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Drug treatment

EBioMedicine. 2016 Feb 4;5:198-203. eCollection 2016.

Regression of Some High-risk Features of Age-related Macular Degeneration (AMD) in Patients Receiving Intensive Statin Treatment.

Vavvas DG, Daniels AB, Kapsala ZG, Goldfarb JW, Ganotakis E, Loewenstein JI, Young LH, Gragoudas ES, Elliott D, Kim IK, Tsilimbaris MK, Miller JW.

IMPORTANCE: Age-related macular degeneration (AMD) remains the leading cause of blindness in developed countries, and affects more than 150 million worldwide. Despite effective anti-angiogenic therapies for the less prevalent neovascular form of AMD, treatments are lacking for the more prevalent dry form. Similarities in risk factors and pathogenesis between AMD and atherosclerosis have led investigators to study the effects of statins on AMD incidence and progression with mixed results. A limitation of these studies has been the heterogeneity of AMD disease and the lack of standardization in statin dosage.

OBJECTIVE: We were interested in studying the effects of high-dose statins, similar to those showing regression of atherosclerotic plaques, in AMD.

DESIGN: Pilot multicenter open-label prospective clinical study of 26 patients with diagnosis of AMD and the presence of many large, soft drusenoid deposits. Patients received 80 mg of atorvastatin daily and were monitored at baseline and every 3 months with complete ophthalmologic exam, best corrected visual acuity (VA), fundus photographs, optical coherence tomography (OCT), and blood work (AST, ALT, CPK, total cholesterol, TSH, creatinine, as well as a pregnancy test for premenopausal women).

RESULTS: Twenty-three subjects completed a minimum follow-up of 12 months. High-dose atorvastatin resulted in regression of drusen deposits associated with vision gain (+ 3.3 letters, $p = 0.06$) in 10 patients. No subjects progressed to advanced neovascular AMD.

CONCLUSIONS: High-dose statins may result in resolution of drusenoid pigment epithelial detachments (PEDs) and improvement in VA, without atrophy or neovascularization in a high-risk subgroup of AMD patients. Confirmation from larger studies is warranted.

PMID: 27077128 [PubMed - in process]

Br J Ophthalmol. 2016 Apr 12. [Epub ahead of print]

Changes in intraocular pressure in study and fellow eyes in the IVAN trial.

Foss AJ, Scott LJ, Rogers CA, Reeves BC, Ghanchi F, Gibson J, Chakravarthy U; IVAN study group.

PURPOSE: To describe changes in intraocular pressure (IOP) in the 'alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)' trial (registered as ISRCTN92166560).

DESIGN: Randomised controlled clinical trial with factorial design.

PARTICIPANTS: Patients (n=610) with treatment naïve neovascular age-related macular degeneration were enrolled and randomly assigned to receive either ranibizumab or bevacizumab and to two regimens, namely monthly (continuous) or as needed (discontinuous) treatment.

METHODS: At monthly visits, IOP was measured preinjection in both eyes, and postinjection in the study eye.

OUTCOME MEASURES: The effects of 10 prespecified covariates on preinjection IOP, change in IOP (postinjection minus preinjection) and the difference in preinjection IOP between the two eyes were examined.

RESULTS: For every month in trial, there was a statistically significant rise in both the preinjection IOP and the change in IOP postinjection during the time in the trial (estimate 0.02 mm Hg, 95% CI 0.01 to 0.03, $p < 0.001$ and 0.03 mm Hg, 95% CI 0.01 to 0.04, $p = 0.002$, respectively). There was also a small but significant increase during the time in trial in the difference in IOP between the two eyes (estimate 0.01 mm Hg, 95% CI 0.005 to 0.02, $p < 0.001$). There were no differences between bevacizumab and ranibizumab for any of the three outcomes ($p = 0.93$, $p = 0.22$ and $p = 0.87$, respectively).

CONCLUSIONS: Anti-vascular endothelial growth factor agents induce increases in IOP of small and uncertain clinical significance.

PMID: 27073205 [PubMed - as supplied by publisher] Free full text

Acta Ophthalmol. 2016 Apr 7. [Epub ahead of print]

Aflibercept vs. Ranibizumab: cost-effectiveness of treatment for wet age-related macular degeneration in Sweden.

Panchmatia HR, Clements KM, Hulbert E, Eriksson M, Wittrup-Jensen K, Nilsson J, Weinstein MC.

PURPOSE: Monthly dosing with ranibizumab (RBZ) is needed to achieve maximal visual gains in patients with neovascular ('wet') age-related macular degeneration (wAMD). In Sweden, dosing is performed as needed (RBZ PRN), resulting in suboptimal efficacy. Intravitreal aflibercept (IVT-AFL) every 2 months after three initial monthly doses was clinically equivalent to RBZ monthly dosing (RBZ q4) in wAMD clinical trials. We assessed the cost-effectiveness of IVT-AFL versus RBZ q4 and RBZ PRN in Sweden.

METHODS: A Markov model compared IVT-AFL to RBZ q4 or RBZ PRN over 2 years. Health states were based on visual acuity in better-seeing eye; a proportion discontinued treatment monthly or upon visual acuity $< 20/400$. Parameters were estimated from trial data, published literature or expert opinion. Analyses were performed from a societal perspective with a lifetime horizon. The model calculated costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs), discounted 3% annually. Deterministic and probabilistic sensitivity analyses were performed.

RESULTS: Lifetime cost of IVT-AFL was 578 400 SEK, compared with 565 700 SEK for RBZ PRN and 686 600 SEK for RBZ q4. Compared with RBZ PRN, the ICER of IVT-AFL was 27 000 SEK/QALY gained. RBZ q4 cost 20.4 million SEK/QALY gained versus IVT-AFL. Results were sensitive to IVT-AFL efficacy, but IVT-AFL had a 100% probability of being cost-effective versus both RBZ PRN and RBZ q4 at a willingness-to-pay threshold of 500 000 SEK.

CONCLUSION: Results suggest, in Sweden, at parity price level, IVT-AFL is less costly than RBZ q4, while demonstrating similar efficacy; IVT-AFL is cost-effective versus RBZ PRN.

PMID: 27061020 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2016 Apr 13. [Epub ahead of print]

FLATTENING OF A TREATMENT-RESISTANT RETINAL PIGMENT EPITHELIAL DETACHMENT AFTER A SINGLE INTRAVITREAL INJECTION OF ZIV-AFLIBERCEPT.

Yogi R, Stewart M, Chhablani J.

PURPOSE: To report flattening of a treatment-resistant retinal pigment epithelial detachment (PED) due to neovascular age-related macular degeneration after a single intravitreal injection of ziv-aflibercept (Zaltrap).

METHODS: A 67-year-old woman with a neovascular age-related macular degeneration-related PED was treated with intravitreal injections of bevacizumab and ranibizumab, and in combination with verteporfin photodynamic therapy, before receiving a single intravitreal injection of ziv-aflibercept (1.25 mg/0.05 mL).

RESULTS: The patient presented with a visual acuity of 20/30 in the right eye, a PED height of 581 μm , and a central macular thickness of 381 μm . She received eight intravitreal injections of bevacizumab and ranibizumab, one in combination with photodynamic therapy. The height of the PED and the central macular thickness varied over time, but 3 years later, they measured 382 μm and 418 μm , respectively. A single intravitreal injection of ziv-aflibercept resulted in a dramatic reduction in PED height to 140 μm , which was maintained 2 months later. The visual acuity remained stable, and there were no clinical signs of toxicity.

CONCLUSION: Intravitreal ziv-aflibercept safely and effectively improved a treatment-resistant PED. Intravitreal ziv-aflibercept could become a treatment option for neovascular age-related macular degeneration in countries where aflibercept (Eylea) is not available or its cost is prohibitive, but further studies are necessary to establish efficacy and safety.

PMID: 27078613 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1798-806.

Intravitreal Anti-Vascular Endothelial Growth Factor Therapy and Retinal Nerve Fiber Layer Loss in Eyes With Age-Related Macular Degeneration: A Meta-Analysis.

Shin HJ, Kim SN, Chung H, Kim TE, Kim HC.

PURPOSE: Clinical study findings regarding the association between repeated injections of intravitreal anti-vascular endothelial growth factor (VEGF) and the risk of retinal nerve fiber layer (RNFL) thinning in patients with age-related macular degeneration (AMD) have been inconsistent. We investigated this association by using a meta-analysis.

METHODS: In August 2015, we systematically reviewed PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials. Two independent evaluators identified eligible articles by using predetermined selection criteria. Average RNFL thickness before and after intravitreal anti-VEGF injections was examined by using data obtained at baseline and at the last follow-up visit.

RESULTS: Six studies on 288 eyes were ultimately included. The meta-analysis revealed that average RNFL thickness following repeated anti-VEGF injections was not significantly different from baseline (mean difference [MD] = -0.171, 95% confidence interval [CI]: -0.371 to 0.029, $P = 0.093$) or control group measurements (MD = -0.091, 95% CI: -0.517 to 0.335, $P = 0.674$). However, subgroup analyses by the methodologic quality of study revealed a significant RNFL thickness loss in two low-biased, controlled experimental studies (MD = -0.534, 95% CI: -0.783 to -0.286, $P = 0.001$), but not in four observational studies (MD = -0.038, 95% CI: -0.171 to 0.095, $P = 0.576$).

CONCLUSIONS: There was no association between anti-VEGF injections and RNFL thickness changes when all studies were examined together. However, when two low-biased, controlled clinical trials were separately examined, repeated anti-VEGF injection was associated with RNFL loss. Large-scale, prospective studies are needed to determine long-term effects of anti-VEGF treatments on the RNFL in

AMD patients.

PMID: 27077733 [PubMed - in process]

Ophthalmologica. 2016 Apr 16. [Epub ahead of print]

Arteriosclerotic Changes after Intravitreal Injections of Anti-Vascular Endothelial Growth Factor Drugs in Patients with Exudative Age-Related Macular Degeneration.

Shiba T, Takahashi M, Yoshida I, Taniguchi H, Matsumoto T, Hori Y.

PURPOSE: The aim of this study was to determine whether multiple intravitreal injections of anti-vascular endothelial growth factor (VEGF) drugs for age-related macular degeneration (AMD) exacerbate systemic arteriosclerosis, using the cardio-ankle vascular index (CAVI) and intima-media thickness (IMT).

METHODS: We analyzed the data of 45 AMD patients who received intravitreal injections of anti-VEGF drugs (ranibizumab and/or aflibercept) and underwent systemic evaluations at baseline and after treatment. Reevaluation was conducted at ≥ 12 months from the initial treatment.

RESULTS: The total number of intravitreal injections of overall anti-VEGF drugs was significantly correlated with x0394;serum cystatin C. The cumulative number of aflibercept injections was identified as an independent protective factor for x0394;CAVI. An increase in the cumulative number of intravitreal injections of overall anti-VEGF drugs was identified as a protective factor for x0394;mean IMT.

CONCLUSION: Repeated intravitreal injections of an anti-VEGF drug for AMD may lead to morphological and functional changes in large arteries.

PMID: 27082736 [PubMed - as supplied by publisher]

Ophthalmology. 2016 Apr 12. [Epub ahead of print]

Comprehensive Review of Ocular and Systemic Safety Events with Intravitreal Aflibercept Injection in Randomized Controlled Trials.

Kitchens JW, Do DV, Boyer DS, Thompson D, Gibson A, Saroj N, Vitti R, Berliner AJ, Kaiser PK.

PURPOSE: To assess the ocular and systemic safety of intravitreal aflibercept injection (IAI) compared with controls in IAI trials in neovascular age-related macular degeneration (nAMD), macular edema following central retinal vein occlusion (MEfCRVO), macular edema following branch retinal vein occlusion (MEfBRVO), and diabetic macular edema (DME).

DESIGN: Comprehensive review of 10 phase II and III trials of IAI in retinal diseases.

PARTICIPANTS: Patients were included from IAI trials in nAMD (CLEAR-IT 2 [52 weeks], VIEW 1 [96 weeks], VIEW 2 [96 weeks], VIEW 1 extension [208 weeks]); MEfCRVO (COPERNICUS [100 weeks], GALILEO [76 weeks]); MEfBRVO (VIBRANT [52 weeks]); and DME (DA VINCI [52 weeks], VIVID [100 weeks], VISTA [100 weeks]).

METHODS: Rates were calculated as events/100 person-years at risk (PYR). When applicable, rate ratios (RRs) and 95% confidence intervals (CIs) were provided.

MAIN OUTCOME MEASURES: Outcomes included rates for intraocular inflammation, endophthalmitis, serious adverse events (SAEs), wound-healing complications, hypertension (HTN), adjudicated Anti-Platelet Trialists' Collaboration (APTC)-defined arterial thromboembolic events (ATEs) (nonfatal myocardial infarction, nonfatal stroke, and vascular death), and death from all causes.

RESULTS: More than 4000 patients contributed >7000 PYR. For all outcomes, there were no meaningful

differences between evaluated adverse event rates for IAI and controls. Overall intraocular inflammation rates were 2.37 (control) and 2.06 (IAI); overall RR was 0.87 (95% CI, 0.61-1.27). Overall endophthalmitis rates were 0.52 (control) and 0.22 (IAI); overall RR was 0.42 (95% CI, 0.18-1.03). Overall SAE rates were 23.09 (control) and 20.80 (IAI); overall RR was 0.90 (95% CI, 0.80-1.02). Overall rates of wound-healing complications were 0.17 (control) and 0.15 (IAI); overall RR was 0.86 (95% CI, 0.24-3.86). Overall HTN rates were 14.87 (control) and 11.27 (IAI), with an overall RR of 0.76 (95% CI, 0.65-0.89); HTN rates were highest in MEfBRVO and lowest in nAMD. For adjudicated APTC-defined ATEs, rates were 2.04 (control) and 2.19 (IAI), with an RR of 1.07 (95% CI, 0.73-1.61). Overall death rates were 1.16 (control) and 1.49 (IAI); overall RR was 1.28 (95% CI, 0.80-2.15).

CONCLUSIONS: Rates of selected ocular and systemic adverse events with IAI were similar to those of controls and similar across disease states in evaluated IAI trials. Intravitreal aflibercept injection was generally well tolerated in the patients evaluated.

PMID: 27084563 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Apr 15. [Epub ahead of print]

Early treatment of acute submacular haemorrhage secondary to wet AMD using intravitreal tissue plasminogen activator, C3F8, and an anti-VEGF agent.

de Silva SR, Bindra MS.

Purpose: Acute submacular haemorrhage secondary to wet age-related macular degeneration (AMD) has a poor prognosis for which there is currently no 'gold standard' treatment. We evaluated the efficacy of early treatment using intravitreal triple therapy of tissue plasminogen activator (tPA), expansile gas, and an anti-VEGF agent.

Methods: This retrospective case series included eight patients presenting with acute submacular haemorrhage involving the fovea. All patients received treatment with 50 µg (0.05 ml) tPA, 0.3 ml 100% perfluoropropane (C3F8), and an anti-VEGF agent (0.05 mg Ranibizumab or 1.25 mg Bevacizumab in 0.05 ml) administered via intravitreal injection. An anterior chamber paracentesis post injection or vitreous tap was performed before injection to prevent retinal vascular occlusion secondary to raised intra-ocular pressure. Outcomes assessed were visual acuity, change in macular morphology, and complications.

Results: Patients presented promptly with delay between symptom onset and clinic review being 1.9±0.6 days (mean±SD). Treatment was delivered quickly with interval from presentation to treatment being 1.1±1.2 days. Symptom onset to treatment was 3.0±1.0 days. Subfoveal haemorrhage was effectively displaced in all patients. LogMAR visual acuity improved from 1.67±0.47 at presentation to 0.63±0.33 at final follow-up ($P<0.0001$), a mean of 7.9±4.8 months after treatment. Central retinal thickness improved from 658.1±174.2 µm at presentation to 316.6±142.4 µm at final follow-up ($P=0.0028$).

Conclusions: Early treatment of submacular haemorrhage using intravitreal tPA, C3F8, and anti-VEGF was effective in significantly improving visual acuity in this series of patients who presented soon after symptom onset. Treatment was well tolerated in this group of elderly and potentially frail patients. Eye advance online publication, 15 April 2016; doi:10.1038/eye.2016.67.

PMID: 27080482 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2016 Apr 12:0. doi: 10.5301/ejo.5000786. [Epub ahead of print]

Response to anti-VEGF-A treatment of retinal pigment epithelial cells in vitro.

Puddu A, Sanguineti R, Traverso CE, Viviani GL, Nicolò M.

PURPOSE: The neovascular or wet form of age-related macular degeneration is characterized by the

growth of abnormal blood vessels in the retina stimulated by vascular endothelial growth factors (VEGF). In the last decade, several anti-VEGF drugs have been developed for treating neovascular diseases of the eyes. This study was conducted to compare the effects of 2 anti-VEGF-A drugs, ranibizumab and aflibercept, on the expression and secretion of VEGF family members in retinal pigment epithelial cells (RPE) in vitro.

METHODS: ARPE-19 cells were exposed for 24 hours to ranibizumab or aflibercept at clinical dose concentration. Cell viability and expression and secretion of VEGF-A, VEGF-B, VEGF-C, and placental growth factor (PIGF) were evaluated respectively by real-time polymerase chain reaction and enzyme-linked immunosorbent assay.

RESULTS: Ranibizumab and aflibercept did not affect ARPE-19 cell viability after 24 hours of treatment. Ranibizumab increased expression of VEGF-A and PIGF. On the contrary, expression and secretion of VEGF-C was decreased by ranibizumab. PIGF secretion was not affected by ranibizumab. Aflibercept strongly increased VEGF-A and PIGF expression but reduced their detection on the culture media, and decreased expression and secretion of VEGF-C. No effect on expression and secretion of VEGF-B was observed after exposure to these drugs.

CONCLUSIONS: Ranibizumab and aflibercept exert similar effects on VEGF expression and secretion, leading to establishing an antiangiogenic environment. Increased VEGF-A expression observed in RPE cells treated with these drugs suggests a compensatory response of the cells to the lack of VEGF-A.

PMID: 27079208 [PubMed - as supplied by publisher]

Case Rep Ophthalmol. 2016 Mar 17;7(1):154-62.

Blockade of Tumor Necrosis Factor-Alpha: A Role for Adalimumab in Neovascular Age-Related Macular Degeneration Refractory to Anti-Angiogenesis Therapy?

Fernández-Vega B, Fernández-Vega Á, Rangel CM, Nicieza J, Villota-Deleu E, Vega JA, Sanchez-Avila RM.

AIMS: To report a case of wet age-related macular degeneration (wet-AMD) refractory to intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy in a patient who showed visual and anatomical improvement and stabilization after starting a subcutaneous treatment course with adalimumab, an anti-tumor necrosis factor-alpha (TNF- α) drug, for concomitant Crohn's disease.

METHODS: Observational case report of a female patient. Ophthalmological evaluation was performed by slit lamp and ophthalmoscopy (posterior pole and anterior segment). Best-corrected visual acuity (BCVA) was determined, and imaging was performed by fluorescein angiography, indocyanine green angiography, and optical coherence tomography (OCT). Intravitreal therapies used and treatment with anti-TNF- α were recorded.

RESULTS: A 64-year-old woman with wet-AMD was treated with fourteen intravitreal injections of ranibizumab (0.5 mg) for a period of 40 months with intervals of 1-6 months. She initially showed a good visual and anatomical response to periodic anti-VEGF treatment but during check visits, anatomical and functional responses deteriorated. At the 40-month follow-up, the patient had developed Crohn's disease, and her rheumatologist started treatment with adalimumab (40 mg subcutaneously every 2 weeks). During the 25 months of treatment with adalimumab, the patient did not require any additional intravitreal anti-VEGF treatments because her BCVA, clinical, and OCT findings improved and remained stable.

CONCLUSIONS: We described a case of a patient with wet-AMD refractory to anti-VEGF therapy, which clinically benefited from subcutaneous adalimumab therapy. Treatment with subcutaneous anti-TNF- α in combination with anti-VEGF therapy avoids the high cost and risks related to multiple intravitreal anti-VEGF injections with good functional and anatomic outcomes.

PMID: 27065854 [PubMed] PMCID: PMC4821150 Free PMC Article

Eur J Ophthalmol. 2016 Apr 12:0. [Epub ahead of print]

Response to bevacizumab after treatment with aflibercept in eyes with neovascular AMD.

Waizel M, Rickmann A, Blanke BR, Wolf K, Kazerounian S, Szurman P.

PURPOSE: To study the visual outcome and change in central macular thickness (CMT) in patients with neovascular age-related macular degeneration (AMD) who were previously treated with aflibercept (VEGF Trap-Eye, Eylea) and were subsequently switched to bevacizumab (Avastin).

METHODS: In this observational analysis, 19 eyes initially treated with at least 3 injections of bevacizumab after initial treatment with at least 3 injections of aflibercept are reported. Outcome measures were Snellen visual acuity (best-corrected visual acuity (BCVA) and CMT measured by spectral-domain optical coherence tomography.

RESULTS: A total of 19 eyes initially treated with 6.5 ± 2.8 intravitreal injections of aflibercept were switched to 5.4 ± 3.2 injections of bevacizumab. Median BCVA decreased from 20/94 to 20/113 after aflibercept and increased slightly to 20/101 after bevacizumab ($p = 0.84$, Friedman test). Of all 19 eyes, 36.8% achieved gain in visual acuity of more than 1 line and 21.1% of more than 3 lines. The CMT decreased slightly from $433 \pm 229 \mu\text{m}$ at baseline to $367 \pm 198 \mu\text{m}$ after aflibercept treatment ($p = 0.18$, Wilcoxon test) and decreased statistically significantly to $335 \pm 184 \mu\text{m}$ after bevacizumab treatment ($p = 0.0065$, Wilcoxon test).

CONCLUSIONS: Switching from aflibercept to bevacizumab treatment has an equivalent anatomical effect in eyes with neovascular AMD as switching from bevacizumab to aflibercept. Therefore, switching back to bevacizumab might represent a reasonable therapy strategy to overcome tachyphylaxis during long-term monotherapy with aflibercept.

PMID: 27079204 [PubMed - as supplied by publisher]

Clin Interv Aging. 2016 Mar 24;11:357-65. eCollection 2016.

Effects of intravitreal ranibizumab on the untreated eye and systemic gene expression profile in age-related macular degeneration.

Michalska-Malecka K, Kabiesz A, Kimsa MW, Strzałka-Mrozik B, Formińska-Kapuścik M, Nita M, Mazurek U.

Abstract: The purpose of this study was to evaluate the systemic effects of intravitreal ranibizumab (Lucentis) treatment in patients with neovascular age-related macular degeneration (AMD). The impact of intravitreal ranibizumab injections on central retinal thickness (CRT) of treated and contralateral untreated eyes, and differences in gene expression patterns in the peripheral blood mononuclear cells were analyzed. The study included 29 patients aged 50 years old and over with diagnosed neovascular AMD. The treatment was defined as 0.5 mg of ranibizumab injected intravitreally in the form of one injection every month during the period of 3 months. CRT was measured by optical coherence tomography. The gene expression profile was assigned using oligonucleotide microarrays of Affymetrix HG-U133A. Studies have shown that there was a change of CRT between treated and untreated eyes, and there were differences in CRT at baseline and after 1, 2, and 3 months of ranibizumab treatment. Three months after intravitreal injection, mean CRT was reduced in the treated eyes from 331.97 ± 123.62 to $254.31 \pm 58.75 \mu\text{m}$, while mean CRT in the untreated fellow eyes reduced from 251.07 ± 40.29 to $235.45 \pm 36.21 \mu\text{m}$ at the same time. Furthermore, the research has shown that among all transcripts, 3,097 expresses change after the ranibizumab treatment in relation to controls. Among these transcripts, 1,339 were up-regulated, whereas 1,758 were down-regulated. Our results show the potential systemic effects of anti-VEGF therapy for AMD. Moreover, our study indicated different gene expression in peripheral blood mononuclear cells before and after intravitreal ranibizumab treatment.

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Retina. 2016 Mar 3. [Epub ahead of print]

RETINAL PIGMENT EPITHELIAL TEAR AFTER INTRAVITREAL RANIBIZUMAB TREATMENT FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Cho HJ, Kim HS, Yoo SG, Han JI, Lew YJ, Cho SW, Lee TG, Kim JW.

PURPOSE: To evaluate the risk factors for retinal pigment epithelium (RPE) tears after intravitreal ranibizumab injections in neovascular age-related macular degeneration (nAMD) and to determine the efficacy of continued ranibizumab treatment after RPE tears.

METHODS: A total of 407 treatment-naïve eyes (377 patients) with nAMD were retrospectively included. All patients were treated with an initial series of 3 monthly loading injections, followed by further injections as required. Baseline characteristics and pigment epithelial detachment (PED) lesion features were evaluated as potential risk factors for RPE tear. The visual and anatomical outcomes after treatment during 12 months were also evaluated.

RESULTS: By 12 months, RPE tears developed in 32 eyes (7.9%). Pigment epithelial detachment height was associated with a higher risk of RPE tear (odds ratio [OR], 1.318; 95% confidence interval [CI], 1.217-2.031, $P = 0.018$). Fibrovascular PED compared with serous PED had a higher risk of developing tears (OR, 9.129; 95% CI, 6.228-32.124, $P = 0.039$), and typical nAMD (OR, 4.166; 95% CI, 2.030-14.913, $P = 0.031$) and retinal angiomatous proliferation (OR, 3.778; 95% CI, 2.185-9.277, $P = 0.040$) had a higher risk of developing tears compared with polypoidal choroidal vasculopathy. Mean best-corrected visual acuity (BCVA) of RPE tear patients showed no significant improvement after treatment at 12 months; however, patients with RPE tears without foveal involvement (19 eyes) showed significant BCVA improvement at 12 months ($P = 0.034$).

CONCLUSION: PED type and nAMD subtype are associated with the development of RPE tears after intravitreal ranibizumab injections. Continued ranibizumab therapy after RPE tear development can maintain visual acuity when the fovea is not involved.

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Br J Ophthalmol. 2016 Apr 12. [Epub ahead of print]

Functional-morphological parameters, aqueous flare and cytokines in macular oedema with branch retinal vein occlusion after ranibizumab.

Noma H, Mimura T, Yasuda K, Shimura M.

BACKGROUND/AIMS: Correlations among functional-morphological parameters, the aqueous flare value (an indicator of inflammation) and aqueous humour levels of cytokines/inflammatory factors were investigated in patients with branch retinal vein occlusion (BRVO) and macular oedema who received intravitreal ranibizumab injection (IRI) and were followed for 6 months.

METHODS: Aqueous humour levels of 11 cytokines or growth inflammatory/factors were measured in 45 patients with BRVO and macular oedema who received IRI. Patients with recurrent macular oedema were given further IRI as needed. Aqueous humour levels of vascular endothelial growth factor (VEGF), soluble VEGF receptor (sVEGFR) and other cytokines/inflammatory factors were measured by the suspension array method. Aqueous flare values were measured with a laser flare metre and macular oedema was examined by optical coherence tomography.

RESULTS: There were significant correlations between the aqueous flare and the aqueous levels of sVEGFR-1, placental growth factor, monocyte chemoattractant protein 1, soluble intercellular adhesion molecule-1, interleukin (IL)-6 and IL-8. There were also significant correlations between the change of the aqueous flare and improvement of central macular thickness after 1 month, after 6 months and at the 1st recurrence. Furthermore, a significant correlation was noted between the change of the aqueous flare and

improvement of best-corrected visual acuity at 6 months after IRI, but not at 1 month or at the 1st recurrence.

CONCLUSIONS: These findings suggest that the aqueous flare is associated with inflammatory factors/ cytokines, and that the change of the aqueous flare value may influence the long-term prognosis in patients with BRVO receiving IRI therapy for macular oedema.

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Clin Experiment Ophthalmol. 2016 Apr 6. [Epub ahead of print]

Combination of vascular endothelial growth factor inhibitors and laser therapy for diabetic macula oedema: a review.

Mehta H, Gillies MC, Fraser-Bell S.

Abstract: This review provides a perspective on published and ongoing clinical trials of vascular endothelial growth factor inhibitors (anti-VEGF agents) combined with laser therapy for diabetic macular oedema (DMO). Although there was little short-term benefit in combining prompt macular laser with anti-VEGF therapy for centre-involving DMO in the Diabetic Retinopathy Clinical Research Network (DRCRnet) Protocol I study, deferred macular laser was still required in over 40% of study eyes in DRCRnet Protocol T. Macular laser was applied in more than 30% of eyes with centre-involving DMO receiving ranibizumab in the RISE and RIDE studies. For non centre-involving DMO the evidence-base still supports use of focal macular laser alone, although clinicians should be cautious about applying laser too close to the foveal avascular zone with the availability of pharmacotherapy. Ongoing clinical trials are assessing whether selectively targeting areas of peripheral retinal ischaemia with laser reduces the number of anti-VEGF injections to stabilise DMO and whether combining macular micropulse laser with anti-VEGF therapy is beneficial in DMO.

PMID: 27061760 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2016 Apr 11. [Epub ahead of print]

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

Hanhart J, Vinker S.

PMID: 27079300 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2016 Apr 13. [Epub ahead of print]

PATTERNS OF FUNDUS AUTOFLUORESCENCE DEFECTS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION SUBTYPES.

Ozkok A, Sigford DK, Tezel TH.

PURPOSE: To test define characteristic fundus autofluorescence patterns of different exudative age-related macular degeneration subtypes.

METHODS: Cross-sectional study. Fifty-two patients with choroidal neovascularization because of three different neovascular age-related macular degeneration subtypes were included in the study. Macular and peripheral fundus autofluorescence patterns of study subjects were compared in a masked fashion.

RESULTS: Fundus autofluorescence patterns of all three neovascular age-related macular degeneration subtypes revealed similar patterns. However, peripapillary hypo-autofluorescence was more common among patients with polypoidal choroidal vasculopathy (88.2%) compared with patients with retinal angiomatous proliferation (12.5%) and patients without retinal angiomatous proliferation and polypoidal choroidal vasculopathy (21.1%) ($P < 0.0001$).

CONCLUSION: Presence of peripapillary fundus autofluorescence defects in neovascular age-related macular degeneration maybe suggestive of polypoidal choroidal vasculopathy as a variant of neovascular age-related macular degeneration.

PMID: 27078800 [PubMed - as supplied by publisher]

Retina. 2016 Apr 13. [Epub ahead of print]

PROGNOSTIC VALUE OF HYPERREFLECTIVE FOCI IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATED WITH BEVACIZUMAB.

Segal O, Barayev E, Nemet AY, Geffen N, Vainer I, Mimouni M.

PURPOSE: To study the prognostic value of optical coherence tomography hyperreflective foci (HF) in neovascular age-related macular degeneration.

METHODS: Charts of naive neovascular age-related macular degeneration eyes treated with intravitreal bevacizumab between January 2011 and January 2014 were reviewed, and optical coherence tomography was collected at baseline, 3 months, and 12 months. The presence, location (inner vs. outer retinal layers), and number (few = [0-10], moderate [11-20], many [>20]) of HF were graded.

RESULTS: Overall, charts of 111 eyes were reviewed and 76 eyes of 73 patients fulfilled inclusion criteria. Baseline best-corrected visual acuity was lower in eyes with HF > 20 ($P = 0.001$), inner layer HF ($P = 0.009$), increased central retinal thickness ($P < 0.001$), and intraretinal fluid ($P < 0.001$). Baseline HF > 20 ($P = 0.002$), inner layer HF ($P = 0.01$), increased central retinal thickness ($P < 0.001$), and intraretinal fluid ($P = 0.001$) had worst best-corrected visual acuity at 12 months. Eyes with intraretinal fluid, HF > 20 , and HF adjacent to intraretinal fluid demonstrated a greater reduction in central retinal thickness; only baseline HF > 20 remained significant in multivariate analysis ($P < 0.001$). Eyes with a reduction in HF ($P = 0.02$) and resolution of inner layer HF ($P = 0.01$) had a greater central retinal thickness reduction.

CONCLUSION: Quantity and location of HF are of prognostic value in intravitreal bevacizumab-treated naive neovascular age-related macular degeneration. Increased awareness of specialists interpreting optical coherence tomography scans toward the number and location of HF is prudent.

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Graefes Arch Clin Exp Ophthalmol. 2016 Apr 14. [Epub ahead of print]

Fixation stability and implication for multifocal electroretinography in patients with neovascular age-related macular degeneration after anti-VEGF treatment.

Pedersen KB, Sjølie AK, Vestergaard AH, Andréasson S, Møller F.

PURPOSE: To quantify fixation stability in patients with neovascular age-related macular degeneration (nAMD) at baseline, 3 and 6 months after anti-vascular endothelial growth factor (anti-VEGF) treatment and furthermore assess the implications of an unsteady fixation for multifocal electroretinography (mfERG) measurements.

METHODS: Fifty eyes of 50 nAMD patients receiving intravitreal anti-VEGF treatment with either bevacizumab or ranibizumab and eight eyes of eight control subjects were included. Fixation stability measurements were performed with the Eye-Link eyetracking system and the retinal area in degrees² (deg²) containing the 68 % most frequently used fixation points (RAF68) was calculated. mfERG P1 amplitude and implicit time were analyzed in six concentric rings and as a summed response. Patients were examined at baseline, 3 and 6 months. Four different mfERG recordings were performed for the control subjects to mimic an involuntary unstable fixation: normal central fixation, 2.4°, 4.8°, and 7.1° fixation instability.

RESULTS: For control subjects, a fixation instability of 2.4° (corresponding to the central hexagon) did not reduce mfERG ring amplitudes significantly, whereas 4.8° and 7.1° fixation instability reduced the amplitudes significantly in rings 1 and 2 ($p < 0.001$) as well as in the peripheral rings in the 7.1° instability condition ($p < 0.001$). Fixation stability improved non-significantly for patients at 3 and 6 months. The size of the retinal area of fixation was at baseline, 3 and 6 months negatively correlated to visual acuity (VA) ($r_{\text{baseline}} = -0.65$, $r_3 \text{ months} = -0.60$, and $r_6 \text{ months} = -0.66$ respectively, $p < 0.001$) and mfERG amplitudes of the three innermost rings ($r_{\text{baseline}} = -0.29$, $p = 0.042$, $r_3 \text{ months} = -0.43$, $p = 0.003$ and $r_6 \text{ months} = -0.31$, $p = 0.042$). The VA cutoff for a fixation area less than 5 deg² (approximately the central hexagon) was 65, 77, and 68 ETDRS letters (corresponding a maximal Snellen equivalent of 0.31) at baseline, 3 and 6 months, respectively.

CONCLUSIONS: mfERG amplitudes in recordings of nAMD patients are at substantial risk of being reduced due to poor fixation as a large number of patients may use a fixation area of more than 5 deg². Fixation monitoring during recording as well as interpretation of results should be performed with care, especially in patients with poor visual acuity.

PMID: 27080862 [PubMed - as supplied by publisher]

Eye (Lond). 2016 Apr 15. [Epub ahead of print]

The role of indocyanine green angiography imaging in further differential diagnosis of patients with nAMD who are morphologically poor responders to ranibizumab in a real-life setting.

Ozkaya A, Alagoz C, Garip R, Alkin Z, Perente I, Yazici AT, Taskapili M.

Purpose: To evaluate the neovascular age-related macular degeneration (nAMD) in patients who were morphologically poor responders to intravitreal ranibizumab (IVR) treatment using indocyanine green angiography (ICGA) for further investigation.

Methods: This was a cross-sectional, retrospective study. The patients with an initial diagnosis of nAMD who made through the clinical examination, optical coherence tomography, and fluorescein angiography imaging, and were treated with at least three monthly IVR injections that resulted with a morphological poor response, were included. ICGA was obtained from the patients and evaluated in regard to differential diagnosis of other macular diseases, which might mimic nAMD.

Results: The study included 132 eyes of 117 patients. The mean age was 67.4 ± 9.4 years. After ICGA imaging, 13 eyes (9.8%) were diagnosed as true nAMD, 74 eyes (56.1%) as polypoidal choroidal vasculopathy (PCV), 35 eyes (26.5%) as chronic central serous chorioretinopathy (CSC), 3 eyes (2.3%) as retinal angiomatous proliferation (RAP), 3 eyes (2.3%) as choroidal neovascularization secondary to CSC, 2 eyes (1.5%) as adult-onset vitelliform macular dystrophy, and 2 eyes (1.5%) as drusenoid pigment epithelial detachment with vitelliform material, respectively. The duration between the initial diagnosis and the revised diagnosis was 15.6 ± 10.5 months in the non-AMD group, and the mean injection number of these patients was 6.6 ± 4.4 .

Conclusions: Most of the nAMD patients who were thought to be morphologically poor responders to IVR were diagnosed as having non-AMD diseases via ICGA. A detailed differential diagnostic work-up is needed before considering these patients as poor responders. Eye advance online publication, 15 April

2016; doi:10.1038/eye.2016.71.

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Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1839-1846.

Drusen Volume as a Predictor of Disease Progression in Patients With Late Age-Related Macular Degeneration in the Fellow Eye.

Abdelfattah NS, Zhang H, Boyer DS, Rosenfeld PJ, Feuer WJ, Gregori G, Sadda SR.

PURPOSE: Increasing drusen volume was proposed to be a predictor of disease progression in age-related macular degeneration (AMD). In patients with late AMD in one eye, the fellow eyes without neovascularization are known to be at higher risk of developing exudative AMD. We evaluated the relationship between drusen volume in these fellow eyes and their progression to late AMD.

METHODS: A retrospective analysis included fellow eyes with drusen associated with nonexudative AMD. All eyes with neovascular AMD were treated with intravitreal ranibizumab, aflibercept, and/or bevacizumab and followed for 2 years. All eyes were scanned with the Cirrus HD-OCT using a 512 × 128 scan pattern. Optical coherence tomography (OCT) data at baseline, month 12, and month 24 were collected using the advanced RPE analysis tool to quantify drusen volume within 3- and 5-mm-diameter circles centered on the fovea. Optical coherence tomography scans were also evaluated for the development of geographic atrophy (GA) or macular neovascularization (MNV).

RESULTS: Eighty-nine patients who had neovascular AMD in only one eye were studied. Optical coherence tomography drusen volume in the absence of MNV could be measured in 61 participants (68.5%). After 12 months, 4 eyes (4.5%) developed MNV and 15 eyes (16.9%) developed GA. By 24 months of follow-up, an additional 5 eyes (7.1%) developed MNV and an additional 10 eyes (14.3%) developed GA. At month 24, the eyes that developed GA or MNV had baseline drusen volumes that were significantly larger than in eyes that did not develop late AMD. Patients with a drusen volume over 0.03 mm³ had a greater than 4-fold increased risk for developing late AMD compared with those with lower drusen volumes.

CONCLUSIONS: Baseline drusen volume appears to be an important predictor for the development of late AMD within 2 years in eyes that have fellow eyes being actively treated for MNV. This suggests that OCT-derived drusen volume measurements may be a useful biomarker to identify eyes at the highest risk for progression to late AMD.

PMID: 27082298 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2016 Apr 8. [Epub ahead of print]

Spectral-domain optical coherence tomography retinal and choroidal thickness metric repeatability in age related macular degeneration.

Hanumunthadu D, Ilginis T, Restori M, Sagoo M, Tufail A, Balaggan KS, Patel PJ.

PURPOSE: To determine the intrasession repeatability of spectral domain-OCT (SD-OCT)-derived macular retinal and choroidal metrics in patients with neovascular age-related macular degeneration (nAMD) in the Distance of Choroid Study (DOCS) DESIGN: Validity and reliability analysis **METHODS:** Enrolled patients underwent repeated SD-OCT imaging using the Spectralis OCT. A single technician certified for clinical trials took 3 macular volume scans. Retinal thicknesses were calculated for each of the nine Early Treatment Diabetic Retinopathy Study (ETDRS) macular subfields. Center-point thickness and total macular volume were also included in the analysis. Manual subfoveal choroidal thickness measurements were made by a masked observer.

RESULTS: A total of 40 eyes of 40 patients were included in this analysis (mean age: 74.1 ($\pm$ 7.2) years, 60% male) The coefficient of repeatability (CR) of the central macular subfield was 30.6 μ m (95% confidence interval (CI) 29.8 -31.4 μ m). The CR for the other macular subfields ranged from 7.0 μ m to 38.2 μ m. The CR for the total macular volume was 0.212 mm³ (95% CI 0.206 -0.217 mm³) and the CR for the center-point was 47.5 μ m (95% CI 46.2 -48.7 μ m). Images were also reviewed for the presence of segmentation error in the central macular subfield, and after exclusion of these eyes the revised CR for this subfield was 13.7 μ m (95% CI 13.3-14.1 μ m). The intrasession CR of subfoveal choroidal thickness (SFCT) was 34.7 μ m (95% CI 33.7-35.7 μ m).

CONCLUSIONS: This study suggests that a change of greater than 31 μ m in Spectralis SD-OCT derived retinal thickness measurement of the central macular subfield and 35 μ m in subfoveal choroidal thickness is necessary to detect true clinical change associated with disease progression or improvement in nAMD with a revised figure of 14 μ m for central macular retinal subfield thickness in the absence of segmentation error.

PMID: 27066726 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2016 Apr 1;47(4):313-21.

En Face Spectral-Domain Optical Coherence Tomography Imaging of Outer Retinal Hard Exudates in Diabetic Macular Edema Based on Optical Coherence Tomography Patterns.

Kim Y, Yu SY, Kwak HW.

BACKGROUND AND OBJECTIVE: To evaluate en face spectral-domain optical coherence tomography (SD-OCT) findings of the outer retinal hard exudates in diabetic macular edema (DME).

PATIENTS AND METHODS: Exploratory analyses of prospective and consecutive case series. Fifty-five eyes treated with intravitreal ranibizumab (IVR) (Lucentis; Genentech, South San Francisco, CA) for 12 months were classified according to OCT features of DME: diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD). Area fraction of outer nuclear layer (ONL) hard exudates (HEs) was assessed from en face OCT images.

RESULTS: Area fraction of ONL HEs increased from 1.45% $\pm$ 1.22% to 2.24% $\pm$ 1.31% in DRT and from 2.24% $\pm$ 1.85% to 3.25% $\pm$ 1.52% in CME. HE gain was greatest during first 3 months (DRT = 0.83%; CME = 1.25%). SRD showed no difference in HEs (P = .462).

CONCLUSIONS: ONL HEs increased in DRT and CME at month 12 following IVR. Rapid gain of HEs was found during the initial loading phase of IVR. [Ophthalmic Surg Lasers Imaging Retina. 2016;47:313-321].

PMID: 27065369 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1782-9.

Visual Function in Older Eyes in Normal Macular Health: Association with Incident Early Age-Related Macular Degeneration 3 Years Later.

Owsley C, Clark ME, Huisinigh CE, Curcio CA, McGwin G Jr.

PURPOSE: In older eyes in normal macular health, we examined associations between impaired photopic acuity, mesopic acuity, spatial contrast sensitivity, light sensitivity, and the presence of low luminance deficit (difference between photopic and mesopic acuity) at baseline and incident AMD 3 years later. Associations were compared with an association between delayed rod-mediated dark adaptation and incident AMD, previously reported for this cohort.

METHODS: Enrollees were 60 years or older. Eyes at step 1 in the AREDS nine-step classification system based on masked grading of color fundus photographs were included. Photopic and mesopic acuity,

contrast sensitivity, and light sensitivity, and the presence of low luminance deficit, were measured at baseline. Demographic, lifestyle, general health, and blood markers were assessed at baseline as potential confounders. Three years later fundus grading was repeated to determine AMD presence.

RESULTS: For the analysis, 827 eyes of 467 persons were eligible. Impaired mesopic acuity at baseline was associated with incident AMD, age-adjusted rate ratio (RR) 1.57 (95% confidence interval [CI] 1.04-2.35), whereas impaired photopic acuity, contrast sensitivity and macular light sensitivity, and the presence of a low luminance deficit were not. The mesopic acuity association was slightly weaker than the association between abnormal dark adaptation and incident AMD (RR 1.85, 95% CI 1.07-3.20).

CONCLUSIONS: Impaired mesopic acuity in eyes in normal macular health is a risk factor for incident early AMD 3 years later, however, photopic acuity, contrast sensitivity, and light sensitivity, and the presence of a low luminance deficit are not risk factors.

PMID: 27074381 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1699-705.

Automated Identification and Quantification of Subretinal Fibrosis in Neovascular Age-Related Macular Degeneration Using Polarization-Sensitive OCT.

Roberts P, Sugita M, Deák G, Baumann B, Zotter S, Pircher M, Sacu S, Hitzenberger CK, Schmidt-Erfurth U.

PURPOSE: To identify and quantify subretinal fibrosis in eyes with advanced neovascular age-related macular degeneration (nAMD) using polarization-sensitive optical coherence tomography (PS-OCT).

METHODS: Eyes of patients with subretinal fibrosis secondary to nAMD were included in this case series. All patients underwent a complete ophthalmic examination to clearly identify advanced nAMD lesions with fibrosis. Examinations of PS-OCT were performed using a novel system with an integrated eye tracker. Areas of fibrosis in PS-OCT, automatically segmented using a custom-built algorithm, were compared with conventional imaging modalities including spectral-domain OCT, fluorescein angiography, and color fundus photography in their potential to visualize fibrosis in nAMD.

RESULTS: Fifteen eyes of 15 consecutive patients were included. In polarization-sensitive OCT B-scans, a distinct "column-like" pattern was observed in averaged axis orientation images. En face analysis provided a precise mapping of the fibrotic scar component. Fibrous tissue was selectively identified by PS-OCT based on birefringence in all lesions, whereas in SD-OCT, subretinal hyperreflective material (SHRM) could not be further classified into scar tissue, fibrovascular material, or other AMD-specific material. Based on simultaneous polarization analyses in PS-OCT, the level of RPE alteration could be evaluated as well, showing thinning and loss of RPE associated with subretinal fibrosis.

CONCLUSIONS: Using PS-OCT, subretinal fibrosis can be identified as an intrinsically birefringent structure and can be segmented based solely on tissue-specific contrast. Polarization-sensitive OCT offers a unique method to identify clinically relevant components of SHRM (i.e., neovascular tissue versus fibrous tissue) and therefore allows for an optimized disease management and evaluation of therapeutic strategies.

PMID: 27064389 [PubMed - in process]

J Ophthalmol. 2016;2016:4367631. Epub 2016 Mar 17.

Epidemiological and Clinical Baseline Characteristics as Predictive Biomarkers of Response to Anti-VEGF Treatment in Patients with Neovascular AMD.

Tsilimbaris MK, López-Gálvez MI, Gallego-Pinazo R, Margaron P, Lambrou GN.

Purpose: To review the current literature investigating patient response to anti-vascular endothelial growth factor-A (VEGF) therapy in the treatment of neovascular age-related macular degeneration (nAMD) and to identify baseline characteristics that might predict response.

Method: A literature search of the PubMed database was performed, using the keywords: AMD, anti-VEGF, biomarker, optical coherence tomography, treatment outcome, and predictor. The search was limited to articles published from 2006 to date. Exclusion criteria included phase 1 trials, case reports, studies focusing on indications other than nAMD, and oncology.

Results: A total of 1467 articles were identified, of which 845 were excluded. Of the 622 remaining references, 47 met all the search criteria and were included in this review.

Conclusion: Several baseline characteristics correlated with anti-VEGF treatment response, including best-corrected visual acuity, age, lesion size, and retinal thickness. The majority of factors were associated with disease duration, suggesting that longer disease duration before treatment results in worse treatment outcomes. This highlights the need for early treatment for patients with nAMD to gain optimal treatment outcomes. Many of the identified baseline characteristics are interconnected and cannot be evaluated in isolation; therefore multivariate analyses will be required to determine any specific relationship with treatment response.

PMID: 27073691 [PubMed] PMCID: PMC4814677

Ophthalmol Ther. 2016 Apr 11. [Epub ahead of print]

The Treatment Paradigm for the Implantable Miniature Telescope.

Hau VS, London N, Dalton M.

Abstract: Advanced or end-stage age-related macular degeneration (AMD) results in significant visual impairment and a substantially reduced quality of life for patients. Therapeutic options for people with bilateral moderate or profound vision loss caused by end-stage AMD are limited. Although medical treatment capable of reversing the functional vision loss that results from end-stage AMD is non-existent, there are now treatments that can reverse some of that functional vision loss, including the implantable miniature telescope (IMT). This review article discusses the science behind the IMT, evaluates the data from clinical studies, and weighs the pros and cons of the technology.

PMID: 27067097 [PubMed - as supplied by publisher]

EBioMedicine. 2016 Feb 2;5:26-7. eCollection 2016.

Targeting Tissue Lipids in Age-related Macular Degeneration.

Apte RS.

PMID: 27077107 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1790.

A Quick and Easy Eye Test for Identifying Those at Most Risk of Developing Early Age-Related Macular Degeneration.

Hogg RE.

PMID: 27074382 [PubMed - in process]

Pathogenesis

Am J Ophthalmol. 2016 Apr 12. [Epub ahead of print]

Retinal ganglion cell layer change in patients treated with anti-VEGF for neovascular age related macular degeneration.

Beck M, Munk MR, Ebnetter A, Wolf S, Zinkernagel MS.

PURPOSE: To evaluate macular retinal ganglion cell thickness in patients with neovascular age-related macular degeneration (AMD) and intravitreal anti-vascular endothelial growth factor (VEGF) therapy.

DESIGN: Retrospective case series with fellow-eye comparison **METHODS:** Patients with continuous unilateral anti-VEGF treatment for sub- and juxtafoveal neovascular AMD and a minimum follow-up of 24 months were included. The retinal nerve fiber (RNFL) and retinal ganglion cell layer (RGCL) in the macula were segmented using an ETDRS grid. RNFL and RGCL thickness of the outer ring of the ETDRS grid were quantified at baseline and after repeated anti-VEGF injections, and compared to the patients' untreated fellow eye. Furthermore, best-corrected visual acuity (BCVA), age, and retinal pigment epithelium (RPE) atrophy were recorded and correlated with RNFL and RGCL.

RESULTS: Sixty eight eyes of 34 patients (23 female and 11 male; mean age 76.7 (SD±8.2) with a mean number of 31.5 (SD ±9.8) anti-VEGF injections and a mean follow-up period of 45.3 months (SD±10.5) were included. Whereas the RGCL thickness decreased significantly compared to the non-injected fellow eye ($p=0.01$) the decrease of the RNFL was not significant. Visual acuity gain was significantly correlated with RGCL thickness ($r=0.52$, $p<0.05$) at follow-up and negatively correlated ($r=-0.41$, $p<0.05$) with age. Presence of RPE atrophy correlated negatively with the RGCL thickness at follow-up ($r=-0.37$, $p=0.03$).

CONCLUSION: During the course of long term anti-VEGF therapy there is a significant decrease of the RGCL in patients with neovascular AMD to the fellow (untreated) eye.

PMID: 27084000 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1728-37.

A Targeted Inhibitor of the Alternative Complement Pathway Accelerates Recovery From Smoke-Induced Ocular Injury.

Woodell A, Jones BW, Williamson T, Schnabolk G, Tomlinson S, Atkinson C, Rohrer B.

PURPOSE: Morphologic and genetic evidence exists that an overactive complement system driven by the complement alternative pathway (AP) is involved in pathogenesis of age-related macular degeneration (AMD). Smoking is the only modifiable risk factor for AMD. As we have shown that smoke-related ocular pathology can be prevented in mice that lack an essential activator of AP, we ask here whether this pathology can be reversed by increasing inhibition in AP.

METHODS: Mice were exposed to either cigarette smoke (CS) or filtered air (6 hours/day, 5 days/week, 6 months). Smoke-exposed animals were then treated with the AP inhibitor (CR2-fH) or vehicle control (PBS) for the following 3 months. Spatial frequency and contrast sensitivity were assessed by optokinetic response paradigms at 6 and 9 months; additional readouts included assessment of retinal morphology by electron microscopy (EM) and gene expression analysis by quantitative RT-PCR.

RESULTS: The CS mice treated with CR2-fH showed significant improvement in contrast threshold compared to PBS-treated mice, whereas spatial frequency was unaffected by CS or pharmacologic intervention. Treatment with CR2-fH in CS animals reversed thinning of the retina observed in PBS-treated mice as analyzed by spectral-domain optical coherence tomography, and reversed most morphologic changes in RPE and Bruch's membrane seen in CS animals by EM.

CONCLUSIONS: Taken together, these findings suggest that AP inhibitors not only prevent, but have the

potential to accelerate the clearance of complement-mediated ocular injury. Improving our understanding of the regulation of the AP is paramount to developing novel treatment approaches for AMD.

PMID: 27064393 [PubMed - in process] PMCID: PMC4829088 [Available on 2016-10-01]

Exp Eye Res. 2016 Apr 6. [Epub ahead of print]

Astrocyte Structural Reactivity and Plasticity in Models of Retinal Detachment.

Luna G, Keeley PW, Reese BE, Linberg KA, Lewis GP, Fisher SK.

Abstract: Although retinal neurodegenerative conditions such as age-related macular degeneration, glaucoma, diabetic retinopathy, retinitis pigmentosa, and retinal detachment have different etiologies and pathological characteristics, they also have many responses in common at the cellular level, including neural and glial remodeling. Structural changes in Müller cells, the large radial glia of the retina in retinal disease and injury have been well described, that of the retinal astrocytes remains less so. Using modern imaging technology to describe the structural remodeling of retinal astrocytes after retinal detachment is the focus of this paper. We present both a review of critical literature as well as novel work focusing on the responses of astrocytes following rhegmatogenous and serous retinal detachment. The mouse presents a convenient model system in which to study astrocyte reactivity since the Müller cell response is muted in comparison to other species thereby allowing better visualization of the astrocytes. We also show data from rat, cat, squirrel, and human retina demonstrating similarities and differences across species. Our data from immunolabeling and dye-filling experiments demonstrate previously undescribed morphological characteristics of normal astrocytes and changes induced by detachment. Astrocytes not only upregulate GFAP, but structurally remodel, becoming increasingly irregular in appearance, and often penetrating deep into neural retina. Understanding these responses, their consequences, and what drives them may prove to be an important component in improving visual outcome in a variety of therapeutic situations. Our data further supports the concept that astrocytes are important players in the retina's overall response to injury and disease.

PMID: 27060374 [PubMed - as supplied by publisher] Free full text

Biochimie. 2016 Apr 6. [Epub ahead of print]

Impairment of extramitochondrial oxidative phosphorylation in mouse rod outer segments by blue light irradiation.

Calzia D, Panfoli I, Heinig N, Schumann U, Ader M, Traverso CE, Funk RH, Roehlecke C.

Abstract: Exposure to short wavelength light causes increased reactive oxygen intermediates production in the outer retina, particularly in the rod Outer Segments (OS). Consistently, the OS were shown to conduct aerobic ATP production through the ectopic expression of the electron transfer chain complexes I-IV and F1Fo-ATP synthase. These facts prompted us to verify if the oxidative phosphorylation in the OS is implied in the oxidative damage of the blue-light (BL) treated OS, in an organotypic model of mouse retina. Whole mouse eyeball cultures were treated with short wavelength BL (peak at 405 nm, output power 1 mW/cm²) for 6 h. Immunogold transmission electron microscopy confirmed the expression of Complex I and F1Fo-ATP synthase in the OS. In situ histochemical assays on unfixed sections showed impairment of respiratory Complexes I and II after BL exposure, both in the OS and IS, utilized as a control. Basal O₂ consumption and ATP synthesis were impaired in the OS purified from blue-light irradiated eyeball cultures. Electron transfer capacity between Complex I and II as well as activity of Complexes I and II was decreased in blue-light irradiated purified OS. The severe malfunctioning of the OS aerobic respiratory capacity after 6 h BL treatment may be the consequence of a self-induced damage. BL exposure would cause an initial over-functioning of both the phototransduction and respiratory chain, with reactive oxygen species production. In a self-renewal vicious cycle, membrane and protein oxidative damage, proton leakage and uncoupling, would impair redox chains, perpetuating the damage and causing hypo-metabolism with eventual apoptosis

of the rod. Data may shed new light on the rod-driven retinopathies such as Age Related Macular Degeneration, of which blue-light irradiated retina represents a model.

PMID: 27059514 [PubMed - as supplied by publisher]

Epidemiology

EBioMedicine. 2016 Jan 19;5:193-7. eCollection 2016.

Increased Burden of Vision Impairment and Eye Diseases in Persons with Chronic Kidney Disease - A Population-Based Study.

Wong CW, Lamoureux EL, Cheng CY, Cheung GC, Tai ES, Wong TY, Sabanayagam C.

BACKGROUND: Chronic kidney disease (CKD) has been shown to be associated with diabetic retinopathy (DR) and age-related macular degeneration (AMD), leading causes of blindness in elderly adults in previous studies. However, the association of CKD with visual impairment (VI) is not clear. We aimed to examine the association of CKD with VI and other age-related ocular diseases in a population-based sample of Asian adults.

METHODS: We analyzed data from 10,033 adults aged 40-80 years who participated in the Singapore Epidemiology of Eye Diseases (SEED, 2004-11) Study. CKD was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m² from serum creatinine. VI was defined as best-corrected visual acuity < 20/40 in the better eye. Cataract, retinopathy, DR, glaucoma and AMD were assessed using standardized ocular examination, retinal photography and visual field assessments. The associations of CKD with VI and ocular conditions were examined using logistic regression models adjusted for age, sex, race, smoking, alcohol intake, education status, body mass index, systolic blood pressure, diabetes mellitus, cholesterol levels and cardiovascular disease.

FINDINGS: The prevalence of VI and ocular disease were significantly higher in participants with CKD (36.1% and 84.7%) than in those without (12.9% and 54.3%, both $p < 0.001$). In multivariable models, CKD was significantly associated with VI (odds ratio [95% confidence interval] = 1.34 [1.14-1.58]), any ocular disease (1.28 [1.03-1.61]), cataract (1.24 [1.01-1.52]), any retinopathy (1.77 [1.45-2.15]), and DR (1.94 [1.47-2.54]).

INTERPRETATION: The burden of VI and eye diseases is high among persons with CKD. Our findings suggest that it may be useful to screen for ocular disease and VI in persons with CKD.

PMID: 27077127 [PubMed - in process]

Genetics

Invest Ophthalmol Vis Sci. 2016 Apr 1;57(4):1714-20.

Identification of PGF as a New Gene for Neovascular Age-Related Macular Degeneration in a Chinese Population.

Chen LJ, Ma L, Chu WK, Lai TY, Chen H, Brelén ME, Rong SS, Young AL, Tam PO, Zhang M, Pang CP.

PURPOSE: To determine the associations of the VEGFA, VEGFB, and placental growth factor (PGF) genes with neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV).

METHODS: Seven single-nucleotide polymorphisms (SNPs) in VEGFA, three SNPs in VEGFB, and five SNPs in PGF were genotyped in 1722 unrelated Chinese participants, including a Hong Kong cohort of 214 nAMD patients, 236 PCV patients, and 365 controls, and an independent Shantou cohort of 189 nAMD

patients, 187 PCV patients, and 531 controls, using TaqMan genotyping assays.

RESULTS: Placental growth factor SNPs rs2268615 (G allele, $P = 0.0047$; odds ratio [OR] = 1.54, 95% confidence interval [CI], 1.14-2.08) and rs2268614 (G allele, $P = 0.015$; OR = 1.46, 95% CI, 1.07-1.97) were associated with nAMD. A significant omnibus haplotype association with nAMD was detected for a two-SNP window containing rs2268615 and rs2268614, with a haplotype G-G conferring a 1.54-fold increased risk ($P = 0.0042$) in the Hong Kong cohort and a 1.42-fold risk ($P = 0.012$) in the Shantou cohort. Pooling of the Hong Kong and Shantou data enhanced the association of nAMD with rs2268615 ($P = 0.0022$; OR = 1.38, 95% CI, 1.12-1.69; $I^2 = 0\%$), rs2268614 ($P = 0.0067$; OR = 1.33, 95% CI, 1.08-1.63; $I^2 = 0\%$), and the G-G haplotype ($P = 0.0013$; OR = 1.46, 95% CI, 1.16-1.84; $I^2 = 0\%$). In contrast, the PGF SNPs and haplotype were not associated with PCV. Our results also revealed no association of SNPs in VEGFA and VEGFB with nAMD or PCV.

CONCLUSION: Placental growth factor is a susceptibility gene for nAMD in a Chinese population, providing new evidence to support a biological role of PGF in choroidal neovascularization.

PMID: 27064391 [PubMed - in process]

Diet, lifestyle and low vision

Ophthalmic Physiol Opt. 2016 Apr 7. [Epub ahead of print]

The value of Tablets as reading aids for individuals with central visual field loss: an evaluation of eccentric reading with static and scrolling text.

Walker R, Bryan L, Harvey H, Riazi A, Anderson SJ.

PURPOSE: Technological devices such as smartphones and tablets are widely available and increasingly used as visual aids. This study evaluated the use of a novel app for tablets (MD_evReader) developed as a reading aid for individuals with a central field loss resulting from macular degeneration. The MD_evReader app scrolls text as single lines (similar to a news ticker) and is intended to enhance reading performance using the eccentric viewing technique by both reducing the demands on the eye movement system and minimising the deleterious effects of perceptual crowding. Reading performance with scrolling text was compared with reading static sentences, also presented on a tablet computer.

METHODS: Twenty-six people with low vision (diagnosis of macular degeneration) read static or dynamic text (scrolled from right to left), presented as a single line at high contrast on a tablet device. Reading error rates and comprehension were recorded for both text formats, and the participant's subjective experience of reading with the app was assessed using a simple questionnaire.

RESULTS: The average reading speed for static and dynamic text was not significantly different and equal to or greater than 85 words per minute. The comprehension scores for both text formats were also similar, equal to approximately 95% correct. However, reading error rates were significantly ($p = 0.02$) less for dynamic text than for static text. The participants' questionnaire ratings of their reading experience with the MD_evReader were highly positive and indicated a preference for reading with this app compared with their usual method.

CONCLUSIONS: Our data show that reading performance with scrolling text is at least equal to that achieved with static text and in some respects (reading error rate) is better than static text. Bespoke apps informed by an understanding of the underlying sensorimotor processes involved in a cognitive task such as reading have excellent potential as aids for people with visual impairments.

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Vitamin A-aldehyde adducts: AMD risk and targeted therapeutics.

Sparrow JR.

Abstract: Although currently available treatment options for age-related macular degeneration (AMD) are limited, particularly for atrophic AMD, the identification of predisposing genetic variations has informed clinical studies addressing therapeutic options such as complement inhibitors and anti-inflammatory agents. To lower risk of early AMD, recommended lifestyle interventions such as the avoidance of smoking and the intake of low glycemic antioxidant-rich diets have largely followed from the identification of nongenetic modifiable factors. On the other hand, the challenge of understanding the complex relationship between aging and cumulative damage leading to AMD has fueled investigations of the visual cycle adducts that accumulate in retinal pigment epithelial (RPE) cells and are a hallmark of aging retina. These studies have revealed properties of these compounds that provide insights into processes that may compromise RPE and could contribute to disease mechanisms in AMD. This work has also led to the design of targeted therapeutics that are currently under investigation.

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Effect of dietary α -tocopherol on the bioavailability of lutein in laying hen.

Islam KM, Khalil M, Männer K, Raila J, Rawel H, Zentek J, Schweigert FJ.

Abstract: Lutein and its isomer zeaxanthin have gained considerable interest as possible nutritional ingredient in the prevention of age-related macular degeneration (AMD) in humans. Egg yolk is a rich source of these carotenoids. As an oxidative sensitive component, antioxidants such as α -tocopherol (T) might contribute to an improved accumulation in egg yolk. To test this, chickens were fed lutein esters (LE) with and without α -tocopherol as an antioxidant. After depletion on a wheat-soya bean-based lutein-poor diet for 21 days, laying hens (n = 42) were equally divided into three groups and fed the following diets for 21 days: control (basal diet), a LE group (40 mg LE/kg feed) and LE + T group (40 mg LE plus 100 mg T/kg feed). Eggs and blood were collected periodically. Carotenoids and α -tocopherol in yolk and blood plasma were determined by HPLC. Egg yolk was also analysed for total carotenoids using a one-step spectrophotometric method (iCheckTM). Lutein, zeaxanthin, α -tocopherol and total carotenoids in egg yolk were highest after 14 days of feeding and decreased slightly afterwards. At the end of the trial, eggs of LE + T group contained higher amount of lutein (13.72), zeaxanthin (0.65), α -tocopherol (297.40) and total carotenoids (21.6) compared to the LE group (10.96, 0.55, 205.20 and 18.0 mg/kg, respectively, p < 0.05). Blood plasma values of LE + T group contain higher lutein (1.3), zeaxanthin (0.06) and tocopherol (20.1) compared to LE group (1.02, 0.04 and 14.90 mg/l, respectively, p < 0.05). In conclusion, dietary α -tocopherol enhances bioavailability of lutein reflecting higher content in egg yolk and blood plasma. Improved bioavailability might be due to increased absorption of lutein in the presence of tocopherol and/or a greater stability of lutein/zeaxanthin due to the presence of α -tocopherol as an antioxidant.

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