

Issue 252

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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

Clin Ophthalmol. 2015 Sep 22;9:1759-66. eCollection 2015.

A single-arm, investigator-initiated study of the efficacy, safety, and tolerability of intravitreal aflibercept injection in subjects with exudative age-related macular degeneration previously treated with ranibizumab or bevacizumab (ASSESS study): 12-month analysis.

Singh RP, Srivastava SK, Ehlers JP, Silva FQ, Bedi R, Schachat AP, Kaiser PK.

SUMMARY STATEMENT: In subjects with active exudative age-related macular degeneration, treating with a fixed intravitreal aflibercept injection dosing regimen for 12 months demonstrated improved anatomic and vision endpoints from baseline.

PURPOSE: Switching therapies in neovascular age-related macular degeneration (AMD) may offer an advantage for some patients. This study evaluates the efficacy of intravitreal aflibercept injection (IAI) in subjects previously treated with ranibizumab and/or bevacizumab.

METHODS: Subjects (n=26) were given monthly 2 mg of IAI for 3 months, followed by 2 mg once in every 2 months for up to 12 months. The mean absolute change from baseline in central subfield thickness (CST) measured by optical coherence tomography and the mean change from baseline in best-corrected visual acuity (BCVA) early treatment in diabetic retinopathy study (ETDRS) letter score were obtained. Additionally, the percentage of subjects who gained or lost ≥ 15 letters of vision and the percentage of subjects who are 20/40 or better or 20/200 or worse were evaluated.

RESULTS: There was a mean decrease in CST of $-50.3 \mu\text{m}$ ($P < 0.001$) and a mean increase in ETDRS BCVA of $+9.2$ letters ($P < 0.001$). Twenty-seven percent of subjects experienced a ≥ 15 -letter improvement in visual acuity, and no subject lost ≥ 3 lines of vision from baseline. Fifty percent of subjects were 20/40 or better, and 11.5% of subjects were 20/200 or worse at month 12.

CONCLUSION: Fixed IAI dosing regimen for 12 months demonstrated improved anatomic and vision endpoints in subjects with active exudative AMD.

PMID: 26445522 [PubMed] PMCID: PMC4590671

Health Technol Assess. 2015 Oct;19(78):1-298.

A randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN).

Chakravarthy U, Harding SP, Rogers CA, Downes S, Lotery AJ, Dakin HA, Culliford L, Scott LJ, Nash RL, Taylor J, Muldrew A, Sahni J, Wordsworth S, Raftery J, Peto T, Reeves BC.

BACKGROUND: Bevacizumab (Avastin®), Roche), which is used in cancer therapy, is the 'parent' molecule from which ranibizumab (Lucentis®), Novartis) was derived for the treatment of neovascular age-related macular degeneration (nAMD). There were reports in the literature on the effectiveness of bevacizumab in treating nAMD, but no trials. The cost per dose of bevacizumab is about 5-10% that of ranibizumab. This trial was a head-to-head comparison of these two drugs.

OBJECTIVE: To compare the clinical effectiveness and cost-effectiveness of ranibizumab and bevacizumab, and two treatment regimens, for nAMD.

DESIGN: Multicentre, factorial randomised controlled trial with within-trial cost-utility and cost-minimisation analyses from the perspective of the UK NHS. Participants, health professionals and researchers were masked to allocation of drug but not regimen. Computer-generated random allocations to combinations of ranibizumab or bevacizumab, and continuous or discontinuous regimen, were stratified by centre, blocked and concealed.

SETTING: Twenty-three ophthalmology departments in NHS hospitals.

PARTICIPANTS: Patients ≥ 50 years old with active nAMD in the study eye with best corrected distance visual acuity (BCVA) ≥ 25 letters measured on a Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Previous treatment for nAMD, long-standing disease, lesion diameter $> 6000 \mu\text{m}$, thick blood at the fovea and any other confounding ocular disease were exclusion criteria. One eye per participant was studied; the fellow eye was treated according to usual care, if required.

INTERVENTIONS: Ranibizumab and bevacizumab were procured commercially. Doses were ranibizumab 0.5 mg or bevacizumab 1.25 mg. The repackaged bevacizumab was quality assured. All participants were treated at visits 0, 1 and 2. Participants randomised to the continuous regimen were treated monthly thereafter. Participants randomised to the discontinuous regimen were not retreated after visit 2 unless pre-specified criteria for active disease were met. If retreatment was needed, monthly injections over 3 months were mandated.

MAIN OUTCOME MEASURES: The primary outcome was BCVA. The non-inferiority margin was 3.5 letters. Secondary outcomes were contrast sensitivity; near visual acuity; reading index; neovascular lesion morphology; generic and disease-specific patient-reported outcomes, including macular disease-specific quality of life; survival free from treatment failure; resource use; quality-adjusted life-years (QALYs); and development of new geographic atrophy (GA) (outcome added during the trial). Results are reported for the study eye, except for patient-reported outcomes.

RESULTS: Between 27 March 2008 and 15 October 2010, 610 participants were allocated and treated (314 ranibizumab, 296 bevacizumab; at 3 months, 305 continuous, 300 discontinuous). After 2 years, bevacizumab was neither non-inferior nor inferior to ranibizumab [-1.37 letters, 95% confidence interval (CI) -3.75 to +1.01 letters] and discontinuous treatment was neither non-inferior nor inferior to continuous treatment (-1.63 letters, 95% CI -4.01 to +0.75 letters). Lesion thickness at the fovea was similar by drug [geometric mean ratio (GMR) 0.96, 95% CI 0.90 to 1.03; $p = 0.24$] but 9% less with continuous treatment (GMR 0.91, 95% CI 0.85 to 0.97; $p = 0.004$). Odds of developing new GA during the trial were similar by drug [odds ratio (OR) 0.87, 95% CI 0.61 to 1.25; $p = 0.46$] but significantly higher with continuous treatment (OR 1.47, 95% CI 1.03 to 2.11; $p = 0.033$). Safety outcomes did not differ by drug but mortality was lower with continuous treatment (OR 0.47, 95% CI 0.22 to 1.03; $p = 0.05$). Continuous ranibizumab cost £3.5M per QALY compared with continuous bevacizumab; continuous bevacizumab cost £30,220 per QALY compared with discontinuous bevacizumab. These results were robust in sensitivity analyses.

CONCLUSIONS: Ranibizumab and bevacizumab have similar efficacy. Discontinuing treatment and restarting when required results in slightly worse efficacy. Safety was worse with discontinuous treatment, although new GA developed more often with continuous treatment. Ranibizumab is not cost-effective, although it remains uncertain whether or not continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at £20,000 per QALY threshold. Future studies should focus on the ocular safety of the two drugs, further optimisation of treatment regimens and criteria for stopping treatment.

PMID: 26445075 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2015 Oct 1;56(11):6448-55.

Correlation Between Hyperreflective Foci and Clinical Outcomes in Neovascular Age-Related Macular Degeneration After Switching to Aflibercept.

Abri Aghdam K, Pielen A, Framme C, Junker B.

PURPOSE: To assess the correlation between hyperreflective foci (HF) and visual and anatomical outcomes in treatment-resistant neovascular age-related macular degeneration (AMD) using spectral-domain optical coherence tomography (SD-OCT).

METHODS: This was a prospective interventional case series. Thirty-three eyes of 30 consecutive patients with treatment-resistant neovascular AMD were enrolled. Intravitreal aflibercept injections were performed at week 0 (baseline), week 4, and week 8. Spectral-domain OCT images were obtained before each injection and 4 weeks after the third injection. The main focus was on the measurement of choroidal neovascularization (CNV) size in the cross-sectional area in the B-scan through the fovea, and HF number along line segments of 1- and 3-mm length passing through the fovea.

RESULTS: Mean number of HF in the radius of 500 μ m decreased from 8.36 ± 7.58 to 4.15 ± 3.39 ($P = 0.02$). Mean number of HF in the radius of 1500 μ m was reduced from 21.30 ± 12.47 to 10.45 ± 6.34 ($P < 0.001$). Mean CNV area decreased from 0.35 ± 0.22 to 0.22 ± 0.16 mm² ($P < 0.001$). There was a significant positive correlation between HF reduction in the radius of 500 μ m and decrease in central subfield thickness (CST) ($r = 0.43$, $P = 0.01$), but no statistically significant correlation was found between HF decline in the radius of 1500 μ m and other parameters.

CONCLUSIONS: Switching from ranibizumab to aflibercept caused significant decrease in the number of HF 1 month after aflibercept upload, and HF decrease in the radius of 500 μ m was correlated positively with the reduction in CST.

PMID: 26444725 [PubMed - in process]

Drugs Aging. 2015 Oct 6. [Epub ahead of print]

Treatment of Exudative Age-related Macular Degeneration: Focus on Aflibercept.

García-Layana A, Figueroa MS, Araiz J, Ruiz-Moreno JM, Gómez-Ulla F, Arias-Barquet L, Reiter N.

Abstract: A formulation of aflibercept for intravitreal injection (Eylea) is approved for the treatment of patients with exudative age-related macular degeneration (AMD). Aflibercept has a significantly higher affinity for Vascular endothelial growth factor (VEGF)-A compared with other monoclonal anti-VEGF antibodies. In addition to binding all VEGF-A isoforms, aflibercept also blocks other proangiogenic factors such as VEGF-B and placental growth factor. The VIEW 1 and 2 trials showed this drug achieves improved results in patients with exudative AMD similar to those obtained with monthly ranibizumab, using a bimonthly treatment regimen after a loading dose of three intravitreal injections, which translates to less use of healthcare resources. There is a subgroup of patients that present with persistent fluid after the loading dose that could benefit from monthly injections or personalized proactive treatment after the first year. In the second year of treatment, the Treat and Extend patterns can permit even more lengthening of the time between injections. More data are needed to confirm the optimal monitoring and retreatment dosing, to maintain long-term efficacy. Other preliminary data suggest that patients that do not respond to other anti-angiogenics and patients with special pathologies such as polypoidal choroidopathy or retinal angiomatous proliferation can improve upon switching to aflibercept. To date, the safety profile of aflibercept is excellent and is comparable to other anti-angiogenic treatments.

PMID: 26442858 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2015 Oct 9. [Epub ahead of print]

Ranibizumab 0.5 mg treat-and-extend regimen for diabetic macular oedema: the RETAIN study.

Prünke C, Fajnkuchen F, Mahmood S, Ricci F, Hatz K, Studnička J, Bezlyak V, Parikh S, Stubbings WJ, Wenzel A, Figueira J; and the RETAIN Study Group.

AIMS: To demonstrate non-inferiority of ranibizumab treat-and-extend (T&E) with/without laser to ranibizumab pro re nata (PRN) for best-corrected visual acuity (BCVA) in patients with diabetic macular oedema (DMO).

METHODS: A 24-month single-masked study with patients randomised 1:1:1 to T&E+laser (n=121), T&E (n=128) or PRN (control; n=123). All patients received monthly injections until BCVA stabilisation. The investigator decided on re-treatment in the PRN and treatment-interval adaptations in the T&E groups based on loss of BCVA stability due to DMO activity. Likewise, laser treatment was at investigator's discretion. Collectively, these features reflect a real-life scenario. Endpoints included mean average change in BCVA from baseline to months 1-12 (primary), mean BCVA change from baseline to months 12 and 24, treatment exposure and safety profile.

RESULTS: Both T&E regimens were non-inferior to PRN based on mean average BCVA change from baseline to months 1-12 (T&E+laser: +5.9 and T&E: +6.1 vs PRN: +6.2 letters; both $p < 0.0001$). Mean BCVA change at month 24 was similar across groups (+8.3, +6.5 and +8.1 letters, respectively). The mean number of injections was 12.4 and 12.8 in the T&E+laser and T&E groups and 10.7 in the PRN group. The T&E regimens showed 46% reduction in the number of clinic visits. Over 70% of patients maintained their BCVA, with treatment intervals of ≥ 2 months over 24 months. Safety profile was consistent with that described in the product information.

CONCLUSIONS: T&E is a feasible treatment option for patients with DMO, with a potential to reduce treatment burden. Slightly more injections were required versus PRN, likely due to the specifics of the T&E regimen applied here.

PMID: 26453639 [PubMed - as supplied by publisher]

J Drug Target. 2015 Aug;23(7-8):710-5.

Controlled release of photoswitch drugs by degradable polymer microspheres.

Groynom R, Shoffstall E, Wu LS, Kramer RH, Lavik EB.

BACKGROUND: QAQ (quaternary ammonium-azobenzene-quaternary ammonium) and DENAQ (diethylamine-azobenzene-quaternary ammonium) are synthetic photoswitch compounds that change conformation in response to light, altering current flow through voltage-gated ion channels in neurons. These compounds are drug candidates for restoring light sensitivity in degenerative blinding diseases, such as age-related macular degeneration (AMD).

PURPOSE: However, these photoswitch compounds are cleared from the eye within several days, they must be administered through repeated intravitreal injections. Therefore, we are investigating local, sustained delivery formulations to constantly replenish these molecules and have the potential to restore sight.

METHODS: Here, we encapsulate QAQ and DENAQ into several molecular weights of poly(lactic-co-glycolic) acid (PLGA) through an emulsion technique to assess the viability of delivering the compounds in their therapeutic window over many weeks. We characterize the loading efficiency, release profile and bioactivity of the compounds after encapsulation.

RESULTS: A very small burst release was observed for all of the formulations with the majority being delivered over the following two months. The lowest molecular weight PLGA led to the highest loading and most linear delivery for both QAQ and DENAQ. Bioactivity was retained for both compounds across the

polymers.

CONCLUSION: These results present encapsulation into polymers by emulsion as a viable option for controlled release of QAQ and DENAQ.

PMID: 26453166 [PubMed - in process]

Ophthalmology. 2015 Oct 6. [Epub ahead of print]

Outcomes with As-Needed Ranibizumab after Initial Monthly Therapy: Long-Term Outcomes of the Phase III RIDE and RISE Trials.

Boyer DS, Nguyen QD, Brown DM, Basu K, Ehrlich JS; RIDE and RISE Research Group.

PURPOSE: To determine whether the efficacy and safety achieved with monthly ranibizumab as treatment for diabetic macular edema (DME) can be maintained with less-than-monthly treatment.

DESIGN: Open-label extension (OLE) phase of randomized, sham-controlled phase III trials: RIDE (NCT00473382) and RISE (NCT00473330).

PARTICIPANTS: Five hundred of 582 adults who completed the 36-month randomized core studies elected to enter the OLE.

METHODS: All patients participating in the OLE were eligible to receive 0.5 mg ranibizumab according to predefined re-treatment criteria: Treatment was administered when DME was identified by the investigator on optical coherence tomography or when best-corrected visual acuity (BCVA) worsened by ≥ 5 Early Treatment Diabetic Retinopathy Study letters versus month 36. Patients were observed at 30-, 60-, or 90-day intervals depending on the need for treatment.

MAIN OUTCOME MEASURES: The incidence and severity of ocular and nonocular events, proportion of patients with ≥ 15 -letter best-corrected visual acuity (BCVA) gain from baseline, mean BCVA change from month 36 (final core study visit), mean central foveal thickness (CFT), and mean CFT change from month 36.

RESULTS: A mean of 4.5 injections were administered over a mean follow-up of 14.1 months. Approximately 25% of patients did not require further treatment based on protocol-defined re-treatment criteria. Mean BCVA was sustained or improved in these patients through the end of follow-up. Approximately 75% of patients received ≥ 1 criteria-based re-treatment; mean time to first re-treatment was approximately 3 months after the last masked-phase visit. Mean BCVA remained stable in re-treated patients; CFT was generally stable with a trend toward slight thickening in all patients when mandatory monthly therapy was relaxed.

CONCLUSIONS: Vision gains achieved after 1 or 3 years of monthly ranibizumab therapy were maintained with a marked reduction in treatment frequency; some patients required no additional treatment. These observations are consistent with other studies evaluating induction followed by maintenance ranibizumab therapy for DME. Patients whose treatment was deferred by 2 years (randomized initially to sham) did not ultimately achieve the same BCVA gains as patients who received ranibizumab from baseline. Ranibizumab's safety profile in the OLE appeared similar to that observed in the controlled core studies and other studies.

PMID: 26452713 [PubMed - as supplied by publisher]

Drug Des Devel Ther. 2015 Sep 28;9:5397-405. eCollection 2015.

Intravitreal anti-VEGF injections for treating wet age-related macular degeneration: a systematic review and meta-analysis.

Ba J, Peng RS, Xu D, Li YH, Shi H, Wang Q, Yu J.

AIMS: Age-related macular degeneration (AMD) is the main cause of blindness. Anti-vascular endothelial growth factor is used to prevent further neovascularization due to wet AMD. The purpose of this systematic review was to investigate the effect and protocol of anti-vascular endothelial growth factor treatment on wet AMD.

METHODS: A comprehensive literature search was performed in PubMed, Embase, the Cochrane Library, CNKI, and reference lists. Meta-analysis was performed using Stata12.0 software, best corrected visual acuity (BCVA), retinal thickness, and lesion size were evaluated.

RESULTS: Twelve randomized controlled trials spanning from 2010 to 2014 and involving 5,225 patients were included. A significant difference was observed between the intravitreal ranibizumab (IVR) group and the intravitreal bevacizumab group (standard mean difference = -0.14, 95% confidence interval [CI] = -0.23 to -0.05). No significant differences were observed in best corrected VA, retinal thickness, or lesion size between IVR and the intravitreal aflibercept group. Compared to monthly injection, IVR as-needed injections (PRN) can raise VA by 1.97 letters (weighted mean difference = 1.97, 95% CI = 0.14-3.794). Combination therapy of IVR and photodynamic therapy can significantly raise VA by 2.74 letters when combined with IVR monotherapy (weighted mean difference = 2.74, 95% CI = 0.26-5.21).

CONCLUSION: The superiority remains unclear between IVR and intravitreal bevacizumab in the treatment of neovascular AMD. Intravitreal aflibercept dosed every 2 months required fewer injection times, but produced similar efficacy as monthly IVR. IVR PRN could significantly increase VA. Combined with photodynamic therapy, IVR therapy could also increase VA effectively.

PMID: 26451092 [PubMed - in process]

Eye (Lond). 2015 Oct 9. [Epub ahead of print]

Intravitreal aflibercept for macular oedema secondary to central retinal vein occlusion in patients with prior treatment with bevacizumab or ranibizumab.

Papakostas TD, Lim L, van Zyl T, Miller JB, Modjtahedi BS, Andreoli CM, Wu D, Young LH, Kim IK, Vavvas DG, Esmaili DD, Husain D, Elliott D, Kim LA.

Purpose: To report the visual and anatomic outcomes in eyes with macular oedema (MO) secondary to central retinal vein occlusion (CRVO) that were switched from either intravitreal bevacizumab or ranibizumab to intravitreal aflibercept.

Methods: Two-center retrospective chart review. Eyes with MO secondary to CRVO that received a minimum of three intravitreal injections of bevacizumab or ranibizumab and were switched to intravitreal aflibercept for persistent or recurrent MO not responding to either bevacizumab and/or ranibizumab.

Results: In all 42 eyes of 42 patients were included in the study. The median visual acuity before the switch was 20/126, 1 month after the first injection of aflibercept 20/89 ($P=0.0191$), and at the end of the follow-up 20/100 ($P=0.2724$). The median CRT before the switch was 536 μm , 1 month after the first injection of aflibercept 293.5 μm ($P=0.0038$), and at the end of the follow-up 279 μm ($P=0.0013$ compared to before the switch). The median number of weeks between injections before the switch was 5.6 and after the switch was 7.6 ($P<0.0001$).

Conclusion: Converting eyes with refractory MO due to CRVO to aflibercept can result in stabilization of the vision, improved macular anatomy, and extension of the injection interval. Eye advance online publication, 9 October 2015; doi:10.1038/eye.2015.175.

PMID: 26449196 [PubMed - as supplied by publisher]

Ophthalmic Res. 2015 Oct 7;54(4):169-174. [Epub ahead of print]

Pharmacogenetic Effect of Complement Factor H Gene Polymorphism in Response to the Initial Intravitreal Injection of Bevacizumab for Wet Age-Related Macular Degeneration.

Medina FM, Alves Lopes da Motta A, Takahashi WY, Carricondo PC, Dos Santos Motta MM, Melo MB, Vasconcellos JP.

PURPOSE: To compare the functional and morphological response to the initial intravitreal (IVT) injection of bevacizumab in exudative age-related macular degeneration (AMD) patients with the complement factor H (CFH) gene polymorphism T1277C in the Brazilian population.

METHODS: Twenty-five unrelated patients with treatment-naïve exudative AMD underwent an IVT injection of 1.25 mg bevacizumab at the initial presentation (D0) and were reexamined 7 days (D7) and 28 days (D28) later. The time and extent of visual acuity (VA) and central retinal thickness (CRT) changes were evaluated according to the presence of the T1277C polymorphism.

RESULTS: In the homozygous risk group (CC), VA improvement was detected mostly from D7 to D28, while in the heterozygous (CT) and homozygous for the wild-type allele (TT) groups, functional response occurred earlier, from D0 to D7. Morphological response to the first IVT injection of bevacizumab was significant in the CT and TT groups, while the CC group presented no significant change in CRT up to D28.

CONCLUSION: The CC variant of the CFH gene polymorphism T1277C is related to delayed functional and limited morphological response to the initial IVT injection of bevacizumab in exudative AMD patients in a sample of the Brazilian population.

PMID: 26439641 [PubMed - as supplied by publisher]

J Control Release. 2015 Oct 1. [Epub ahead of print]

Delivery strategies for treatment of age-related ocular diseases: From a biological understanding to biomaterial solutions.

Delplace V, Payne S, Shoichet M.

Abstract: Age-related ocular diseases, such as age-related macular degeneration (AMD), diabetic retinopathy, and glaucoma, result in life-long functional deficits and enormous global health care costs. As the worldwide population ages, vision loss has become a major concern for both economic and human health reasons. Due to recent research into biomaterials and nanotechnology major advances have been gained in the field of ocular delivery. This review provides a summary and discussion of the most recent strategies employed for the delivery of both drugs and cells to the eye to treat a variety of age-related diseases. It emphasizes the current challenges and limitations to ocular delivery and how the use of innovative materials can overcome these issues and ultimately provide treatment for age-related degeneration and regeneration of lost tissues. This review also provides critical considerations and an outlook for future studies in the field of ophthalmic delivery.

PMID: 26435454 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Oct 9. [Epub ahead of print]

Comment on 'Transitioning to intravitreal aflibercept following a previous treat-and-extend dosing regimen in neovascular age-related macular degeneration: 24-month results'.

Dave VP.

PMID: 26449194 [PubMed - as supplied by publisher]

Eye (Lond). 2015 Oct 9. [Epub ahead of print]

Response to: 'Comment on Transitioning to intravitreal aflibercept following a previous treat-and-extend dosing regimen in neovascular age-related macular degeneration: 24-month results'.

Homer N, Grewal DS, Mirza RG, Lyon AT, Gill MK.

PMID: 26449193 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2015 Oct 5. [Epub ahead of print]

TYPE 2 NEOVASCULARIZATION SECONDARY TO AGE-RELATED MACULAR DEGENERATION IMAGED BY OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY.

El Ameen A, Cohen SY, Semoun O, Miere A, Srour M, Quaranta-El Maftouhi M, Oubraham H, Blanco-Garavito R, Querques G, Souied EH.

PURPOSE: Optical coherence tomography angiography is a novel and noninvasive technique for imaging retinal microvasculature by detecting changes in reflectivity that is related to blood flow. The purpose of this study was to describe Type 2 neovascularization characteristics in age-related macular degeneration using optical coherence tomography angiography.

METHODS: Fourteen eyes of 14 consecutive patients with Type 2 neovascularization were prospectively included. All patients underwent a complete ophthalmological examination, including color and infrared fundus photography, fluorescein and indocyanine green angiography, spectral domain optical coherence tomography angiography, and optical coherence tomography angiography.

RESULTS: In all cases, Type 2 lesions could be detected by optical coherence tomography angiography, presenting as a hyperflow lesion in the outer retina, with a glomerulus (4/14) or medusa shape (10/14), surrounded by a dark halo. The superficial layer and the deep retina showed no abnormal flow. Surprisingly, the Type 2 lesions could also be observed in the presumed choriocapillaris layer. These glomerulus- or medusa-shaped lesions were connected, in 10/14 eyes, to a thicker main branch, which seemed to continue deep into the choroidal layers.

CONCLUSION: Optical coherence tomography angiography may be a new imaging method for the diagnosis of Type 2 neovascularization in clinical routine. However, the specificity of the features needs to be investigated in further studies.

PMID: 26441269 [PubMed - as supplied by publisher]

J Tissue Eng Regen Med. 2015 Oct 9. [Epub ahead of print]

A Bruch's membrane substitute fabricated from silk fibroin supports the function of retinal pigment epithelial cells in vitro.

Shadforth AM, Suzuki S, Theodoropoulos C, Richardson NA, Chirila TV, Harkin DG.

Abstract: Silk fibroin provides a promising biomaterial for ocular tissue reconstruction, including the damaged outer blood-retinal barrier of patients afflicted with age-related macular degeneration (AMD). The aim of the present study was to evaluate the function of retinal pigment epithelial (RPE) cells in vitro, when grown on fibroin membranes manufactured to a thickness similar to that of Bruch's membrane (3 µm). Confluent cultures of RPE cells (ARPE-19) were established on fibroin membranes and maintained under conditions designed to promote maturation over 4 months. Control cultures were grown on polyester cell culture well inserts (Transwell®). Cultures established on either material developed a cobblestone morphology, with partial pigmentation, within 12 weeks. Immunocytochemistry at 16 weeks revealed a

similar distribution pattern between cultures for F-actin, ZO-1, ezrin, cytokeratin pair 8/18, RPE-65 and Na⁺ /K⁺ -ATPase. Electron microscopy revealed that cultures grown on fibroin displayed a rounder apical surface with a more dense distribution of microvilli. Both cultures avidly ingested fluorescent microspheres coated with vitronectin and bovine serum albumin (BSA), but not controls coated with BSA alone. VEGF and PEDF were detected in the conditioned media collected from above and below the two membrane types. Levels of PEDF were significantly higher than for VEGF on both membranes and a trend was observed towards larger amounts of PEDF in apical compartments. These findings demonstrated that RPE cell functions on fibroin membranes are equivalent to those observed for standard test materials (polyester membranes). As such, these studies support advancement to studies of RPE cell implantation on fibroin membranes in a preclinical model.

PMID: 26449636 [PubMed - as supplied by publisher]

Pathogenesis

J Neurosci. 2015 Oct 7;35(40):13568-76.

APOE Isoforms Control Pathogenic Subretinal Inflammation in Age-Related Macular Degeneration.

Levy O, Lavalette S, Hu SJ, Housset M, Raoul W, Eandi C, Sahel JA, Sullivan PM, Guillonneau X, Sennlaub F.

Abstract: Contrary to Alzheimer's disease (AD), the APOE2 allele increases and the APOE4 allele reduces the risk to develop age-related macular degeneration (AMD) compared with the most common APOE3 allele. The underlying mechanism for this association with AMD and the reason for the puzzling difference with AD are unknown. We previously demonstrated that pathogenic subretinal mononuclear phagocytes (MPs) accumulate in Cx3cr1-deficient mice due to the overexpression of APOE, interleukin-6, and CC chemokine ligand 2 (CCL2). We here show using targeted replacement mice expressing the human APOE isoforms (TRE2, TRE3, and TRE4) that MPs of TRE2 mice express increased levels of APOE, interleukin-6, and CCL2 and develop subretinal MP accumulation, photoreceptor degeneration, and exaggerated choroidal neovascularization similar to AMD. Pharmacological inhibition of the cytokine induction inhibited the pathogenic subretinal inflammation. In the context of APOE-dependent subretinal inflammation in Cx3cr1(GFP/GFP) mice, the APOE4 allele led to diminished APOE and CCL2 levels and protected Cx3cr1(GFP/GFP) mice against harmful subretinal MP accumulation observed in Cx3cr1(GFP/GFP)TRE3 mice. Our study shows that pathogenic subretinal inflammation is APOE isoform-dependent and provides the rationale for the previously unexplained implication of the APOE2 isoform as a risk factor and the APOE4 isoform as a protective factor in AMD pathogenesis.

SIGNIFICANCE STATEMENT:

The understanding of how genetic predisposing factors, which play a major role in age-related macular degeneration (AMD), participate in its pathogenesis is an important clue to decipher the pathomechanism and develop efficient therapies. In this study, we used transgenic, targeted replacement mice that carry the three human APOE isoform-defining sequences at the mouse APOE chromosomal location and express the human APOE isoforms. Our study is the first to show how APOE2 provokes and APOE4 inhibits the cardinal AMD features, inflammation, degeneration, and exaggerated neovascularization. Our findings reflect the clinical association of the genetic predisposition that was recently confirmed in a major pooled analysis. They emphasize the role of APOE in inflammation and inflammation in AMD.

PMID: 26446211 [PubMed - in process]

Cell Cycle. 2015 Oct 6:0. [Epub ahead of print]

Identification of functional networks associated with cell death in the retina of OXYS rats during the development of retinopathy.

Telegina DV, Korbolina EE, Ershov NI, Kolosova NG, Kozhevnikova OS.

PURPOSE: Age-related macular degeneration (AMD) is a major cause of blindness in developed countries, and the molecular pathogenesis of early events in AMD is poorly understood. Senescence-accelerated OXYS rats develop AMD-like retinopathy. The aim of this study was to explore the differences in retinal gene expression between OXYS and Wistar (control) rats at age 20 days and to identify the pathways of retinal cell death involved in the OXYS retinopathy initiation and progression.

METHODS: Retinal mRNA profiles of 20-day-old OXYS and Wistar rats were generated at the sequencing read depth 40 mln, in triplicate, using Illumina GALLX. A terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNEL) assay was performed to measure the apoptosis level. GeneMANIA was used to construct interaction networks for differentially expressed (DE) apoptosis-related genes at ages 20 days and three and 18 months.

RESULTS: Functional analysis was suggestive of a developmental process, signal transduction, and cell differentiation as the most enriched biological processes among 245 DE genes at age 20 days. An increased level of apoptosis was observed in OXYS rats at age 20 days but not at advanced stages. We identified functional clusters in the constructed interaction networks and possible hub genes (Rasa1, cFLAR, Birc3, Cdk1, Hspa1b, Erbb3, and Ntf3). We also demonstrated the significance of the extrinsic apoptotic pathway at preclinical, early, and advanced stages of retinopathy development. Besides the cell death signaling pathways, immune system-related processes and lipid-metabolic processes showed overrepresentation in the clusters of all networks.

CONCLUSIONS: These characteristics of the expression profile of the genes functionally associated with apoptosis may contribute to the pathogenesis of AMD-like retinopathy in senescence-accelerated OXYS rats.

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Epidemiology

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The Association of Statin Use with Age-Related Macular Degeneration Progression: The Age-Related Eye Disease Study 2 Report Number 9.

Al-Holou SN, Tucker WR, Agrón E, Clemons TE, Cukras C, Ferris FL 3rd, Chew EY; Age-Related Eye Disease Study 2 Research Group.

PURPOSE: To evaluate the association of statin use with progression of age-related macular degeneration (AMD).

DESIGN: Preplanned, prospective cohort study within a controlled clinical trial of oral supplementation for age-related eye diseases.

PARTICIPANTS: Age-Related Eye Disease Study 2 (AREDS2) participants, aged 50 to 85 years.

METHODS: Factors, including age, gender, smoking status, aspirin use, and history of diabetes, hypertension, heart disease, angina, and stroke-all known to be associated with statin use-were included in a logistic regression model to estimate propensity scores for each participant. Age-adjusted proportional hazards regression models, with and without propensity score matching, were performed to evaluate the association of statin use with progression to late AMD. Analyses adjusting for the competing risk of death were also performed.

MAIN OUTCOME MEASURES: Baseline and annual stereoscopic fundus photographs were assessed centrally by masked graders for the development of late AMD, either neovascular AMD or geographic atrophy (GA).

RESULTS: Of the 3791 participants (2462 with bilateral large drusen and 1329 with unilateral late AMD at baseline), 1659 (43.8%) were statin users. The overall analysis, with no matching of propensity scores and no adjustment for death as a competing risk, showed that statin use was not associated with progression to late AMD (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.83-1.41; $P = 0.56$). When matched for propensity scores and adjusted for death as a competing risk, the result was not statistically significant (HR, 0.81; 95% CI, 0.55-1.20; $P = 0.29$). Furthermore, subgroup analyses of persons with or without late AMD at baseline and the various components of late AMD (neovascular AMD, central GA, or any GA) also showed no statistically significant association of statin use with progression to AMD.

CONCLUSIONS: Statin use was not statistically significantly associated with progression to late AMD in the AREDS2 participants, and these findings are consistent with findings in the majority of previous studies. Statins have been demonstrated to reduce the risk of cardiovascular disease, but our data do not provide evidence of a beneficial effect on slowing AMD progression.

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Retina. 2015 Oct 5. [Epub ahead of print]

HISTORY OF SUNLIGHT EXPOSURE IS A RISK FACTOR FOR AGE-RELATED MACULAR DEGENERATION.

Schick T, Ersoy L, Lechanteur YT, Saksens NT, Hoyng CB, den Hollander AI, Kirchhof B, Fauser S.

PURPOSE: To evaluate effects of current and past sunlight exposure and iris color on early and late age-related macular degeneration (AMD).

METHODS: Of 3,701 individuals from the EUGENDA database, 752 (20.3%) showed early AMD, 1,179 (31.9%) late AMD, and 1,770 (47.8%) were controls. Information about current and past sunlight exposure, former occupation type, subdivided in indoor working and outdoor working, and iris color were obtained by standardized interviewer-assisted questionnaires. Associations between environmental factors adjusted for age, gender, and smoking and early and late AMD were performed by multivariate regression analysis.

RESULTS: Current sunlight exposure showed no association with early AMD or late AMD, but past sunlight exposure (≥ 8 hours outside daily) was significantly associated with early AMD (odds ratio: 5.54, 95% confidence interval 1.25-24.58, $P = 0.02$) and late AMD (odds ratio: 2.77, 95% confidence interval 1.25-6.16, $P = 0.01$). Outside working was found to be associated with late AMD (odds ratio: 2.57, 95% confidence interval 1.89-3.48, $P = 1.58 \times 10^{-3}$). No association was observed between iris color and early or late AMD.

CONCLUSION: Sunlight exposure during working life is an important risk factor for AMD, whereas sunlight exposure after retirement seems to have less influence on the disease development. Therefore, preventive measures, for example, wearing sunglasses to minimize sunlight exposure, should start early to prevent development of AMD later in life.

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Epidemiology of Age-Related Macular Degeneration among the Elderly Population in Thailand.

Khotcharrat R, Patikulsil D, Hanutsaha P, Khiaocham U, Ratanapakorn T, Sutheerawatananonda M, Pannarunothai S.

OBJECTIVE: To estimate the prevalence and associated factors of age-related macular degeneration (AMD) in Thailand.

MATERIAL AND METHOD: This cross-sectional survey was undertaken in 2010. Five provinces were selected and people aged 50 years and over were invited for eye examination. Demographic and health behaviors and data from eye examination equipment were registered. Ophthalmologists graded AMD as early or late based on fundus color photograph and image from optical coherence tomography. Logistic regressions were analyzed to establish association factors for AMD.

RESULTS: Of the 7,043 participants, AMD was found in 862 people (12.2%), with more than half (53.1%) found in both eyes. Most cases (94.3%) were early dry, 1.8% early wet, 3.4% late dry, and 0.7% late wet AMD. Factors positively associated with AMD were age (OR 1.03, 95% CI 1.02-1.04), diabetes mellitus (OR 1.20, 95% CI 1.03-1.39), and consumption of yellow vegetable (OR 2.32, 95% CI 1.23-4.39). Factors that conversely associated with AMD were consumption of green vegetable (OR 0.51, 95% CI 0.33-0.79), physical exercise (OR 0.67, 95% CI 0.51-0.87), high blood pressure (OR 0.75, 95% CI 0.63-0.89), and heavy drinking habit (OR 0.45, 95% CI 0.26-0.75).

CONCLUSION: The prevalence of AMD in Thai population age 50 and over was 12.2%. More than half (53.1%) of the cases were found in both eyes, but few at severe stages. The present study confirmed age and DM as positive associated factors, and green vegetable, exercise as negative associated factors. Further research should investigate the effects of hypertension, yellow vegetable, and alcohol drinking on AMD.

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Diet, lifestyle and low vision

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Intakes of Lutein, Zeaxanthin, and Other Carotenoids and Age-Related Macular Degeneration During 2 Decades of Prospective Follow-up.

Wu J, Cho E, Willett WC, Sastry SM, Schaumburg DA.

IMPORTANCE: Despite strong biological plausibility, evidence from epidemiologic studies and clinical trials on the relations between intakes of lutein and zeaxanthin and age-related macular degeneration (AMD) has been inconsistent. The roles of other carotenoids are less thoroughly investigated.

OBJECTIVE: To investigate the associations between intakes of carotenoids and AMD.

DESIGN, SETTING, AND PARTICIPANTS: Prospective cohort study, with cohorts from the Nurses' Health Study and the Health Professionals Follow-up Study in the United States. A total of 63 443 women and 38 603 men were followed up, from 1984 until May 31, 2010, in the Nurses' Health Study and from 1986 until January 31, 2010, in the Health Professionals Follow-up Study. All participants were aged 50 years or older and were free of diagnosed AMD, diabetes mellitus, cardiovascular disease, and cancer at baseline.

MAIN OUTCOMES AND MEASURES: Predicted plasma carotenoid scores were computed directly from food intake, assessed by repeated food frequency questionnaires at baseline and follow-up, using validated regression models to account for bioavailability and reporting validity of different foods, and associations between predicted plasma carotenoid scores and AMD were determined.

RESULTS: We confirmed 1361 incident intermediate and 1118 advanced AMD cases (primarily neovascular AMD) with a visual acuity of 20/30 or worse by medical record review. Comparing extreme quintiles of predicted plasma lutein/zeaxanthin score, we found a risk reduction for advanced AMD of about 40% in both women and men (pooled relative risk comparing extreme quintiles = 0.59; 95% CI, 0.48-0.73; P for trend < .001). Predicted plasma carotenoid scores for other carotenoids, including β -cryptoxanthin, α -carotene, and β -carotene, were associated with a 25% to 35% lower risk of advanced AMD when comparing extreme quintiles. The relative risk comparing extreme quintiles for the predicted plasma total carotenoid index was 0.65 (95% CI, 0.53-0.80; P for trend < .001). We did not identify any associations of

carotenoids, either as predicted plasma score or calculated intake, with intermediate AMD.

CONCLUSIONS AND RELEVANCE: Higher intake of bioavailable lutein/zeaxanthin is associated with a long-term reduced risk of advanced AMD. Given that some other carotenoids are also associated with a lower risk, a public health strategy aimed at increasing dietary consumption of a wide variety of fruits and vegetables rich in carotenoids may reduce the incidence of advanced AMD.

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Drug Des Devel Ther. 2015 Sep 25;9:5337-44. eCollection 2015.

Effect of curcumin on aging retinal pigment epithelial cells.

Zhu W, Wu Y, Meng YF, Wang JY, Xu M, Tao JJ, Lu J.

Abstract: Age-related macular degeneration (AMD) is now one of the leading causes of blindness in the elderly population. The antioxidative effects of curcumin on aging retinal pigment epithelial (RPE) cells are still unclear. We conducted an in vitro study to investigate the effects of curcumin on aging RPE cells. A pulsed H₂O₂ exposure aging model was adopted. Aging RPE cells were treated with curcumin 20 μ M, 40 μ M, and 80 μ M. Apoptosis of RPE cells was analyzed by flow cytometry. The intracellular reactive oxygen species concentration was detected using a specific probe and apoptosis-associated proteins were detected by Western blot. Expression of oxidative biomarkers, including superoxide dismutase, maleic dialdehyde, and glutathione, was detected commercially available assay kits. Compared with normal cells, lower cell viability, higher apoptosis rates, and more severe oxidation status were identified in the aging RPE cell model. Curcumin improved cell viability and decreased apoptosis and oxidative stress. Further, curcumin had a significant influence on expression of apoptosis-associated proteins and oxidative stress biomarkers. In conclusion, treatment with curcumin was able to regulate proliferation, oxidative stress, and apoptosis in aging RPE cells. Accordingly, application of curcumin may be a novel strategy to protect against age-related change in AMD.

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The design and implementation of a study to investigate the effectiveness of community vs hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease.

Taylor J, Scott LJ, Rogers CA, Muldrew A, O'Reilly D, Wordsworth S, Mills N, Hogg R, Violato M, Harding SP, Peto T, Townsend D, Chakravarthy U, Reeves BC.

Introduction: Standard treatment for neovascular age-related macular degeneration (nAMD) is intravitreal injections of anti-VEGF drugs. Following multiple injections, nAMD lesions often become quiescent but there is a high risk of reactivation, and regular review by hospital ophthalmologists is the norm. The present trial examines the feasibility of community optometrists making lesion reactivation decisions.

Methods: The Effectiveness of Community vs Hospital Eye Service (ECHOES) trial is a virtual trial; lesion reactivation decisions were made about vignettes that comprised clinical data, colour fundus photographs, and optical coherence tomograms displayed on a web-based platform. Participants were either hospital ophthalmologists or community optometrists. All participants were provided with webinar training on the disease, its management, and assessment of the retinal imaging outputs. In a balanced design, 96 participants each assessed 42 vignettes; a total of 288 vignettes were assessed seven times by each professional group. The primary outcome is a participant's judgement of lesion reactivation compared with a reference standard. Secondary outcomes are the frequency of sight threatening errors; judgements about specific lesion components; participant-rated confidence in their decisions about the primary outcome; cost effectiveness of follow-up by optometrists rather than ophthalmologists.

Discussion: This trial addresses an important question for the NHS, namely whether, with appropriate training, community optometrists can make retreatment decisions for patients with nAMD to the same standard as hospital ophthalmologists. The trial employed a novel approach as participation was entirely through a web-based application; the trial required very few resources compared with those that would have been needed for a conventional randomised controlled clinical trial.

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[Evaluation of the German version of the caregiver reaction assessment questionnaire for informal caregivers of patients with neovascular age-related macular degeneration].[Article in German]

Weyer-Wendl H, Tamm M, Walter P.

BACKGROUND: Informal caregivers of patients with loss of vision often have to give physical and emotional support because of the high level of dependence induced. Although it is known that these informal caregivers suffer a higher risk of being affected by burn-out syndrome or depression, the various dimensions of burden, especially of informal caregivers of patients with neovascular age-related macular degeneration (nv-AMD) have not yet been investigated.

OBJECTIVE: The objective of this study was the evaluation of the German version of the caregiver reaction assessment (CRA) questionnaire in a collective of informal caregivers of patients with nv-AMD. In this context the positive and negative influences on the informal caregivers were assessed.

MATERIAL AND METHODS: Between January 2013 and July 2014 a total of 150 informal caregivers of patients with nv-AMD filled out the CRA independently using a questionnaire survey which had been translated into German. Based on this collective, the psychometric characteristics of the translated questionnaire were evaluated.

RESULTS: The informal caregivers of the current collective reported a lower burden in the five subgroups disrupted schedule, lack of family support, self-esteem, health problems and financial problems, compared to the previous CRA studies with caregivers of patients with other diseases. The informal caregivers saw the greatest burden as the disruption of their schedule. Through a principal component analysis the five subgroups could be identified as five factors. It was shown that 19 out of the 24 items could be assigned to the same factors as in the original English version. The internal consistency of the five subgroups was acceptable except for the subscale on self-esteem.

CONCLUSION: In this study the CRA has been confirmed as a suitable instrument to assess both positive and negative reactions of informal caregivers related to caregiving of patients with nv-AMD. The results provide support for a five subscale structure of the CRA in the original English version but five items of the questionnaire could be assigned to another subscale.

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Diet rich in carotenoids is linked to reduced risk of advanced age related macular degeneration.

Wise J.

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