intravitreal aflibercept 2q8 and ranibizumab 0.5q4, respectively).

CONCLUSIONS: Visual function outcomes were similar across all NEI VFQ-25 subscales over 52 weeks for intravitreal aflibercept 2q8 and ranibizumab 0.5q4, with clinically meaningful improvement recorded in 6 of 12 subscales.

PMID: 25439429 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Nov 6. [Epub ahead of print]

Time to Initial Clinician-Reported Inactivation of Neovascular Age-Related Macular Degeneration Treated Primarily with Ranibizumab.

Gillies MC, Campain A, Walton R, Simpson JM, Arnold JJ, Guymer RH, McAllister IL, Hunyor AP, Essex RW, Morlet N, Barthelmes D; Fight Retinal Blindness Study Group*.

PURPOSE: To characterize in more detail routine treatment patterns of intravitreal ranibizumab for neovascular age-related macular degeneration (nAMD), we analyzed the length of time and the number of injections required until lesions with choroidal neovascularization (CNV) were first graded inactive.

DESIGN: Database observational study.

PARTICIPANTS: Treatment-naïve eyes receiving predominantly ranibizumab for nAMD in routine clinical practice that were tracked in the Fight Retinal Blindness! observational registry.

METHODS: Eyes treated with ranibizumab were followed until CNV was first reported to be "inactive" (i.e., absence of intraretinal fluid and hemorrhages).

MAIN OUTCOME MEASURES: The length of time until lesion inactivation occurred and the number of injections required.

RESULTS: A total of 1096 eyes (65.8% from women) were included in the study. The median number of

weeks until a lesion was graded as inactive after beginning treatment was 15 weeks. One to 3 injections were sufficient to inactivate the lesion in 61.1% of eyes. A mean change in visual acuity of +5.5 logarithm of the minimum angle of resolution letters (95% confidence interval, 4.8-6.3) was found from treatment initiation to the time that eyes were reported as inactive. In eyes with a mean treatment frequency less than every 5.3 weeks, a median of only 3 injections (mean = 3.7) were required before lesions with CNV were graded as inactive, but if the mean treatment interval extended beyond 5.3 weeks, the median number of injections required increased sharply to 6 injections (mean, 7 injections). Occult lesions became inactive more slowly than classic lesions.

CONCLUSIONS: Most lesions with CNV became inactive with 3 injections of ranibizumab, but a small proportion remained active for more than 12 months. Injection frequency and lesion type were the main factors that predicted the time and number of injections required to render lesions inactive.

PMID: 25458197 [PubMed - as supplied by publisher]

Case Rep Ophthalmol. 2014 Oct 22;5(3):335-342. eCollection 2014.

Management of Macular Edema Secondary to Branch Retinal Vein Occlusion in an Eye with Prior Vitrectomy and Lensectomy.

Malhotra P, Kishore K.

Abstract: An 82-year-old male with a history of pars plana vitrectomy and lensectomy 6 years before presented with symptomatic macular edema (ME) from superotemporal branch retinal vein occlusion. He was sequentially treated with intravitreal agents, bevacizumab (IVB) 1.25 mg, ranibizumab (RBZ) 0.5, 1.0 and 2 mg, triamcinolone acetonide (IVTA) 1 mg, and aflibercept (IAI) 2 mg. The therapeutic benefit from IVB and RBZ was short-lived - although a decrease in ME and improvement in visual acuity were observed, a completely dry macula was not achieved even after 1 week of treatment with any dose of these agents, including 2.0 mg RBZ. IVTA achieved a dry macula for 7 weeks. IAI yielded a dry macula and improved vision with monthly injections. However, regression of the therapeutic benefit was noted at 5 weeks after the IAI injection. A stronger affinity of IAI to vascular endothelial growth factor (VEGF) compared to other anti-VEGF agents is likely responsible for the observed therapeutic effect for 1 month, making this agent preferable for the management of symptomatic ME in a vitrectomized eye.

PMID: 25473401 [PubMed - as supplied by publisher] PMCID: PMC4250002

Med Hypotheses. 2014 Oct 29;83(6):835-837. [Epub ahead of print]

Bruch's membrane diffusivity for vascular endothelial growth factors may explain variable response to wet age-related macular degeneration treatment: Clinical implications.

Peddada RR.

Abstract: The hypothesis presented is that diffusivity of vascular endothelial growth factors (VEGF) across Bruch's membrane is an important parameter that distinguishes prompt and slow responders to anti-VEGF treatment in wet age-related macular degeneration (AMD). Accordingly, slow-responders have a high diffusivity and will attain peak VEGF levels on the choroidal side of Bruch's membrane rapidly, probably before or around the time of the next monthly anti-VEGF injection. If a fixed dose of anti-VEGF is used at each monthly treatment (as is the current practice), depending on the initial level of VEGF at that time of injection, VEGF with each treatment will vary. Therefore, diffusion will occur at a different concentration gradient in each treatment cycle subsequent to the injection. Hence, by Fick's Second Law of Diffusion, the slope of the concentration versus time curve for each treatment cycle will be different from the preceding cycle. This leads to a different peak concentration just prior to the next monthly injection. So, when a fixed dose of the anti-VEGF is used at each monthly treatment peak VEGF level fluctuates instead of going down continuously which prolongs the treatment. Thus, doses of anti-VEGF may have to be tapered to decrease

the concentration gradient and to slow down the rate of diffusion of VEGF. Diffusivity of Bruch's membrane with regards to VEGF is a simple concept that can explain the variable response to anti-VEGF treatment in wet AMD. If validated through clinical trial the treatment protocol for wet AMD can be more precise and tailored to individual patients.

PMID: 25468789 [PubMed - as supplied by publisher]

Can J Diabetes. 2014 Oct 22. [Epub ahead of print]

Impact of Insulin Treatment in Diabetic Macular Edema Therapy in Type 2 Diabetes.

Matsuda S, Tam T, Singh RP, Kaiser PK, Petkovsek D, Zanella MT, Ehlers JP.

OBJECTIVE: To evaluate the impact of insulin therapy on the outcomes of diabetic macular edema (DME) treatment with vascular endothelial growth factor (VEGF) inhibitors in people with type 2 diabetes.

METHODS: A retrospective consecutive case series of 95 patients with type 2 diabetes and DME who were treated with anti-VEGF therapy. We examined 2 cohorts: patients taking only oral antidiabetic agents and patients on insulin therapy. The main outcome measures were change in visual acuity and change in central subfield macular thickness measured by spectral-domain optical coherence tomography. The additional variables analyzed included glycated hemoglobin (A1C), creatinine, blood pressure and body mass index and their correlations with clinical findings.

RESULTS: Both groups had a statistically significant improvement in visual acuity (oral antidiabetic agents group: 20/61 to 20/49, p=0.003; insulin therapy group: 20/76 to 20/56, p=0.005). There was no difference between groups at initial or 12-month examination (p=0.239 and p=0.489, respectively). From an anatomic standpoint, central subfield macular thickness also improved significantly in both groups: from 454.7 μm to 354.9 μm (p<0.001) in the oral antidiabetic agents group and from 471.5 μm to 368.4 μm (p<0.001) in the insulin therapy group. Again, there was no significant difference between groups at initial or 12-month follow-up examinations (p=0.586 and p=0.591, respectively). Mean A1C levels remained relatively stable during the follow up in both groups.

CONCLUSION: Anti-VEGF therapy is a useful treatment for DME. This study suggests that chronic insulin therapy, compared with oral antidiabetic agents, does not modify the anatomic or functional effectiveness of DME treatment.

PMID: 25444681 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Oct 28. [Epub ahead of print]

Intravitreal Ranibizumab for Diabetic Macular Edema with Prompt versus Deferred Laser Treatment: 5-Year Randomized Trial Results.

Elman MJ, Ayala A, Bressler NM, Browning D, Flaxel CJ, Glassman AR, Jampol LM, Stone TW; Diabetic Retinopathy Clinical Research Network.

OBJECTIVE: To report 5-year results from a previously reported trial evaluating intravitreal 0.5 mg ranibizumab with prompt versus deferred (for ≥24 weeks) focal/grid laser treatment for diabetic macular edema (DME).

DESIGN: Multicenter, randomized clinical trial.

PARTICIPANTS: Among participants from the trial with 3 years of follow-up who subsequently consented to a 2-year extension and survived through 5 years, 124 (97%) and 111 (92%) completed the 5-year visit in the prompt and deferred groups, respectively.

METHODS: Random assignment to ranibizumab every 4 weeks until no longer improving (with resumption

if worsening) and prompt or deferred (≥24 weeks) focal/grid laser treatment.

MAIN OUTCOME MEASURES: Best-corrected visual acuity at the 5-year visit.

RESULTS: The mean change in visual acuity letter score from baseline to the 5-year visit was +7.2 letters in the prompt laser group compared with +9.8 letters in the deferred laser group (mean difference, -2.6 letters; 95% confidence interval, -5.5 to +0.4 letters; P = 0.09). At the 5-year visit in the prompt versus deferred laser groups, there was vision loss of ≥10 letters in 9% versus 8%, an improvement of ≥10 letters in 46% versus 58%, and an improvement of ≥15 letters in 27% versus 38% of participants, respectively. From baseline to 5 years, 56% of participants in the deferred group did not receive laser. The median number of injections was 13 versus 17 in the prompt and deferral groups, including 54% and 45% receiving no injections during year 4 and 62% and 52% receiving no injections during year 5, respectively.

CONCLUSIONS: Five-year results suggest focal/grid laser treatment at the initiation of intravitreal ranibizumab is no better than deferring laser treatment for ≥24 weeks in eyes with DME involving the central macula with vision impairment. Although more than half of eyes in which laser treatment is deferred may avoid laser for at least 5 years, such eyes may require more injections to achieve these results when following this protocol. Most eyes treated with ranibizumab and either prompt or deferred laser maintain vision gains obtained by the first year through 5 years with little additional treatment after 3 years.

PMID: 25439614 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Nov 18. [Epub ahead of print]

Long-term Effects of Therapy with Ranibizumab on Diabetic Retinopathy Severity and Baseline Risk Factors for Worsening Retinopathy.

Ip MS, Domalpally A, Sun JK, Ehrlich JS.

PURPOSE: To assess the effects of intravitreal ranibizumab on diabetic retinopathy (DR) severity when administered for up to 3 years, evaluate the effect of delayed initiation of ranibizumab therapy on DR severity, and identify baseline patient characteristics associated with the development of proliferative DR (PDR).

DESIGN: Exploratory analyses of phase III, randomized, double-masked, sham-controlled multicenter clinical trials.

PARTICIPANTS: Adults with diabetic macular edema (DME) (N = 759), baseline best-corrected visual acuity 20/40 to 20/320 Snellen equivalent, and central foveal thickness ≥275 μm.

METHODS: Patients were randomized to monthly 0.3 or 0.5 mg ranibizumab or sham injections. Sham participants could switch to 0.5 mg ranibizumab during the third year (sham/0.5 mg crossover). Baseline risk factors were evaluated to explore potential associations with development of PDR. Time to first development of PDR was analyzed by Kaplan-Meier methods to calculate cumulative probabilities by group.

MAIN OUTCOME MEASURES: Study eye change on the Early Treatment Diabetic Retinopathy Study severity scale and a composite clinical outcome evaluating progression to PDR based on photographic changes plus clinically important events defining PDR.

RESULTS: At month 36, a greater proportion of ranibizumab-treated eyes had ≥2- or ≥3-step DR improvement compared with sham/0.5 mg crossover. A ≥3-step improvement was achieved at 36 months by 3.3%, 15.0%, and 13.2% of sham/0.5 mg, 0.3 mg, and 0.5 mg ranibizumab-treated eyes, respectively (P < 0.0001). Through 36 months, 39.1% of eyes in the sham/0.5 mg group developed PDR, as measured by composite outcome, compared with 18.3% and 17.1% of eyes treated with 0.3 or 0.5 mg ranibizumab, respectively. The presence of macular capillary nonperfusion at baseline seems to be associated with progression to PDR in ranibizumab-treated eyes but did not meaningfully influence visual acuity improvement in eyes with DME after ranibizumab therapy.

CONCLUSIONS: Ranibizumab, as administered to patients with DME for 12 to 36 months in these studies, can both improve DR severity and prevent worsening. Prolonged delays in initiation of ranibizumab therapy may limit this therapeutic effect. Although uncommon, the development of PDR still occurs in a small percentage of eyes undergoing anti-vascular endothelial growth factor therapy and may be related to the presence of macular nonperfusion.

PMID: 25439595 [PubMed - as supplied by publisher]

Korean J Ophthalmol. 2014 Dec;28(6):466-72. Epub 2014 Nov 19.

Intravitreal Anti-vascular Endothelial Growth Factor for Typical Exudative Age-related Macular Degeneration in Eyes with Good Baseline Visual Acuity.

Chang YS, Han JI, Yoo SJ, Lew YJ, Kim JH.

PURPOSE: To investigate 12-month treatment outcomes of anti-vascular endothelial growth factor therapy in eyes with typical exudative age-related macular degeneration with good baseline visual acuity.

METHODS: This retrospective observational case series included 18 eyes (18 patients) with typical exudative age-related macular degeneration with a baseline best-corrected visual acuity of 20 / 25 or better. Patients were treated with anti-vascular endothelial growth factor monotherapy during the 12-month follow-up period. Baseline visual acuity and central foveal thickness were compared to the values at 12 months.

RESULTS: Patients received an average of 4.4 ± 1.3 intravitreal anti-vascular endothelial growth factor injections. The mean logarithm of minimum angle of resolution visual acuity was 0.08 ± 0.04, 0.08 ± 0.07, 0.12 ± 0.09, and 0.16 ± 0.11 at baseline, three months, six months, and 12 months, respectively. Visual acuity at 12 months was significantly worse than the baseline value at diagnosis ($p = 0.017$), and the mean central foveal thickness at the defined time points was 270.2 ± 55.6, 204.4 ± 25.4, 230.1 ± 56.3, and 216.8 ± 48.7 μm, respectively. The central foveal thickness at 12 months was significantly less than the baseline value at diagnosis ($p = 0.042$).

CONCLUSIONS: Deterioration in visual acuity was noted in eyes with typical exudative age-related macular degeneration with good baseline visual acuity, suggesting the need for close patient monitoring and prompt treatment even in patients with good baseline visual acuity.

PMID: 25435749 [PubMed - in process] PMCID: PMC4239465

Ophthalmology. 2014 Nov 27. [Epub ahead of print]

Safety of Intravitreal Ocriplasmin for Focal Vitreomacular Adhesion in Patients with Exudative Age-Related Macular Degeneration.

Novack RL, Staurenghi G, Girach A, Narendran N, Tolentino M.

PURPOSE: The evaluation of the safety and preliminary efficacy of 125 μg ocriplasmin intravitreal injection in patients with focal vitreomacular adhesion (VMA) and exudative age-related macular degeneration (AMD).

DESIGN: Randomized, sham-injection controlled, double-masked, multicenter, phase II trial.

PARTICIPANTS: A total of 100 patients with VMA and wet AMD were randomized 3:1 to receive 125 μg ocriplasmin intravitreal injection or sham injection.

METHODS: Study treatment was administered in the mid-vitreous cavity by injection. Post-treatment safety and efficacy assessments were made at baseline and on days 7, 14, and 28 and months 3, 6, and 12 after injection. Secondary efficacy end points were exploratory in nature.

MAIN OUTCOME MEASURES: The safety and tolerability of ocriplasmin were evaluated. The primary efficacy end point was the proportion of patients with VMA release at day 28 after injection. Secondary end points reported included VMA release over time, total posterior vitreous detachment (PVD), change in visual acuity from baseline, and number of anti-vascular endothelial growth factor (VEGF) injections.

RESULTS: The safety of ocriplasmin in patients with VMA and wet AMD was shown to be comparable to the known safety profile, with the majority of adverse events in the study eye occurring in the first 7 days after study treatment. A greater proportion of patients achieved VMA resolution and total PVD at month 12 with ocriplasmin compared with sham treatment. There was a decrease in the number of anti-VEGF injections with ocriplasmin at month 12 compared with the sham group, although no differences in visual acuity were observed.

CONCLUSIONS: Ocriplasmin treatment in this population seems to be generally safe and well tolerated and resulted in more patients achieving VMA resolution and PVD with less anti-VEGF use compared with sham treatment.

PMID: 25435217 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Nov 25. [Epub ahead of print]

Clinical Evaluation of Pazopanib Eye Drops versus Ranibizumab Intravitreal Injections in Subjects with Neovascular Age-Related Macular Degeneration.

Csaky KG, Dugel PU, Pierce AJ, Fries MA, Kelly DS, Danis RP, Wurzelmann JI, Xu CF, Hossain M, Trivedi T.

PURPOSE: To evaluate pazopanib eye drops in subjects with active subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

DESIGN: Multicountry, randomized, parallel-group, double-masked, active and placebo-controlled, dose-ranging study of eye drops.

PARTICIPANTS: A total of 510 subjects (93% white; 58% female; mean age, 75.3 years) whose AMD was previously managed by anti-vascular endothelial growth factor intravitreal injections.

METHODS: Treatments administered for 52 weeks included placebo eye drops instilled 4 times daily (n = 73); pazopanib 5 mg/ml instilled 3 (n = 72) or 4 times daily (n = 74); pazopanib 10 mg/ml instilled 2 (n = 73), 3 (n = 73), or 4 times daily (n = 72); or ranibizumab injection administered once every 4 weeks (n = 73). In addition, for all eye drop treatment groups, open-label ranibizumab was administered as needed.

MAIN OUTCOME MEASURES: The main outcome measures were best-corrected visual acuity (BCVA) and injection frequency assessed at week 52. Safety was assessed every 4 weeks and pazopanib plasma concentrations were determined at weeks 4 and 24.

RESULTS: At week 52, pazopanib, with allowance for as-needed ranibizumab injections, was noninferior to monthly ranibizumab as well as to as-needed ranibizumab administered with placebo eye drops in maintaining BCVA (estimated BCVA gains of 0.3-1.8 vs. 1.4 vs. 0.2 letters, respectively). Pazopanib treatment did not reduce as-needed ranibizumab injections by ≥50% (prespecified efficacy criterion). At week 52, there were no clinically meaningful changes from baseline in retinal thickness or morphology, CNV size, or lesion characteristics on optical coherence tomography or fluorescein angiography. Complement factor H genotype had no effect on the responses to pazopanib and/or ranibizumab (BCVA, injection rate, or optical coherence tomography/fluorescein angiography changes). Steady-state concentrations of pazopanib in plasma seemed to be reached by week 4. The most common ocular adverse events related to pazopanib and ranibizumab were application site pain (3%) and injection site hemorrhage (1%), respectively. No treatment-related serious adverse events were reported.

CONCLUSIONS: Pazopanib was well tolerated. Daily pazopanib eye drops in neovascular AMD subjects

did not result in therapeutic benefit beyond that obtained with ranibizumab alone.

PMID: 25432081 [PubMed - as supplied by publisher]

Saudi J Ophthalmol. 2014 Oct;28(4):325-328. Epub 2014 Feb 25.

Retino-choroidal ischemia in central retinal vein occlusion.

Hussain N, Hussain A.

Abstract: A 41-year-old gentleman with insulin dependent diabetes had decreased vision in the right eye due to non-ischemic central retinal vein occlusion with macular edema. One month following intravitreal ranibizumab, he developed retino-choroidal ischemia with further loss of vision. Authors show the fluorescein angiographic transition from non-ischemic central retinal vein occlusion to retino-choroidal ischemia.

PMID: 25473353 [PubMed - as supplied by publisher] PMCID: PMC4250501

Nat Med. 2014 Dec 4;20(12):1372-5.

IL-18 is not therapeutic for neovascular age-related macular degeneration.

Hirano Y, Yasuma T, Ambati J1 et al.

PMID: 25473914 [PubMed - in process]

Nat Med. 2014 Dec 4;20(12):1376-7.

Reply to IL-18 is not therapeutic for neovascular age-related macular degeneration.

Doyle SL, Adamson P, López FJ, Humphries P, Campbell M.

PMID: 25473915 [PubMed - in process]

Other treatment & diagnosis

Lancet. 2014 Oct 15. [Epub ahead of print]

Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies.

Schwartz SD, Regillo CD, Lam BL, Eliott D, Rosenfeld PJ, Gregori NZ, Hubschman JP, Davis JL, Heilwell G, Spirn M, Maguire J, Gay R, Bateman J, Ostrick RM, Morris D, Vincent M, Anglade E, Del Priore LV, Lanza R.

BACKGROUND: Since they were first derived more than three decades ago, embryonic stem cells have been proposed as a source of replacement cells in regenerative medicine, but their plasticity and unlimited capacity for self-renewal raises concerns about their safety, including tumour formation ability, potential immune rejection, and the risk of differentiating into unwanted cell types. We report the medium-term to long-term safety of cells derived from human embryonic stem cells (hESC) transplanted into patients.

METHODS: In the USA, two prospective phase 1/2 studies were done to assess the primary endpoints safety and tolerability of subretinal transplantation of hESC-derived retinal pigment epithelium in nine patients with Stargardt's macular dystrophy (age >18 years) and nine with atrophic age-related macular

degeneration (age >55 years). Three dose cohorts (50 000, 100 000, and 150 000 cells) were treated for each eye disorder. Transplanted patients were followed up for a median of 22 months by use of serial systemic, ophthalmic, and imaging examinations. The studies are registered with ClinicalTrials.gov, numbers NCT01345006 (Stargardt's macular dystrophy) and NCT01344993 (age-related macular degeneration).

FINDINGS: There was no evidence of adverse proliferation, rejection, or serious ocular or systemic safety issues related to the transplanted tissue. Adverse events were associated with vitreoretinal surgery and immunosuppression. 13 (72%) of 18 patients had patches of increasing subretinal pigmentation consistent with transplanted retinal pigment epithelium. Best-corrected visual acuity, monitored as part of the safety protocol, improved in ten eyes, improved or remained the same in seven eyes, and decreased by more than ten letters in one eye, whereas the untreated fellow eyes did not show similar improvements in visual acuity. Vision-related quality-of-life measures increased for general and peripheral vision, and near and distance activities, improving by 16-25 points 3-12 months after transplantation in patients with atrophic age -related macular degeneration and 8-20 points in patients with Stargardt's macular dystrophy.

INTERPRETATION: The results of this study provide the first evidence of the medium-term to long-term safety, graft survival, and possible biological activity of pluripotent stem cell progeny in individuals with any disease. Our results suggest that hESC-derived cells could provide a potentially safe new source of cells for the treatment of various unmet medical disorders requiring tissue repair or replacement.

PMID: 25458728 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2014 Nov 4. pii: S1350-9462(14)00064-0. doi: 10.1016/j.preteyeres.2014.10.002. [Epub ahead of print]

Patient-specific induced pluripotent stem cells (iPSCs) for the study and treatment of retinal degenerative diseases.

Wiley LA, Burnight ER, Songstad AE, Drack AV, Mullins RF, Stone EM, Tucker BA.

Abstract: Vision is the sense that we use to navigate the world around us. Thus it is not surprising that blindness is one of people's most feared maladies. Heritable diseases of the retina, such as age-related macular degeneration and retinitis pigmentosa, are the leading cause of blindness in the developed world, collectively affecting as many as one-third of all people over the age of 75, to some degree. For decades, scientists have dreamed of preventing vision loss or of restoring the vision of patients affected with retinal degeneration through drug therapy, gene augmentation or a cell-based transplantation approach. In this review we will discuss the use of the induced pluripotent stem cell technology to model and develop various treatment modalities for the treatment of inherited retinal degenerative disease. We will focus on the use of iPSCs for interrogation of disease pathophysiology, analysis of drug and gene therapeutics and as a source of autologous cells for cell transplantation and replacement.

PMID: 25448922 [PubMed - as supplied by publisher]

J Ophthalmol. 2014;2014:720243. Epub 2014 Oct 13.

A Method for En Face OCT Imaging of Subretinal Fluid in Age-Related Macular Degeneration.

Mohammad F, Wanek J, Zelkha R, Lim JI, Chen J, Shahidi M.

Purpose: The purpose of the study is to report a method for en face imaging of subretinal fluid (SRF) due to age-related macular degeneration (AMD) based on spectral domain optical coherence tomography (SDOCT).

Methods: High density SDOCT imaging was performed at two visits in 4 subjects with neovascular AMD and one healthy subject. En face OCT images of a retinal layer anterior to the retinal pigment epithelium

were generated. Validity, repeatability, and utility of the method were established.

Results: En face OCT images generated by manual and automatic segmentation were nearly indistinguishable and displayed similar regions of SRF. En face OCT images displayed uniform intensities and similar retinal vascular patterns in a healthy subject, while the size and appearance of a hypopigmented fibrotic scar in an AMD subject were similar at 2 visits. In AMD subjects, dark regions on en face OCT images corresponded to reduced or absent light reflectance due to SRF. On en face OCT images, a decrease in SRF areas with treatment was demonstrated and this corresponded with a reduction in the central subfield retinal thickness.

Conclusion: En face OCT imaging is a promising tool for visualization and monitoring of SRF area due to disease progression and treatment.

PMID: 25478209 [PubMed - as supplied by publisher]

Health Technol Assess. 2014 Dec;18(69):1-254.

Optical coherence tomography for the diagnosis, monitoring and guiding of treatment for neovascular age-related macular degeneration: a systematic review and economic evaluation.

Mowatt G, Hernández R, Castillo M, Lois N, Elders A, Fraser C, Aremu O, Amoaku W, Burr J, Lotery A, Ramsay C, Azuara-Blanco A.

BACKGROUND: Age-related macular degeneration is the most common cause of sight impairment in the UK. In neovascular age-related macular degeneration (nAMD), vision worsens rapidly (over weeks) due to abnormal blood vessels developing that leak fluid and blood at the macula.

OBJECTIVES: To determine the optimal role of optical coherence tomography (OCT) in diagnosing people newly presenting with suspected nAMD and monitoring those previously diagnosed with the disease.

DATA SOURCES: Databases searched: MEDLINE (1946 to March 2013), MEDLINE In-Process & Other Non-Indexed Citations (March 2013), EMBASE (1988 to March 2013), Biosciences Information Service (1995 to March 2013), Science Citation Index (1995 to March 2013), The Cochrane Library (Issue 2 2013), Database of Abstracts of Reviews of Effects (inception to March 2013), Medion (inception to March 2013), Health Technology Assessment database (inception to March 2013).

REVIEW METHODS: Types of studies: direct/indirect studies reporting diagnostic outcomes.

INDEX TEST: time domain optical coherence tomography (TD-OCT) or spectral domain optical coherence tomography (SD-OCT).

COMPARATORS: clinical evaluation, visual acuity, Amsler grid, colour fundus photographs, infrared reflectance, red-free images/blue reflectance, fundus autofluorescence imaging, indocyanine green angiography, preferential hyperacuity perimetry, microperimetry. Reference standard: fundus fluorescein angiography (FFA). Risk of bias was assessed using quality assessment of diagnostic accuracy studies, version 2. Meta-analysis models were fitted using hierarchical summary receiver operating characteristic curves. A Markov model was developed (65-year-old cohort, nAMD prevalence 70%), with nine strategies for diagnosis and/or monitoring, and cost-utility analysis conducted. NHS and Personal Social Services perspective was adopted. Costs (2011/12 prices) and quality-adjusted life-years (QALYs) were discounted (3.5%). Deterministic and probabilistic sensitivity analyses were performed.

RESULTS: In pooled estimates of diagnostic studies (all TD-OCT), sensitivity and specificity [95% confidence interval (CI)] was 88% (46% to 98%) and 78% (64% to 88%) respectively. For monitoring, the pooled sensitivity and specificity (95% CI) was 85% (72% to 93%) and 48% (30% to 67%) respectively. The FFA for diagnosis and nurse-technician-led monitoring strategy had the lowest cost (£39,769; QALYs 10.473) and dominated all others except FFA for diagnosis and ophthalmologist-led monitoring (£44,649; QALYs 10.575; incremental cost-effectiveness ratio £47,768). The least costly strategy had a 46.4% probability of being cost-effective at £30,000 willingness-to-pay threshold.

LIMITATIONS: Very few studies provided sufficient information for inclusion in meta-analyses. Only a few studies reported other tests; for some tests no studies were identified. The modelling was hampered by a lack of data on the diagnostic accuracy of strategies involving several tests.

CONCLUSIONS: Based on a small body of evidence of variable quality, OCT had high sensitivity and moderate specificity for diagnosis, and relatively high sensitivity but low specificity for monitoring. Strategies involving OCT alone for diagnosis and/or monitoring were unlikely to be cost-effective. Further research is required on (i) the performance of SD-OCT compared with FFA, especially for monitoring but also for diagnosis; (ii) the performance of strategies involving combinations/sequences of tests, for diagnosis and monitoring; (iii) the likelihood of active and inactive nAMD becoming inactive or active respectively; and (iv) assessment of treatment-associated utility weights (e.g. decrements), through a preference-based study.

PMID: 25436855 [PubMed - in process]

JAMA Ophthalmol. 2014 Dec 4. [Epub ahead of print]

Prospective Evaluation of Teleophthalmology in Screening and Recurrence Monitoring of Neovascular Age-Related Macular Degeneration: A Randomized Clinical Trial.

Li B, Powell AM, Hooper PL, Sheidow TG.

Importance: Teleophthalmology has the potential to reduce costs and inconveniences associated with frequent patient visits. Evaluating teleophthalmology in the management of age-related macular degeneration (AMD) will allow for future implementation of this technology.

Objective: To evaluate teleophthalmology as a tool for the screening and monitoring of neovascular AMD.

Design, Setting, and Participants: Prospective, randomized clinical trial that included 106 referral eyes for suspected neovascular AMD and 63 eyes with stable neovascular AMD. New referrals for patients with suspected neovascular AMD and patients with stable neovascular AMD were randomized into either routine or teleophthalmologic groups. In the routine group, patients received clinical assessment and diagnostic imaging at a tertiary hospital-based retina clinic. In the teleophthalmologic group, patients received basic examination and diagnostic imaging at a stand-alone teleophthalmologic site, where patient information and imaging studies were acquired and electronically sent over to tertiary hospital-based retina specialists. Patients in the teleophthalmologic group were called back to the tertiary treatment center if the teleophthalmologic data set suggested pathology or was inconclusive for diagnosis.

Main Outcomes and Measures: Patient wait times for diagnosis and/or treatment, referral accuracy, and visual outcome.

Results: For neovascular AMD screening, the average referral-to-diagnostic imaging time was 22.5 days for the teleophthalmologic group and 18.0 days for the routine group, for a difference of 4.5 days (95% CI, 11.8 to -2.8 days; P = .23). The average diagnostic imaging to treatment time was 16.4 days for the teleophthalmologic group and 11.6 days for the routine group, for a difference of 4.8 days (95% CI, 10.7 to -1.1 days; P = .11). For neovascular AMD monitoring, the average recurrence to treatment time was shorter for the routine group (0.04 days) compared with 13.6 days for the teleophthalmologic group, for a difference of -13.5 days (95% CI, -18.2 to -9.0 days; P < .01). There was no difference identified between end-of-study visual acuities in the 2 groups (P = .99).

Conclusions and Relevance: A delay of referral to treatment time could not be identified when comparing teleophthalmologic screening for suspected neovascular AMD with retinal specialist-based screening. Teleophthalmologic monitoring for neovascular AMD recurrence resulted in longer wait times for treatment reinitiation, but no adverse visual outcomes were identified.

PMID: 25473945 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Oct 22. [Epub ahead of print]

Optical Coherence Tomography for the Monitoring of Neovascular Age-Related Macular Degeneration: A Systematic Review.

Castillo MM, Mowatt G, Elders A, Lois N, Fraser C, Hernández R, Amoaku W, Burr JM, Lotery A, Ramsay CR, Azuara-Blanco A.

TOPIC: To compare the accuracy of optical coherence tomography (OCT) with alternative tests for monitoring neovascular age-related macular degeneration (nAMD) and detecting disease activity among eyes previously treated for this condition.

CLINICAL RELEVANCE: Traditionally, fundus fluorescein angiography (FFA) has been considered the reference standard to detect nAMD activity, but FFA is costly and invasive. Replacement of FFA by OCT can be justified if there is a substantial agreement between tests.

METHODS: Systematic review and meta-analysis. The index test was OCT. The comparator tests were visual acuity, clinical evaluation (slit lamp), Amsler chart, color fundus photographs, infrared reflectance, red -free images and blue reflectance, fundus autofluorescence imaging, indocyanine green angiography (ICGA), preferential hyperacuity perimetry, and microperimetry. We searched the following databases: MEDLINE, MEDLINE In-Process, EMBASE, Biosis, Science Citation Index, the Cochrane Library, Database of Abstracts of Reviews of Effects, MEDION, and the Health Technology Assessment database. The last literature search was conducted in March 2013. We used the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) to assess risk of bias.

RESULTS: We included 8 studies involving more than 400 participants. Seven reported the performance of OCT (3 time-domain [TD] OCT, 3 spectral-domain [SD] OCT, 1 both types) and 1 reported the performance of ICGA in the detection of nAMD activity. We did not find studies directly comparing tests in the same population. The pooled sensitivity and specificity of TD OCT and SD OCT for detecting active nAMD was 85% (95% confidence interval [CI], 72%-93%) and 48% (95% CI, 30%-67%), respectively. One study reported ICGA with sensitivity of 75.9% and specificity of 88.0% for the detection of active nAMD. Half of the studies were considered to have a high risk of bias.

CONCLUSIONS: There is substantial disagreement between OCT and FFA findings in detecting active disease in patients with nAMD who are being monitored. Both methods may be needed to monitor patients comprehensively with nAMD.

PMID: 25444343 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2014 Nov 24:0. [Epub ahead of print]

Corneal thickness of eyes with unilateral age-related macular degeneration.

Arikan S, Ersan I, Kara S, Gencer B, Korkmaz S, Vural AS.

PURPOSE: To compare the central corneal thicknesses (CCT), peripheral corneal thicknesses, and corneal volumes (CV) of the 2 eyes of patients with unilateral age-related macular degeneration (AMD).

METHODS: Twenty patients who were diagnosed with unilateral AMD were included in this prospective study for the purpose of making comparison between the diseased and healthy eyes. Optical coherence tomography and fundus fluorescein angiography imaging were applied to all patients in order to confirm and reveal the presence of unilateral AMD. Then, the measurements of CCT, peripheral corneal thickness measured 4 mm distant from the center of the cornea (4 mm CT), and CV of each eye of these patients were obtained through the rotating Scheimpflug corneal topographer.

RESULTS: Wilcoxon signed-rank test did not demonstrate a statistically sig nificant difference between the 2 eyes of patients with unilateral AMD when we compared the CCT and CV of diseased and healthy eyes (p>0.05). However, 4 mm CT of the diseased eyes of these patients were statistically significantly thicker

than the healthy eyes (p<0.05).

CONCLUSIONS: The significant difference in terms of 4 mm CT between the diseased and healthy eyes of patients with unilateral AMD may demonstrate the possible effect of peripheral corneal thickness on the development of AMD.

PMID: 25449636 [PubMed - as supplied by publisher]

Trends Mol Med. 2014 Nov 1. pii: [Epub ahead of print]

Seeing through VEGF: innate and adaptive immunity in pathological angiogenesis in the eye.

Sene A, Chin-Yee D, Apte RS.

Abstract: The central role of vascular endothelial growth factor (VEGF) signaling in regulating normal vascular development and pathological angiogenesis has been documented in multiple studies. Ocular anti-VEGF therapy is highly effective for treating a subset of patients with blinding eye disorders such as diabetic retinopathy and neovascular age-related macular degeneration (AMD). However, chronic VEGF suppression can lead to adverse effects associated with poor visual outcomes due to the loss of prosurvival and neurotrophic capacities of VEGF. In this review, we discuss emerging evidence for immune-related mechanisms that regulate ocular angiogenesis in a VEGF-independent manner. These novel molecular and cellular pathways may provide potential therapeutic avenues for a multitarget strategy, preserving the neuroprotective functions of VEGF in those patients whose disease is unresponsive to VEGF neutralization.

PMID: 25457617 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Dec;129C:31-37. Epub 2014 Oct 16.

Iron increases APP translation and amyloid-beta production in the retina.

Guo LY, Alekseev O, Li Y, Song Y, Dunaief JL.

Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness among older adults in developed countries, and retinal iron accumulation may exacerbate the disease. Iron can upregulate the production of amyloid precursor protein (APP). Since amyloid-β (Aβ), a byproduct of APP proteolysis, is found in drusen, the histopathological hallmark of AMD, we tested the role of iron in regulating APP and Aβ levels in the retinal pigment epithelial cell line ARPE-19. We found that treatment with ferric ammonium citrate (FAC) increases APP at the translational level. FAC treatment also results in increased generation of APP C-terminal fragments C83 and C99, the products of APP proteolysis by α- and β-secretase, respectively, as well as levels of Aβ42, a highly aggregative amyloid species. Additionally, retinal tissue sections from a patient with aceruloplasminemia, a disease causing iron overload in the retinal pigment epithelium (RPE), showed increased Aβ deposition in the RPE and drusen. Overall, our results suggest that RPE iron overload could contribute to Aβ accumulation in the retina.

PMID: 25456519 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Oct 14. [Epub ahead of print]

Subjective and Objective Screening Tests for Hydroxychloroquine Toxicity.

Cukras C, Huynh N, Vitale S, Wong WT, Ferris FL 3rd, Sieving PA.

OBJECTIVE: To compare subjective and objective clinical tests used in the screening for hydroxychloroquine retinal toxicity to multifocal electroretinography (mfERG) reference testing.

DESIGN: Prospective, single-center, case control study.

PARTICIPANTS: Fifty-seven patients with a previous or current history of hydroxychloroquine treatment of more than 5 years' duration.

METHODS: Participants were evaluated with a detailed medical history, dilated ophthalmologic examination, color fundus photography, fundus autofluorescence (FAF) imaging, spectral-domain (SD) optical coherence tomography (OCT), automated visual field testing (10-2 visual field mean deviation [VFMD]), and mfERG testing. We used mfERG test parameters as a gold standard to divide participants into 2 groups: those affected by hydroxychloroquine-induced retinal toxicity and those unaffected.

MAIN OUTCOME MEASURES: We assessed the association of various imaging and psychophysical variables in the affected versus the unaffected group.

RESULTS: Fifty-seven study participants (91.2% female; mean age, 55.7±10.4 years; mean duration of hydroxychloroquine treatment, 15.0±7.5 years) were divided into affected (n = 19) and unaffected (n = 38) groups based on mfERG criteria. Mean age and duration of hydroxychloroquine treatment did not differ statistically between groups. Mean OCT retinal thickness measurements in all 9 macular subfields were significantly lower (<40 μm) in the affected group ($P < 0.01$ for all comparisons) compared with those in the unaffected group. Mean VFMD was 11 dB lower in the affected group ($P < 0.0001$). Clinical features indicative of retinal toxicity were scored for the 2 groups and were detected in 68.4% versus 0.0% using color fundus photographs, 73.3% versus 9.1% using FAF images, and 84.2% versus 0.0% on the scoring for the perifoveal loss of the photoreceptor ellipsoid zone on SD-OCT for affected and unaffected participants, respectively. Using a polynomial modeling approach, OCT inner ring retinal thickness measurements and Humphrey 10-2 VFMD were identified as the variables associated most strongly with the presence of hydroxychloroquine as defined by mfERG testing.

CONCLUSIONS: Optical coherence tomography retinal thickness and 10-2 VFMD are objective measures demonstrating clinically useful sensitivity and specificity for the detection of hydroxychloroquine toxicity as identified by mfERG, and thus may be suitable surrogate tests.

PMID: 25444344 [PubMed - as supplied by publisher]

Pathogenesis

Ophthalmic Res. 2014 Nov 29;53(1):2-7. [Epub ahead of print]

Aqueous Humor Cytokine Levels in Patients with Polypoidal Choroidal Vasculopathy and Neovascular Age-Related Macular Degeneration.

Sakurada Y, Nakamura Y, Yoneyama S, Mabuchi F, Gotoh T, Tateno Y, Sugiyama A, Kubota T, Iijima H.

Purpose: To investigate the possible roles of various cytokines or growth factors in the pathogenesis of exudative age-related macular degeneration (AMD) by comparing aqueous humor levels of 14 cytokines between eyes with polypoidal choroidal vasculopathy (PCV) and those with neovascular AMD.

Methods: Forty eyes from 40 patients with treatment-naïve exudative AMD consisting of 18 eyes with neovascular AMD and 22 eyes with PCV were studied. Twenty eyes from 20 patients with no retinal pathology who underwent cataract surgery served as controls. Aqueous humor samples were collected just before intravitreal ranibizumab injection in 40 eyes with exudative AMD and before cataract surgery in 20 control eyes. Concentrations of 14 cytokines were determined by chemiluminescence-based ELISA: interleukin (IL)-1α, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, vascular endothelial growth factor (VEGF), monocyte chemoattractant protein 1, interferon-γ-inducible protein (IP)-10 and C-reactive protein (CRP).

Results: After adjusting for gender, age and axial length, concentrations of CRP and IP-10 were significantly higher in eyes with neovascular AMD or PCV compared with control eyes ($p < 0.05$), and IP-10

levels were strongly associated with lesion size (p = 0.002). None of the 14 cytokines, including VEGF, were significantly different between eyes with neovascular AMD and those with PCV.

Conclusion: Aqueous humor concentrations of CRP and IP-10 were elevated in eyes with PCV or neovascular AMD. IP-10 could be associated with the pathogenesis of neovascular AMD and PCV. PMID: 25472810 [PubMed - as supplied by publisher]

Prog Retin Eye Res. 2014 Dec 1. [Epub ahead of print]

Retinal Microglia: Just Bystander or Target for Therapy ?

Karlstetter M, Scholz R, Rutar M, Wong WT, Provis JM, Langmann T.

Abstract: Resident microglial cells can be regarded as the immunological watchdogs of the brain and the retina. They are active sensors of their neuronal microenvironment and rapidly respond to various insults with a morphological and functional transformation into reactive phagocytes. There is strong evidence from animal models and in situ analyses of human tissue that microglial reactivity is a common hallmark of various retinal degenerative and inflammatory diseases. These include rare hereditary retinopathies such as retinitis pigmentosa and X-linked juvenile retinoschisis but also comprise more common multifactorial retinal diseases such as age-related macular degeneration, diabetic retinopathy, glaucoma, and uveitis as well as neurological disorders with ocular manifestation. In this review, we describe how microglial function is kept in balance under normal conditions by cross-talk with other retinal cells and summarize how microglia respond to different forms of retinal injury. In addition, we present the concept that microglia play a key role in local regulation of complement in the retina and specify aspects of microglial aging relevant for chronic inflammatory processes in the retina. We conclude that this resident immune cell of the retina cannot be simply regarded as bystander of disease but may instead be a potential therapeutic target to be modulated in the treatment of degenerative and inflammatory diseases of the retina.

PMID: 25476242 [PubMed - as supplied by publisher]

FEBS Open Bio. 2014 Nov 15;4:1007-1014. eCollection 2014.

Inhibition of autophagy induces retinal pigment epithelial cell damage by the lipofuscin fluorophore A2E.

Saadat KA, Murakami Y, Tan X, Nomura Y, Yasukawa T, Okada E, Ikeda Y, Yanagi Y.

Abstract: In this study, we show augmented autophagy in the retinal pigment epithelial cell line ARPE-19 when cultured in the presence of the lipofuscin pigment A2E. A2E alone does not induce RPE cell death, but cell death was induced in the presence of A2E with the autophagy inhibitor 3-methyladenine (3MA), with a concomitant increase in the generation of mitochondrial reactive oxygen species. On the other hand, the ATP production capacity of mitochondria was decreased in the presence of A2E, and pharmacological inhibition of autophagy had no additional effects. The altered mRNA expression level of mitochondrial function markers was confirmed by real-time polymerase chain reaction, which showed that the antioxidant enzymes SOD1 and SOD2 were not reduced in the presence of A2E alone, but significantly suppressed with the addition of 3MA. Furthermore, transmission electron micrography revealed autophagic vacuole formation in the presence of A2E, and inhibition of autophagy resulted in the accumulation of abnormal mitochondria with loss of cristae. Spheroid culture of human RPE cells demonstrated debris accumulation in the presence of A2E, and this accumulation was accelerated in the presence of 3MA. These results indicate that autophagy in RPE cells is a vital cytoprotective process that prevents the accumulation of damaged cellular molecules.

PMID: 25473597 [PubMed - as supplied by publisher] PMCID: PMC4250541

Anal Bioanal Chem. 2014 Dec 4. [Epub ahead of print]

Changes in spectral properties and composition of lipofuscin fluorophores from human-retinal-pigment epithelium with age and pathology.

Feldman TB, Yakovleva MA, Arbukhanova PM, Borzenok SA, Kononikhin AS, Popov IA, Nikolaev EN, Ostrovsky MA.

Abstract: Fundus autofluorescence mostly originates from bisretinoid fluorophores in lipofuscin granules, which accumulate in retinal-pigment-epithelium cells with age. The dynamics of accumulation, photo-oxidation, and photodegradation of bisretinoids during aging or in the presence of pathology have been insufficiently investigated. Changes in spectral properties and composition of human lipofuscin-granule fluorophores with age and pathology have now been investigated by a high-performance liquid chromatography method using spectrophotometric and fluorescent detectors connected in series. It was found that: (i) N-retinylidene-N-retinylethanolamine (A2E) fluorescence intensity is not predominant in the chloroform extract of human-cadaver-eye retinal pigment epithelium studied; bisretinoid photo-oxidation and photodegradation products have much higher fluorescent properties; (ii) the relative emission maximum in the fluorescence spectrum of suspended retinal-pigment-epithelium cells obtained from an individual human-cadaver eye without pathology is irrespective of donor age and falls within the range 575 ± 15 nm; in two cadaver eyes with signs of age-related macular degeneration, emission maxima were shifted by 23-36 nm towards the shortwave region; and (iii) the ratio of bisretinoid photo-oxidation and photodegradation products to unoxidized bisretinoids in the chloroform extract of cadaver-eye retinal pigment epithelium increases with donor age, from 0.69 ± 0.03 to 1.32 ± 0.04. The differences in fluorescence properties between chloroform extracts obtained from cadaver eyes with and without signs of age-related macular degeneration could be used to increase the potential of fundus autofluorescence imaging as a noninvasive diagnostic method.

PMID: 25471291 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2014 Dec 2. [Epub ahead of print]

Senescent Retinal Pigment Epithelial Cells Are More Sensitive to Vascular Endothelial Growth Factor: Implications for "Wet" Age-Related Macular Degeneration.

Kozlowski MR.

Purpose: Senescence of the retinal pigment epithelial (RPE) cell layer has been implicated in the occurrence of age-related macular degeneration (AMD). The present study examines whether the ability of vascular endothelial growth factor (VEGF) to decrease the barrier function of RPE cells is enhanced in senescent RPE cells, which could contribute to the pathology of "wet" AMD.

Methods: Low or high population doubling level (PDL) range ARPE-19 human RPE cells were cultured in 6-well plates on membrane-containing inserts. After 2 weeks, the cells were treated with either VEGF or its vehicle and their transepithelial electrical resistance (TEER) was measured. One week later, the cells were stained for senescence-associated β-galactosidase (SABG) activity.

Results: VEGF was significantly more effective in reducing the TEER of the high PDL ARPE-19 cell layers than the low PDL layers (25% decrease vs. 6% decrease; t-test, P=0.0013). The low PDL cell layers had a modest uniform level of SABG staining. In contrast, the high PDL layers displayed darker and more mottled SABG staining indicative of the presence of senescent cells.

Conclusions: The present results show that the ability of VEGF to reduce the barrier function of RPE cell layers is greater in high PDL layers, which display signs of senescence, than in low PDL layers. Senescence-induced changes in the responsiveness of RPE cell layers to VEGF could contribute to the pathology of AMD. Agents that strengthen the barrier properties of RPE cells or reduce their responsiveness to VEGF could be effective in treating "wet" AMD.

PMID: 25453983 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Dec;129C:24-30. Epub 2014 Oct 25.

Hydroxyl radicals cause fluctuation in intracellular ferrous ion levels upon light exposure during photoreceptor cell death.

Imamura T, Hirayama T, Tsuruma K, Shimazawa M, Nagasawa H, Hara H.

Abstract: Iron accumulation is a potential pathogenic event often seen in age-related macular degeneration (AMD) patients. In this study, we focused on the relationship between AMD pathology and concentrations of ferrous ion, which is a highly reactive oxygen generator in biological systems. Murine cone-cells-derived 661W cells were exposed to white florescence light at 2500 lx for 1, 3, 6, or 12 h. Levels of ferrous ions, reactive oxygen species (ROS), and hydroxyl radicals were detected by RhoNox-1, a novel fluorescent probe for the selective detection of ferrous ion, 5-(and-6)-chloromethyl-2',7'-dichlorodihydrofluorescein diacetate, acetyl ester (CM-H2DCFDA), and 3'-p-(aminophenyl) fluorescein, respectively. Reduced glutathione, total iron levels and photoreceptor cell death were also measured. Two genes related to iron metabolism, transferrin receptor 1 (TfR1) and H ferritin (HFt), were quantified by RT-PCR. The effects of ferrous ion on cell death and hydroxyl radical production were determined by treatment with a ferrous ion chelating agent, 2,2'-bipyridyl. We found that the ferrous ion level decreased with light exposure in the short time frame, whereas it was upregulated during a 6-h light exposure. Total iron, ROS, cell death rate, and expression of TfR and HFt genes were significantly increased in a time-dependent manner in 661W cells exposed to light. Chelation with 2,2'-bipyridyl reduced the level of hydroxyl radicals and protected against light-induced cell death. These results suggest that light exposure decreases ferrous ion levels and enhances iron uptake in photoreceptor cells. Ferrous ion may be involved in light-induced photoreceptor cell death through production of hydroxyl radicals.

PMID: 25447561 [PubMed - as supplied by publisher]

Am J Pathol. 2014 Nov 1. [Epub ahead of print]

Expression of Human Complement Factor H Prevents Age-Related Macular Degeneration-Like Retina Damage and Kidney Abnormalities in Aged Cfh Knockout Mice.

Ding JD, Kelly U, Landowski M, Toomey CB, Groelle M, Miller C, Smith SG, Klingeborn M, Singhapricha T, Jiang H, Frank MM, Bowes Rickman C.

Abstract: Complement factor H (CFH) is an important regulatory protein in the alternative pathway of the complement system, and CFH polymorphisms increase the genetic risk of age-related macular degeneration dramatically. These same human CFH variants have also been associated with dense deposit disease. To mechanistically study the function of CFH in the pathogenesis of these diseases, we created transgenic mouse lines using human CFH bacterial artificial chromosomes expressing full-length human CFH variants and crossed these to Cfh knockout (Cfh-/-) mice. Human CFH protein inhibited cleavage of mouse complement component 3 and factor B in plasma and in retinal pigment epithelium/choroid/sclera, establishing that human CFH regulates activation of the mouse alternative pathway. One of the mouse lines, which express relatively higher levels of CFH, demonstrated functional and structural protection of the retina owing to the Cfh deletion. Impaired visual function, detected as a deficit in the scotopic electroretinographic response, was improved in this transgenic mouse line compared with Cfh-/- mice, and transgenics had a thicker outer nuclear layer and less sub-retinal pigment epithelium deposit accumulation. In addition, expression of human CFH also completely protected the mice from developing kidney abnormalities associated with loss of CFH. These humanized CFH mice present a valuable model for study of the molecular mechanisms of age-related macular degeneration and dense deposit disease and for testing therapeutic targets.

PMID: 25447048 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Dec;129C:93-106. Epub 2014 Nov 5.

Transcriptomic analysis across nasal, temporal, and macular regions of human neural retina and RPE/choroid by RNA-Seq.

Whitmore SS, Wagner AH, DeLuca AP, Drack AV, Stone EM, Tucker BA, Zeng S, Braun TA, Mullins RF, Scheetz TE.

Abstract: Proper spatial differentiation of retinal cell types is necessary for normal human vision. Many retinal diseases, such as Best disease and male germ cell associated kinase (MAK)-associated retinitis pigmentosa, preferentially affect distinct topographic regions of the retina. While much is known about the distribution of cell types in the retina, the distribution of molecular components across the posterior pole of the eye has not been well-studied. To investigate regional difference in molecular composition of ocular tissues, we assessed differential gene expression across the temporal, macular, and nasal retina and retinal pigment epithelium (RPE)/choroid of human eyes using RNA-Seq. RNA from temporal, macular, and nasal retina and RPE/choroid from four human donor eyes was extracted, poly-A selected, fragmented, and sequenced as 100 bp read pairs. Digital read files were mapped to the human genome and analyzed for differential expression using the Tuxedo software suite. Retina and RPE/choroid samples were clearly distinguishable at the transcriptome level. Numerous transcription factors were differentially expressed between regions of the retina and RPE/choroid. Photoreceptor-specific genes were enriched in the peripheral samples, while ganglion cell and amacrine cell genes were enriched in the macula. Within the RPE/choroid, RPE-specific genes were upregulated at the periphery while endothelium associated genes were upregulated in the macula. Consistent with previous studies, BEST1 expression was lower in macular than extramacular regions. The MAK gene was expressed at lower levels in macula than in extramacular regions, but did not exhibit a significant difference between nasal and temporal retina. The regional molecular distinction is greatest between macula and periphery and decreases between different peripheral regions within a tissue. Datasets such as these can be used to prioritize candidate genes for possible involvement in retinal diseases with regional phenotypes.

PMID: 25446321 [PubMed - as supplied by publisher]

J Ophthalmol. 2014;2014:281010. Epub 2014 Nov 11.

Ocular Surface Temperature in Age-Related Macular Degeneration.

Sodi A, Matteoli S, Giacomelli G, Finocchio L, Corvi A, Menchini U.

Background: The aim of this study is to investigate the ocular thermographic profiles in age-related macular degeneration (AMD) eyes and age-matched controls to detect possible hemodynamic abnormalities, which could be involved in the pathogenesis of the disease.

Methods: 32 eyes with early AMD, 37 eyes with atrophic AMD, 30 eyes affected by untreated neovascular AMD, and 43 eyes with fibrotic AMD were included. The control group consisted of 44 healthy eyes. Exclusion criteria were represented by any other ocular diseases other than AMD, tear film abnormalities, systemic cardiovascular abnormalities, diabetes mellitus, and a body temperature higher than 37.5°C. A total of 186 eyes without pupil dilation were investigated by infrared thermography (FLIR A320). The ocular surface temperature (OST) of three ocular points was calculated by means of an image processing technique from the infrared images. Two-sample t-test and one-way analysis of variance (ANOVA) test were used for statistical analyses.

Results: ANOVA analyses showed no significant differences among AMD groups (P value >0.272). OST in AMD patients was significantly lower than in controls (P > 0.05).

Conclusions: Considering the possible relationship between ocular blood flow and OST, these findings might support the central role of ischemia in the pathogenesis of AMD.

PMID: 25436140 [PubMed - as supplied by publisher] PMCID: PMC4244689

Diagn Pathol. 2014 Nov 29;9(1):154. [Epub ahead of print]

Wogonin modulates hydroperoxide-induced apoptosis via PI3K/Akt pathway in retinal pigment epithelium cells.

Yan Y, Bi H, Wang X.

Background: Oxidative stress causes the defects of retinal pigment epithelial (RPE) cells that contribute to age-related macular degeneration (AMD). This study was conducted to determine whether wogonin could prevent H2O2-induced oxidative stress in RPE cells.

Methods: A RPE cell line, ARPE-19, was obtained for the cell model. ARPE-19 cells were pre-treated with various concentrations of wogonin for 24 h before being exposed to H2O2 for 2 h to induce oxidative stress. Cell metabolic activity was measured using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cellular apoptosis was quantified by the flow cytometry. Protein level was assed by western blot.

Results: The RPE cells exposed to to 200 mM H2O2 demonstrated a significant depression in the cell viability; whereas pre-treatment with 50 and 100 mmol/l wogonin could significantly improve the cell viability in a dose-dependent manner. The proportion of PI-positive cells was increased significantly in RPE cells treated with H2O2 alone; whereas pretreatment with 100 mM wogonin significantly reduced H2O2 -induced RPE cell death rate. In protein level, the wogonin use could reduce the level of p-Akt significantly and this is the possible mechanism of the antioxidant effect of wogonin.

Conclusions: Our study showed that wogonin pre-treatment can protect RPE cells from H2O2-induced apoptosis. This suggests potential effect of wogonin in the prevention of retinal diseases associated with H2O2-induced oxidative stress such as AMD.

PMID: 25432585 [PubMed - as supplied by publisher]

Methods Mol Biol. 2015;1214:49-66.

Vascular casting for the study of vascular morphogenesis.

Ackermann M, Konerding MA.

Abstract: Microvascularity and angiogenesis play a pivotal role during normal growth and in a variety of pathological conditions such as inflammation, tumor growth, macular degeneration, and tissue regeneration. Vascular corrosion casting has been established as a method to analyze and evaluate two- and three-dimensionally the morphology and architecture of blood vessels of organs and tissues, such as tumors, brains, embryos, or the chorioallantoic membrane. Microvascular casts may be further dissected for visualizing and quantifying vascular morphology using scanning electron microscopy (SEM), micro computed tomographic (μCT) imaging, or synchrotron radiation-based micro computed tomographic (SRμCT) imaging.

PMID: 25468599 [PubMed - in process]

Biochem Biophys Res Commun. 2014 Nov 4;454(4):594-599. [Epub ahead of print]

Microphthalmia-associated transcription factor as the molecular target of cadmium toxicity in human melanocytes.

Chantarawong W, Takeda K, Sangartit W, Yoshizawa M, Pradermwong K, Shibahara S.

Abstract: Dietary intake of cadmium is inevitable, causing age-related increase in cadmium accumulation in many organs, including hair, choroid and retinal pigment epithelium (RPE). Cadmium has been implicated in the pathogenesis of hearing loss and macular degeneration. The functions of cochlea and retina are

maintained by melanocytes and RPE, respectively, and the differentiation of these pigment cells is regulated by microphthalmia-associated transcription factor (MITF). In the present study, we explored the potential toxicity of cadmium in the cochlea and retina by using cultured human melanocytes and human RPE cell lines. MITF consists of multiple isoforms, including melanocyte-specific MITF-M and widely expressed MITF-H. Levels of MITF-M protein and its mRNA in human epidermal melanocytes and HMV-II melanoma cells were decreased significantly by cadmium. In parallel with the MITF reduction, mRNA levels of tyrosinase, the key enzyme of melanin biosynthesis that is regulated by MITF-M, were also decreased. In RPE cells, however, the levels of total MITF protein, constituting mainly MITF-H, were not decreased by cadmium. We thus identify MITF-M as the molecular target of cadmium toxicity in melanocytes, thereby accounting for the increased risk of disability from melanocyte malfunction, such as hearing and vision loss among people with elevated cadmium exposure.

PMID: 25449283 [PubMed - as supplied by publisher]

Eur J Pharmacol. 2014 Oct 18. pii: S0014-2999(14)00713-4. doi: 10.1016/j.ejphar.2014.10.007. [Epub ahead of print]

The kallikrein system in retinal damage/protection.

Masuda T, Shimazawa M, Hara H.

Abstract: Kallikrein is a serine protease involved in the kallikrein-kinnin system. Kallikrein is derived from the blood plasma or tissue, and is correlated with aggravation and improvement in eye diseases, such as, glaucoma, diabetic retinopathy, age-related macular degeneration, and ocular ischemic syndrome. The plasma kallikrein stimulates retinal vascular permeability and intraocular hemorrhage. On the other hand, we had reported that the tissue kallikrein normalizes retinal vasopermeability and inhibited retinal neovascularization and retinal ischemic injury. The protective mechanisms of the tissue-derived kallikrein include the cleavage of vascular endothelial growth factor (VEGF), which suggests that the tissue kallikrein could be potentially-effective against any disease involving the VEGF production.

PMID: 25448306 [PubMed - as supplied by publisher]

Acta Biomater. 2014 Nov 8. [Epub ahead of print]

Supramolecular assembly of multifunctional maspin-mimetic nanostructures as a potent peptide-based angiogenesis inhibitor.

Zha RH, Sur S, Boekhoven J, Shi HY, Zhang M, Stupp SI.

Abstract: Aberrant angiogenesis plays a large role in pathologies ranging from tumor growth to macular degeneration. Anti-angiogenic proteins have thus come under scrutiny as versatile, potent therapeutics but face problems with purification and tissue retention. We report here on the synthesis of supramolecular nanostructures that mimic the anti-angiogenic activity of maspin, a class II tumor suppressor protein. These maspin-mimetic nanostructures are formed via self-assembly of small peptide amphiphiles containing the g-helix motif of maspin. Using tubulogenesis assays with human umbilical vein endothelial cells, we demonstrate that maspin-mimetic nanostructures show anti-angiogenic activity at concentrations that are significantly lower than those necessary for the g-helix peptide. Furthermore, in vivo assays in the chick chorioallantoic membrane show maspin-mimetic nanostructures to be effective over controls at inhibiting angiogenesis. Thus, the nanostructures investigated here offer an attractive alternative to the use of anti-angiogenic recombinant proteins in the treatment of cancer or other diseases involving abnormal blood vessel formation.

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Prog Retin Eye Res. 2014 Nov 13. [Epub ahead of print]

βA3/A1-crystallin: More than a lens protein.

Zigler JS Jr, Sinha D.

Abstract: Crystallins, the highly abundant proteins of the ocular lens, are essential determinants of the transparency and refractivity required for lens function. Initially thought to be lens-specific and to have evolved as lens proteins, it is now clear that crystallins were recruited to the lens from proteins that existed before lenses evolved. Crystallins are expressed outside of the lens and most have been shown to have cellular functions distinct from their roles as structural elements in the lens. For one major crystallin group, the β/γ-crystallin superfamily, no such functions have yet been established. We have explored possible functions for the polypeptides (βA3-and βA1-crystallins) encoded by Cryba1, one of the 6 β-crystallin genes, using a spontaneous rat mutant and genetically engineered mouse models. βA3-and βA1-crystallins are expressed in retinal astrocytes and retinal pigment epithelial (RPE) cells. In both cell types, these proteins appear to be required for the proper acidification of the lysosomes. In RPE cells, elevated pH in the lysosomes is shown to impair the critical processes of phagocytosis and autophagy, leading to accumulation of undigested cargo in (auto) phagolysosomes. We postulate that this accumulation may cause pathological changes in the cells resembling some of those characteristic of age-related macular degeneration (AMD). Our studies suggest an important regulatory function of βA3/A1-crystallin in astrocytes. We provide evidence that the cellular function of βA3/A1-crystallin involves its interaction with V-ATPase, the proton pump responsible for acidification of the endolysosomal system.

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Epidemiology

J Clin Pharm Ther. 2014 Dec 5. [Epub ahead of print]

Is aspirin use associated with age-related macular degeneration? A meta-analysis.

Li L, Li W, Chen CZ, Yi ZH, Zhou YY.

WHAT IS KNOWN AND OBJECTIVES:nAspirin is one of the most widely used medications in the world. The evidence on its effect on the risk of age-related macular degeneration (AMD) appears inconsistent across different types of studies. The aim of this meta-analysis was to evaluate the association between aspirin use and the risk of AMD.

METHODS: Relevant studies were searched using databases including PubMed, EMBASE, Cochrane Library and MEDLINE up to March 2014. Summary relative risks (RRs) and 95% confidence intervals (CIs) were calculated by random-effects or fixed-effect models. The heterogeneity was assessed by the inconsistency index (I2). The publication bias was evaluated by Begg's funnel plot and Egger's weighted regression. Sensitivity analysis was also performed in different ways.

RESULTS: Ten eligible studies including 180 834 individuals based on the inclusion criteria were analysed in this meta-analysis. The pooled RR for the aspirin use on the risk of AMD was 1·137 (95% CI, 1·003-1·289; I2 , 68·4%). The pooled RR for the aspirin use on the risk of early and late AMD was 1·19 (95% CI, 0·92-1·53; I2 , 82·6%) and 1·22 (95% CI, 0·87-1·72; I2 , 55·7%), respectively. In different types of late AMD, the pooled RR was 1·95 (95% CI, 1·40-2·72; I2 , 27%) for neovascularization and 0·84 (95% CI, 0·62-1·15; I2 , 0%) for geographic atrophy. The pooled RR in studies with standardized AMD classification was 1·307 (95% CI, 1·006-1·698; I2 , 79·2%).

WHAT IS NEW AND CONCLUSION: This meta-analysis updates similar reviews that included studies with various types of biases. A rigorous analysis shows a weak but statistically significant association between aspirin use and the risk of AMD; a result which is different to that previously reported.

PMID: 25475899 [PubMed - as supplied by publisher]

Int J Cardiol. 2014 Oct 22;178C:96-98. [Epub ahead of print]

Relationship between macular and retinal diseases with prevalent atrial fibrillation - An analysis of the Australian Heart Eye Study.

Phan K, Mitchell P, Liew G, Wang SB, Plant AJ, Thiagalingam A, Burlutsky G, Gopinath B.

PMID: 25464229 [PubMed - as supplied by publisher]

Genetics

J Ophthalmol. 2014;2014:582842. Epub 2014 Nov 12.

Age-Related Macular Degeneration: Insights into Inflammatory Genes.

Cascella R, Ragazzo M, Strafella C, Missiroli F, Borgiani P, Angelucci F, Marsella LT, Cusumano A, Novelli G, Ricci F, Giardina E.

Abstract: Age-related macular degeneration (AMD) is a progressive neurodegenerative disease that affects approximately 8.7% of elderly people worldwide (>55 years old). AMD is characterized by a multifactorial aetiology that involves several genetic and environmental risk factors (genes, ageing, smoking, family history, dietary habits, oxidative stress, and hypertension). In particular, ageing and cigarette smoking (including oxidative compounds and reactive oxygen species) have been shown to significantly increase susceptibility to the disease. Furthermore, different genes (CFH, CFI, C2, C3, IL-6, IL-8, and ARMS2) that play a crucial role in the inflammatory pathway have been associated with AMD risk. Several genetic and molecular studies have indicated the participation of inflammatory molecules (cytokines and chemokines), immune cells (macrophages), and complement proteins in the development and progression of the disease. Taking into consideration the genetic and molecular background, this review highlights the genetic role of inflammatory genes involved in AMD pathogenesis and progression.

PMID: 25478207 [PubMed - as supplied by publisher]

Biochim Biophys Acta. 2014 Oct 27. [Epub ahead of print]

Triamcinolone regulated apopto-phagocytic gene expression patterns in the clearance of dying retinal pigment epithelial cells. A key role of Mertk in the enhanced phagocytosis.

Albert R, Kristóf E, Zahuczky G, Tóth M, Veréb Z, Oláh B, Moe MC, Facskó A, Fésüs L, Petrovski G.

BACKGROUND: The apopto-phagocytic gene expression patterns during clearance of dying cells in the retina and the effect of triamcinolone (TC) upon these processes has relevance to development of age-related macular degeneration (AMD).

METHODS: ARPE-19 cells and primary human retinal pigment epithelium (hRPE) were induced to undergo cell death by anoikis and the clearance of these cells by living hRPE/ARPE-19 or human monocyte-derived macrophages (HMDMs) in the presence or absence of TC was quantified by flow cytometry. TaqMan low-density gene expression array determining known markers of phagocytosis and loss-of-function studies on selected apopto-phagocytic genes was carried out in HMDMs engulfing anoikic cells.

RESULTS: The glucocorticoid TC had a profound phagocytosis-enhancing effect on HMDMs engulfing anoikic ARPE-19 or hRPE cells, causing a selective upregulation of the Mer tyrosine kinase (MERTK) receptor, while decreasing the expression of the AXL receptor tyrosine kinase and thrombospondin-1 (THSB-1). The key role of the MERTK could be demonstrated in HMDMs engulfing dying cells using gene silencing as well as blocking antibodies. Similar pathways were found upregulated in living ARPE-19 engulfing anoicic ARPE-19 cells. Gas6 treatment enhanced phagocytosis in TC treated HMDMs.

CONCLUSIONS: Specific agonists of the Mertk receptor may have a potential role as phagocytosis enhancers in the retina and serve as future targets for AMD therapy.

GENERAL SIGNIFICANCE: The use of Gas6 as enhancer of retinal phagocytosis via the MerTK receptor, alone or in combination with other specific ligands of the tyrosine kinase receptors' family may have a potential role in AMD therapy.

PMID: 25450174 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Nov 6. [Epub ahead of print]

Chronic Central Serous Chorioretinopathy Is Associated with Genetic Variants Implicated in Age-Related Macular Degeneration.

de Jong EK, Breukink MB, Schellevis RL, Bakker B, Mohr JK, Fauser S, Keunen JE, Hoyng CB, den Hollander AI, Boon CJ.

PURPOSE: In this study, single nucleotide polymorphisms (SNPs) at 19 loci, previously associated with age-related macular degeneration (AMD), were systematically tested for association in patients with chronic central serous chorioretinopathy (cCSC). In addition, we evaluated the effect of detailed phenotyping on these genetic associations.

DESIGN: Case-control study.

PARTICIPANTS: We included 292 cCSC patients, 1147 AMD patients, and 1311 control individuals.

METHODS: We genotyped SNPs at 19 AMD-associated loci and 6 additional SNPs at the complement factor H (CFH) locus. Phenotyping of all patients was based on fundoscopy, spectral-domain optical coherence tomography, fluorescein angiography (FA), and indocyanine green angiography.

MAIN OUTCOME MEASURES: We measured the allele frequencies of 25 AMD-associated SNPs and CFH haplotype frequencies in patients with cCSC and the effect of phenotypic subdivision of cCSC on genetic associations.

RESULTS: One SNP in ARMS2 (rs10490924) was significant after Bonferroni correction (Punadjusted = 0.002; odds ratio [OR] = 0.64). The SNPs at 3 other AMD loci (CFH, TNFRSF10A, ADAMTS9) showed a trend toward association with typical cCSC. Further analysis of the CFH locus identified 2 SNPs that significantly conferred increased risk for cCSC and 1 that was protective. The CFH-H3 haplotype was also found to be protective (P = 0.01; OR = 0.54). Using multimodal imaging, 197 patients were classified as having typical cCSC, 52 patients had unilateral abnormalities on FA that were otherwise typical of cCSC, and 43 patients had a clinical picture that could be compatible with cCSC, but with features that could also indicate other macular diseases. Significant differences of the minor allele frequencies of the tested SNPs were observed between these 3 phenotypic subgroups.

CONCLUSIONS: Chronic CSC is associated with genetic variants in ARMS2 and CFH, indicating a genetic and pathophysiologic overlap between cCSC and AMD. Intriguingly, alleles in ARMS2 and CFH that confer risk of AMD may be protective for cCSC, and alleles in CFH that are protective for AMD confer risk for cCSC. Significant differences in allele frequencies were found among the phenotypic subgroups for several SNPs, illustrating the importance of correct clinical classification.

PMID: 25439433 [PubMed - as supplied by publisher]

Diet & lifestyle

Ophthalmology. 2014 Nov 18. [Epub ahead of print]

Genetic Testing in Persons with Age-Related Macular Degeneration and the Use of the AREDS Supplements: To Test or Not to Test?

Chew EY, Klein ML, Clemons TE, Agrón E, Abecasis GR.

PMID: 25456150 [PubMed - as supplied by publisher]

Maturitas. 2014 Oct 31. [Epub ahead of print]

Carotenoids and health in older people.

Woodside JV, McGrath AJ, Lyner N, McKinley MC.

Abstract: As the proportion of older people increases, so will chronic disease incidence and the proportion of the population living with disability. Therefore, new approaches to maintain health for as long as possible in this age group are required. Carotenoids are a group of polyphenolic compounds found predominantly in fruit and vegetables that have been proposed to have anti-inflammatory and antioxidant effects. Such properties may impact on the risk diseases which predominate in older people, and also ageing-related physiological changes. Working out the effect of carotenoid intake versus fruit and vegetable intake is difficult, and the strong correlation between individual carotenoid intakes also complicates any attempt to examine individual carotenoid health effects. Similarly, research to determine whether carotenoids consumed as supplements have similar benefits to increased dietary intake through whole foods, is still required. However, reviewing the recent evidence suggests that carotenoid intake and status are relatively consistently associated with reduced CVD risk, although β-carotene supplementation does not reduce CVD risk and increases lung cancer risk. Increased lycopene intake may reduce prostate cancer progression, with a potential role for carotenoids at other cancer sites. Lutein and zeaxanthin have a plausible role in the maintenance of eye health, whilst an association between carotenoid intake and cognitive and physical health appears possible, although research is limited to date. Given this accruing evidence base to support a specific role for certain carotenoids and ageing, current dietary advice to consume a diet rich in fruit and vegetables would appear prudent, and efforts maintained to encourage increased intake.

PMID: 25466302 [PubMed - as supplied by publisher]

J Vis. 2014 Dec 1;14(14).

Metamorphopsia and letter recognition.

Wiecek E, Dakin SC, Bex P.

Abstract: Acuity is the most commonly used measure of visual function, and reductions in acuity are associated with most eye diseases. Metamorphopsia-a perceived distortion of visual space-is another common symptom of visual impairment and is currently assessed qualitatively using Amsler (1953) charts. In order to quantify the impact of metamorphopsia on acuity, we measured the effect of physical spatial distortion on letter recognition. Following earlier work showing that letter recognition is tuned to specific spatial frequency (SF) channels, we hypothesized that the effect of distortion might depend on the spatial scale of visual distortion just as it depends on the spatial scale of masking noise. Six normally sighted observers completed a 26 alternate forced choice (AFC) Sloan letter identification task at five different viewing distances, and the letters underwent different levels of spatial distortion. Distortion was controlled using spatially band-pass filtered noise that spatially remapped pixel locations. Noise was varied over five spatial frequencies and five magnitudes. Performance was modeled with logistic regression and worsened linearly with increasing distortion magnitude and decreasing letter size. We found that retinal SF affects distortion at midrange frequencies and can be explained with the tuning of a basic contrast sensitivity

function, while object-centered distortion SF follows a similar pattern of letter object recognition sensitivity and is tuned to approximately three cycles per letter (CPL). The interaction between letter size and distortion makes acuity an unreliable outcome for metamorphopsia assessment.

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Food Chem Toxicol. 2014 Oct 13;74C:216-224. [Epub ahead of print]

Photooxidative damage in retinal pigment epithelial cells via GRP78 and the protective role of grape skin polyphenols.

Zhao Z, Sun T, Jiang Y, Wu L, Cai X, Sun X, Sun X.

Abstract: Blue light induced oxidative damage and ER stress are related to the pathogenesis of age-related macular degeneration (AMD). However, the mechanism of blue light-induced damage remained obscure. The objective of this work is to assess the photooxidative damage to retinal pigment epithelial cells (RPE) and oxidation-induced changes in expression of ER stress associated apoptotic proteins, and investigate the mechanism underlying the protective effects of grape skin extracts. To mimic lipofuscin-mediated photooxidation in vivo, ARPE-19 cells that accumulated A2E, one of lipofuscin fluorophores, were used as a model system to investigate the mechanism of photooxidative damage and the protective effects of grape skin polyphenols. Exposure of A2E containing ARPE-19 cells to blue light resulted in significant apoptosis and increases in levels of GRP78, CHOP, p-JNK, Bax, cleaved caspase-9, and cleaved caspase-3, indicating that photooxidative damage to RPE cells is mediated by the ER-stress-induced intrinsic apoptotic pathway. Cells in which GRP78 had been knocked down with shRNA were more vulnerable to photooxidative damage. Pre-treatment of blue-light-exposed A2E containing ARPE-19 cells, with grape skin extracts, inhibited apoptosis, in a dose dependent manner. Knockdown GRP78 blocked the protective effect of grape skin extracts.

PMID: 25447759 [PubMed - as supplied by publisher]