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Drug treatment

Acta Ophthalmol. 2016 Jul 30. [Epub ahead of print]

Intravitreal ranibizumab for diabetic macular oedema in previously vitrectomized eyes.

Laugesen CS, Ostri C, Brynskov T, Lund-Andersen H, Larsen M, Vorum H, Sørensen TL.

PURPOSE: There is little information about the efficacy of intravitreal vascular endothelial growth factor (VEGF) inhibition in vitrectomized eyes. This study aimed to evaluate the efficacy of anti-VEGF (ranibizumab) on diabetic macular oedema in previously vitrectomized eyes.

METHODS: A nationwide retrospective review of medical records from 2010 to 2013.

RESULTS: We identified 33 previously vitrectomized eyes in 28 patients treated with ranibizumab injections for diabetic macular oedema. Median follow-up was 323 days (interquartile range 72-1404 days). Baseline mean visual acuity was 0.57 logMAR (95% CI 0.13-1.01) before injections. After an average of 4.7 injections (range 1-15), mean visual acuity remained stable at 0.54 logMAR (95% CI 0.13-0.95) with a mean improvement of 0.03 ($p = 0.45$, 95% CI -0.12 to 0.06). In 12 eyes (36%), visual acuity improved 0.1 logMAR or more, in 12 eyes (36%), vision was unchanged (gain or loss of 0-0.05 logMAR), and in nine eyes (27%), vision decreased 0.1 logMAR or more. Mean central foveal thickness (CFT) on optical coherence tomography (OCT) scan was 412 μm (95% CI 390-434 μm) before injections. After injections, the mean CFT decreased to 352 μm (95% CI 334-370 μm). The mean reduction in CFT was 14% (95% CI 4-24%, $p = 0.01$). Sixteen eyes (48.5%) became devoid of oedema on the last OCT scan. Despite the significant reduction in CFT, the visual acuity remained unchanged.

CONCLUSION: Intravitreal ranibizumab can be effective in previously vitrectomized eyes with diabetic macular oedema. However, the response is variable and should be carefully monitored.

PMID: 27473397

Retin Cases Brief Rep. 2016 Jul 28. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB AS AN ADJUNCTIVE TREATMENT FOR COATS DISEASE (6-YEAR FOLLOW-UP).

Giannakopoulos M, Drimtzias E, Panteli V, Vasilakis P, Gartaganis SP.

PURPOSE: To evaluate the effectiveness of intravitreal ranibizumab in combination with laser photocoagulation in the management of Coats disease.

METHOD: Six intravitreal injections of 0.5 mg (0.05 mL) ranibizumab were performed, each 4 weeks apart. Correspondence to therapy was evaluated using visual acuity measurements and optical coherence tomography images. Six months after the initiation of treatment, laser photocoagulation was applied on the telangiectasias and on the surrounding ischemic areas, followed by a single intravitreal ranibizumab injection. Three months later, laser photocoagulation was repeated in purpose to prevent recurrence.

RESULTS: In the sixth month, no improvement in visual acuity was recorded, as thick circinate hard exudates still remained in the submacular space. Nevertheless, retinal detachment had completely subsided, and fluorescein angiography showed a significant decrease of leakage from the telangiectatic vessels. At the 12-month follow-up visit, an impressive improvement was recorded, with total absorption of the submacular exudate and visual acuity being 20/30. At the 20-month follow-up visit, his visual acuity was 20/20 and the retina was flat with no signs of macular edema or exudates. At the 6-year follow-up visit, the patient was absolutely stable.

DISCUSSION: Elevated vascular endothelial growth factor levels have been demonstrated in Coats disease. Anti-vascular endothelial growth factor agents assist to the decrease of vascular permeability of the capillary endothelial cells, thus increasing the efficiency of laser application.

PMID: 27472513

Retina. 2016 Jul 28. [Epub ahead of print]

RANIBIZUMAB FOR MACULAR EDEMA AFTER BRANCH RETINAL VEIN OCCLUSION: One Initial Injection Versus Three Monthly Injections.

Miwa Y, Muraoka Y, Osaka R, Ooto S, Murakami T, Suzuma K, Takahashi A, Iida Y, Yoshimura N, Tsujikawa A.

PURPOSE: To compare the 12-month-efficacy of 1 initial intravitreal ranibizumab injection (IVR) followed by pro re nata (PRN) dosing with that of three initial monthly IVR followed by PRN dosing in patients with macular edema (ME) after branch retinal vein occlusion.

DESIGN: Prospective, interventional study.

METHODS: Of 81 eyes, 42 received 1 initial IVR injection (1+PRN group) and 39 eyes received 3 monthly IVRs (3+PRN). Pro re nata injections were performed when fovea exudative changes were evident.

RESULTS: At Month 12, the visual acuity (VA) changes from baseline were -0.245 ± 0.227 and -0.287 ± 0.222 , in the 1+PRN and 3+PRN groups, respectively; there were no significant difference between groups ($P = 0.728$). The stratified analysis showed that patients with better VA (baseline VA $>20/40$) had similar significant improvement in VA at Month 12 ($P < 0.001$) to that of those with poorer VA ($\leq 20/40$). Better VA at Month 12 was significantly associated with younger age, better baseline VA, and thinner baseline central foveal thickness ($P = 0.003$, < 0.001 , and < 0.001 , respectively). Mean total number of IVR injections in the 1+PRN and 3+PRN groups were 3.8 ± 1.8 and 4.6 ± 1.4 , respectively ($P = 0.060$). In both groups, shorter durations to the first PRN injection were associated with greater total PRN injection number (1+PRN, $P = 0.006$; 3+PRN; group, $P < 0.001$).

CONCLUSION: In IVR treatment for ME after branch retinal vein occlusion, 1+PRN and 3+PRN regimens achieved similar 12-month functional outcomes. Patients with shorter durations to initial PRN injection may require more PRN treatments.

PMID: 27471827

Arq Bras Oftalmol. 2016 May-Jun;79(3):155-8.

Effect of intravitreal anti-VEGF on choroidal thickness in patients with diabetic macular edema using spectral domain OCT.

Kniggenndorf VF, Novais EA, Kniggenndorf SL, Xavier C, Cole ED, Regatieri CV.

PURPOSE: To evaluate choroidal thickness (CT) using spectral domain optical coherence tomography (SD-OCT) imaging at baseline and 6 months after intravitreal anti-vascular endothelial growth factor (anti-VEGF) treatment in patients with diabetic macular edema (DME).

METHODS: A retrospective chart review was performed to identify patients with DME who underwent intravitreal injection of anti-VEGF (bevacizumab or ranibizumab) in a pro re nata (PRN) regimen. Subfoveal choroidal thickness was compared between values obtained at baseline and at 6-month follow-up visits.

RESULTS: Thirty-nine eyes (15 females, 24 males) from 39 patients were enrolled (mean age, 62.43 ± 8.7 years; range, 44-79 years). Twenty-three and 16 eyes were treated with ranibizumab and bevacizumab respectively. The mean number of anti-VEGF injections was 2.28 ± 1.27 (range, 1-5). Mean nasal, subfoveal, and temporal choroidal thickness (CT) measurements at baseline were $234.10 \pm 8.63 \mu\text{m}$, $246.89 \pm 8.94 \mu\text{m}$, and $238.12 \pm 8.20 \mu\text{m}$, respectively, and those at 6 months post-treatment were $210.46 \pm 8.00 \mu\text{m}$, $215.66 \pm 8.29 \mu\text{m}$, and $212.43 \pm 8.14 \mu\text{m}$, respectively. Significant differences in CT were observed between baseline and the 6-month follow-up at all measured points ($p=0.0327$).

CONCLUSIONS: Over a 6-month period, the use of intravitreal anti-VEGF was associated with significant thinning of the choroid in patients with DME. The clinical significance of a thinner choroid in DME is currently unknown; however, it may contribute to long-term adverse effects on choroidal and retinal function, representing an area requiring future investigation.

PMID: 27463625

Case Rep Ophthalmol. 2016 Apr 29;7(1):230-6.

A Case of Sustained Intraocular Pressure Elevation after Multiple Intravitreal Injection of Ranibizumab and Aflibercept for Neovascular Age-Related Macular Degeneration.

Matsubara H, Miyata R, Kobayashi M, Tsukitome H, Ikesugi K, Kondo M.

Abstract: Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents are widely used to treat neovascular age-related macular degeneration (nAMD). Although these treatments are effective, multiple injections have recently been recommended to ensure that there is a good long-term prognosis. However, sustained intraocular pressure (IOP) elevations have been reported to develop after multiple injections of anti-VEGF agents. We present our findings of a case of uncontrolled and persistent IOP elevation after switching from intravitreal ranibizumab injections to intravitreal aflibercept injections. A 74-year-old Japanese man without a history of glaucoma underwent 22 ranibizumab injections for nAMD and suddenly developed an elevated IOP after the 22nd injection. Although the subsequent medical treatment led to normalization of his IOP, the subretinal fluid under the central fovea remained even after the 25th injection of ranibizumab. Thus, ranibizumab treatment was switched to bimonthly intravitreal aflibercept injections in conjunction with glaucoma medications. His IOP recovered to within the normal range; however, after the 11th aflibercept injection, there was a sudden elevation of his IOP in spite of the continued glaucoma medications. Due to this sustained IOP elevation, his aflibercept injections were suspended for 16 weeks. Because his IOP could not be normalized by a full glaucoma medication regimen, the patient underwent trabeculotomy, which resulted in a lowering of the IOP to normal levels. We conclude that patients who receive serial intravitreal injections of anti-VEGF agents need to be closely monitored because severe and sustained ocular hypertension can develop.

PMID: 27462248 PMCID: PMC4943768

Adv Ther. 2016 Jul 25. [Epub ahead of print]

The Cost-Effectiveness of Ranibizumab Treat and Extend Regimen Versus Aflibercept in the UK.

Ghosh W, Wickstead R, Claxton L, Kusel J, Taylor M, Fleetwood K, Pulikottil-Jacob R.

INTRODUCTION: Wet age-related macular degeneration (AMD) is a chronic eye condition that causes severe deterioration of vision and even blindness. Current wet AMD treatment in the UK involves the vascular endothelial growth factor inhibitors ranibizumab and aflibercept. Patients with wet AMD require frequent and long-term monitoring for treatment to be effective, contributing to a substantial resource burden at wet AMD centers. The European license for ranibizumab was recently updated with an individualized 'treat and extend' (T&E) regimen, comprising a structured monitoring and treatment protocol. This study evaluated the cost-effectiveness of ranibizumab T&E versus aflibercept within a UK setting.

METHODS: An individual patient-level simulation model was developed utilizing treatment effects from a network meta-analysis of randomized controlled trials. The model was conducted from a UK National Health

Service (NHS) perspective over a lifetime horizon and the base case utilized probabilistic sensitivity analysis to assess uncertainty in the model. Additional scenario analyses were conducted to assess the impact of changes to the model inputs.

RESULTS: Ranibizumab T&E was found to be more effective and less costly than aflibercept, providing, on average, an additional 1.058 quality-adjusted life years (QALYs) and a cost-saving of £19,604 over a lifetime horizon. At list price, ranibizumab T&E was found to be cost-effective versus aflibercept in 100% of simulations at a willingness-to-pay threshold of £20,000 per QALY. The robustness of the results was tested in several scenario analyses; ranibizumab T&E was found to be more effective, and less costly, than aflibercept in the vast majority of cases.

CONCLUSION: This evaluation suggests that treating patients with ranibizumab according to the T&E regimen could be a better use of NHS resources than aflibercept, and could, therefore, be considered as a first-line regimen for patients with wet AMD in the UK.

PMID: 27457470

**Klin Monbl Augenheilkd. 2016 Jul 25. [Epub ahead of print]
[Functional and Morphological Microstructural Changes in SD-OCT in Long-Term Treatment for Neovascular AMD with Ranibizumab - Monotherapy Versus Combination Therapy with PDT]. [**

Wand K, Tetz K, Fischinger IR, Lohmann CP, Maier MM, Feucht N.

Background: Intravitreal anti-VEGF therapy is the gold standard in the treatment of neovascular age-related macular degeneration (nAMD). In recent literature, the benefit of additional photodynamic therapy (PDT) has been debated. The aim of our study was to compare the functional and structural effects of long-term combination therapy with PDT plus ranibizumab with monotherapy with ranibizumab.

Material and Methods: In a retrospective study, patients suffering from nAMD were followed up for at least 42 months. Patients were assigned to group A (monotherapy with ranibizumab according to pro re nata [PRN]) or group B (combination therapy with one-time PDT plus ranibizumab according to PRN). The best-corrected visual acuity (BCVA) was evaluated at the starting and end points, together with central retinal thickness (CRT), maximal retinal thickness (MRT) and the maximal diameter of the base of the subretinal plaque in spectral-domain optical coherence tomography (SD-OCT), at the first measurement and at the end point.

Results: Group A consisted of 21 eyes (17 patients) and group B consisted of 12 eyes (11 patients). The average follow-up from starting to end point was 64 months and 47 months, from the first measurement of SD-OCT to the end point. Within this period, patients in group A received 19 ± 14 intravitreal injections, and patients in group B received 22 ± 10 intravitreal injections. BCVA at the starting point was 0.31 ± 0.26 in group A and 0.31 ± 0.17 in group B. At the end point, BCVA in group A was 0.29 ± 0.25 ($p = 0.405$), and in group B 0.25 ± 0.20 ($p = 0.142$). CRT decreased in group A by $72 \pm 178 \mu\text{m}$ ($p = 0.024$) and group B by 28 ± 98 ($p = 0.1335$). MRT decreased in group A by $25 \pm 135 \mu\text{m}$ ($p = 0.166$) and in group B by $2 \pm 118 \mu\text{m}$ ($p = 0.421$). The base of the subretinal plaque increased in group A by $32 \pm 1468 \mu\text{m}$ ($p = 0.242$) and in group B by 748 ± 1024 ($p = 0.025$).

Conclusion: In a long-term follow-up of 5.3 years, patients with nAMD in both groups exhibited good stabilisation of visual acuity. In both groups, retinal thickness decreased and the base of the subretinal plaque increased. With respect to SD-OCT morphological criteria, patients in group A (monotherapy) responded slightly better to therapy than patients in group B (combination group).

PMID: 27454303

Retina. 2016 Jul 21. [Epub ahead of print]

TREAT-AND-EXTEND REGIMEN USING RANIBIZUMAB FOR POLYPOIDAL CHOROIDAL VASCULOPATHY: One-Year Results.

Pak KY, Park SW, Byon IS, Lee JE.

PURPOSE: To investigate the efficacy of a treat-and-extend regimen (TER) using ranibizumab to treat polypoidal choroidal vasculopathy (PCV).

METHODS: We retrospectively reviewed the medical records of 29 patients with PCV, who had been treated with a TER for 1 year. The primary outcome was the proportion of eyes that did not lose ≥ 3 best-corrected visual acuity (BCVA) lines. The number of intravitreal injections and recurrences as well as the maximum treatment interval without recurrence were analyzed.

RESULTS: The mean BCVA improved from 0.64 ± 0.42 logMAR (median, 20/80) at baseline to 0.30 ± 0.31 logMAR (median, 20/30) at 12 months ($P < 0.001$). The mean central subfield macular thickness improved from 307.0 ± 70.2 μm to 237.5 ± 64.4 μm ($P < 0.001$). None of the subjects lost ≥ 3 lines, and 15 (51.7%) gained ≥ 3 lines. The mean number of injections was 7.0. The mean maximum treatment interval without recurrence was 10.0 weeks. After the loading phase, 12 eyes (41.4%) showed no recurrence. Seven eyes (24.1%) demonstrated disease activity at 12 months, and 4 (13.8%) of them were never dry during the entire 12-month follow-up duration.

CONCLUSION: The TER effectively improved visual acuity in PCV while reducing the number of injections.

PMID: 27454224

Clin Experiment Ophthalmol. 2016 Jul 23. [Epub ahead of print]

Disparities in access to anti-VEGF treatment for neovascular age-related macular degeneration.

Finger RP, Xie J, Fotis K, Parikh S, Cummins R, Mitchell P, Guymer RH.

BACKGROUND: Late neovascular age-related macular degeneration (nvAMD) is very common and causes irreversible severe visual loss unless treated swiftly with vascular endothelial growth factor (VEGF) inhibitors. Although publicly subsidized, access to treatment may be inequitable, which is why we assessed treatment provision across Australia.

DESIGN: Secondary analysis of Australian data

PARTICIPANTS: All Pharmaceutical Benefits Scheme (incl. Repatriation PBS) beneficiaries

METHODS: Treatment and incidence data were obtained from Medicare Australia, the Royal Australian and New Zealand College of Ophthalmologists, Optometry Australia, the Blue Mountains Eye Study, and the Australian Bureau of Statistics. Data were mapped using geographical information software, and factors associated with treatment provision assessed using multiple linear regression models.

MAIN OUTCOME MEASURE: Unmet need (%) for anti-VEGF treatment for nvAMD

RESULTS: On average we estimated 7,316 incident cases of nvAMD not to be treated per year from 2010 to 2014 (50.1% of total). Number of ophthalmologists and optometrists (per 1,000, $\beta = -0.024$; 95% confidence interval (CI) -0.041, -0.007) and being located in remote regions ($\beta = 0.186$; 95% CI 0.110, 0.262) were associated with percentage of untreated cases. A higher proportion of the population speaking a language other than English at home was associated in univariate analyses only ($\beta = 0.0015$; 95% CI -0.0004, 0.0027; $p = 0.007$).

CONCLUSION: A large proportion of incident nvAMD is not treated with anti-VEGF. Not receiving treatment is more likely in regional or remote areas and areas with fewer service providers. Not speaking English at home may further limit access. Service delivery models for more equitable service provision are needed.

PMID: 27449314

N Z Med J. 2016 Jul 15;129(1438):32-8.

Nurse specialists for the administration of anti-vascular endothelial growth factor intravitreal injections.

Samalia P, Garland D, Squirrel D.

AIM: The number of individuals with chronic conditions such as age-related macular degeneration (AMD) is increasing, and consequently the treatment burden for anti-vascular endothelial growth factor (anti-VEGF) intravitreal injections is also increasing. The use of nurse specialists to administer anti-VEGF intravitreal injections has been proposed to address this treatment burden. This was a prospective safety audit to determine the safety of nurse specialists for the delivery of anti-VEGF intravitreal injections.

METHOD: A prospective safety audit was undertaken for a nurse specialist-delivered injection service in the Ophthalmology Clinic, Greenlane Clinical Centre. The department's senior medical retinal consultant supervised the nurse specialist training programme. The clinical safety of anti-VEGF intravitreal injections delivered by nurse specialists, and the impact of this programme on clinical capacity at our Institute was reviewed.

RESULTS: The nurse specialists administered a total of 2,900 injections over an 18-month period. Two patients developed endophthalmitis post injection (1 infective, 1 non-infective). Two patients had a vitreous haemorrhage, and five patients had raised intraocular pressure. The incidence of post-injection endophthalmitis, vitreous haemorrhage and raised intraocular pressure was 0.07%, 0.07% and 0.17%, respectively.

CONCLUSION: The nurse specialist-delivered injection service is a safe and effective service for treatment of wet AMD, diabetic macular oedema and vein occlusion.

PMID: 27447133

Eur J Ophthalmol. 2016 Jul 18:0. [Epub ahead of print]

Ranibizumab for persistent diabetic macular edema after bevacizumab treatment.

Katz G, Moisseiev E, Goldenberg D, Moisseiev J, Lomnicki Y, Abend Y, Treister G, Levkovitch-Verbin H.

PURPOSE: To evaluate the efficacy of switching from bevacizumab to ranibizumab in patients with diabetic macular edema (DME).

METHODS: This was a retrospective study of patients with DME initially treated with bevacizumab and switched to ranibizumab. Visual acuity (VA) and central retinal thickness (CRT) were retrieved at fixed timepoints prior to and after the switch.

RESULTS: Forty eyes of 32 patients were included in the study. The difference in VA between any of these fixed timepoints was not statistically significant. A significant gain in VA was found in eyes that lost more than 0.1 logMAR during treatment with the last 3 bevacizumab injections. The mean CRT was significantly lower after the first 3 ranibizumab injections and at the final follow-up ($p < 0.001$), a $67 \pm 14 \mu\text{m}$ and $78 \pm 18 \mu\text{m}$ reduction in thickness, respectively.

CONCLUSIONS: Switching to ranibizumab resulted in a significant decrease in the CRT of eyes with DME, and should be considered when there is a lack of response or deterioration while on bevacizumab injections. A significant gain in VA was observed in a subgroup of eyes that lost more than one line while receiving the last 3 bevacizumab injections prior to the switch.

PMID: 27445070

**Int Ophthalmol. 2016 Jul 21. [Epub ahead of print]
Intravitreal aflibercept in treatment-resistant pigment epithelial detachment.**

Kocak I.

Abstract: The purpose of the study was to assess the efficacy and safety of transition from ranibizumab to aflibercept intravitreal injections in treatment-resistant retinal pigment epithelial detachment (PED). The data of intravitreal ranibizumab treatment-resistant patients who have been switched to aflibercept treatment were reviewed retrospectively. After three monthly injections, bimonthly regimen was performed. The changes of PED height and radius, and the best-corrected visual acuity (BCVA) were analyzed retrospectively. Mean baseline PED height decreased from 297 ± 151 to 122 ± 42 μ m at month 12 ($P = 0.0007$). Mean baseline PED radius decreased from 2371 ± 882 to 1859 ± 779 μ m at month 12 ($P = 0.0007$). No complete PED resolution occurred in any of the patients at the end of the 12 months. Baseline BCVA improved from 0.63 ± 0.21 to 0.43 ± 0.17 logMar at month 12 ($P = 0.0049$). Mean BCVA gain was 1.4 decimal chart lines (7 letters) at month 12. Switching to aflibercept seems to have promising functional and anatomical outcomes with a reasonable complication rate in treatment-resistant PED.

PMID: 27444307

**Retina. 2016 Jul 26. [Epub ahead of print]
EVALUATION OF SHORT-TERM OUTCOMES OF INTRAVITREAL AFLIBERCEPT INJECTIONS FOR AGE-RELATED MACULAR DEGENERATION USING FOCAL MACULAR ELECTRORETINOGRAPHY.**

Takayama K, Kaneko H, Ueno S, Maruko R, Piao CH, Yasuda S, Kawano K, Ito Y, Terasaki H.

PURPOSE: To evaluate the relationship between morphological changes and functional improvements assessed using focal macular electroretinograms after intravitreal aflibercept (IVA) injections in eyes with wet age-related macular degeneration.

METHODS: The clinical records of 42 eyes of 42 consecutive patients with naive, wet age-related macular degeneration received 3 monthly IVA were reviewed. The best-corrected visual acuity, central foveal thickness, outer retinal thickness, inner retinal thickness at baseline and 1 month after each IVA, and focal macular electroretinograms at baseline and 1 month after the first and third IVA were compared.

RESULTS: Best-corrected visual acuity was improved after the third IVA ($P = 0.0091$). Central foveal thickness and outer retinal thickness showed decreases after every IVA ($P < 0.001$, respectively). Inner retinal thickness showed a decrease after the second IVA ($P = 0.002$), after and third IVA ($P = 0.001$). On focal macular electroretinograms, a- and b-wave amplitudes showed increases after the third IVA ($P = 0.0028$, $P = 0.0012$, respectively). Significant correlations were observed between best-corrected visual acuity and central foveal thickness, a-wave amplitude and outer retinal thickness, and b-wave amplitude and inner retinal thickness changes after the third IVA.

CONCLUSION: All parameters significantly recovered after three monthly IVA, with a correlation between functional improvements and morphological changes.

PMID: 27465570

**BMC Ophthalmol. 2016 Jul 27;16(1):127.
Prospective clinical trial of Intravitreal aflibercept treatment for Polypoidal choroidal vasculopathy with hemorrhage or exudation (EPIC study): 6 month results.**

Kokame GT, Lai JC, Wee R, Yanagihara R, Shantha JG, Ayabe J, Hirai K.

BACKGROUND: Polypoidal choroidal vasculopathy is a variant of choroidal neovascularization and neovascular age related macular degeneration presenting with hemorrhagic and exudative changes within the macula and/or peripapillary region leading to vision loss. In contrast to neovascular age related macular degeneration,

polypoidal choroidal vasculopathy has differing clinical manifestations and treatment strategies. Historically, polypoidal choroidal vasculopathy complexes are less responsive to anti-vascular endothelial growth factor therapy with no prospective clinical trials evaluating aflibercept in management of polypoidal choroidal vasculopathy. Herein we prospectively evaluate the efficacy and safety of intravitreal aflibercept in polypoidal choroidal vasculopathy.

METHODS: A prospective, open-label, investigator-sponsored trial of intravitreal aflibercept for polypoidal choroidal vasculopathy in 21 eyes was conducted. Injections were administered monthly for 3 initial treatments, then every other month with monthly evaluations. The primary outcome measures were the mean change in best corrected visual acuity and adverse events. Secondary outcome measures included stabilization of vision, presence of subretinal hemorrhage, serous detachment, retinal pigment epithelial detachment, and regression of polypoidal complexes on indocyanine green angiography.

RESULTS: At 6 months, the median visual acuity was 20/40 (range 20/25-20/200) with a mean Early Treatment Diabetic Retinopathy Study vision of 68.4 letters. There was a gain of 2.76 Early Treatment Diabetic Retinopathy Study letters at 6 months ($p = 0.15$). No patient developed severe vision loss (≤ 15 letters) and vision was stable or improved in 19/21 eyes (91 %). Subretinal fluid resolved in 13/18 eyes (72 %), and subretinal hemorrhage resolved in 6/8 eyes (75 %) respectively. The polyps regressed in 14/21 eyes (67 %) and the branching vascular network decreased in 1 eye and was stable in all other eyes. The retinal pigment epithelial detachment improved in 13/15 eyes (87 %). Bimonthly treatment occurred in 15/21 patients (71 %). There were no adverse events.

CONCLUSIONS: Intravitreal aflibercept results in stabilization of vision, resolution of exudative and hemorrhagic complications with regression of polyps in polypoidal choroidal vasculopathy. Eyes with polypoidal choroidal vasculopathy previously treated with ranibizumab and bevacizumab can show marked improvement in the retinal pigment epithelial detachments and persistent polyps with aflibercept therapy.

PMID: 27465105 PMCID: PMC4964097

Retina. 2016 Jul 21. [Epub ahead of print]

TREAT-AND-EXTEND REGIMEN USING RANIBIZUMAB FOR POLYPOIDAL CHOROIDAL VASCULOPATHY: One-Year Results.

Pak KY, Park SW, Byon IS, Lee JE.

PURPOSE: To investigate the efficacy of a treat-and-extend regimen (TER) using ranibizumab to treat polypoidal choroidal vasculopathy (PCV).

METHODS: We retrospectively reviewed the medical records of 29 patients with PCV, who had been treated with a TER for 1 year. The primary outcome was the proportion of eyes that did not lose ≥ 3 best-corrected visual acuity (BCVA) lines. The number of intravitreal injections and recurrences as well as the maximum treatment interval without recurrence were analyzed.

RESULTS: The mean BCVA improved from 0.64 ± 0.42 logMAR (median, 20/80) at baseline to 0.30 ± 0.31 logMAR (median, 20/30) at 12 months ($P < 0.001$). The mean central subfield macular thickness improved from 307.0 ± 70.2 μm to 237.5 ± 64.4 μm ($P < 0.001$). None of the subjects lost ≥ 3 lines, and 15 (51.7%) gained ≥ 3 lines. The mean number of injections was 7.0. The mean maximum treatment interval without recurrence was 10.0 weeks. After the loading phase, 12 eyes (41.4%) showed no recurrence. Seven eyes (24.1%) demonstrated disease activity at 12 months, and 4 (13.8%) of them were never dry during the entire 12-month follow-up duration.

CONCLUSION: The TER effectively improved visual acuity in PCV while reducing the number of injections.

PMID: 27454224

Other treatment & diagnosis

Retina. 2016 Jul 27. [Epub ahead of print]

SYSTEMIC BETA-BLOCKERS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Traband A, Shaffer JA, VanderBeek BL.

PURPOSE: To evaluate whether oral beta-blockers (BBs) are associated with a decreased number of intravitreal injections in patients with incident neovascular age-related macular degeneration.

METHODS: A retrospective cohort study of subjects with a new diagnosis of neovascular age-related macular degeneration was conducted using a medical claims database from a large national US insurer. Two cohorts were created for comparison consisting of patients with regular use of BBs or calcium channel blockers. The main outcome measured was the difference in the mean number of intravitreal injections administered between the two cohorts.

RESULTS: After inclusion and exclusion criteria, 239 BB and 155 calcium channel blocker subjects remained for analysis. Univariate analysis revealed that the mean number of injections in the BB cohort was 6.43 (95% confidence interval [CI] 5.90-6.95) versus 6.55 (95% CI 5.85-7.25) in the calcium channel blocker cohort ($P = 0.78$). After multivariate adjustment, the mean number of injections in the BB group was 6.32 (95% CI 5.77-6.87) versus 6.71 (95% CI 6.02-7.40) in the calcium channel blocker group. The overall difference between the 2 groups was -0.39 (95% CI difference -1.29 to 0.51; $P = 0.40$).

CONCLUSION: The use of oral BBs is not associated with a decreased number of intravitreal injections in incident neovascular age-related macular degeneration patients.

PMID: 27467380

Case Rep Ophthalmol. 2016 Jun 13;7(2):309-14.

Is Spectral-Domain Optical Coherence Tomography Always Able to Detect the Anti-Vascular Endothelial Growth Factor Action on Neovascular Membrane?

Borgia L, Del Noce C, Iester M.

PURPOSE: To show the presence of an active neovascular membrane in age-related macular degeneration even if optical coherence tomography (OCT) does not detect intra- or subretinal edema.

METHODS: This is a retrospective case report. During the follow-up after the intravitreal injection, 3 patients showed no intraretinal or subretinal edema by OCT; however, there was a progressive reduction in their visual acuity; thus, a fluorangiography (FA) examination was performed.

RESULTS: In these 3 cases, FA showed an active neovascular network.

CONCLUSION: OCT could show a real reduction in the edema, but it is not always able to detect neovessel presence. Intravitreal injection could improve the vessel permeability without care and delete the neovascular network.

PMID: 27462260 PMCID: PMC4943303

Klin Monbl Augenheilkd. 2016 Jul 26. [Epub ahead of print]

[Systematic Review of the Application of Complementary and Alternative Medicine and their Potential Therapeutic Benefits in the Treatment of Ophthalmology Patients].[Article in German]

Welte AK, Hahn U, Büssing A, Krummenauer F.

Purpose: A systematic review was carried out of the reported therapeutic effects of complementary and alternative medicine methods as supplementary or primary treatments for patients suffering from glaucoma, cataract or age-related macular degeneration (AMD).

Material and Methods: For the years 1990 to 2013, the following databases were screened for reports of the application of complementary and alternative treatments: PubMed, Cochrane Library, EMBASE, CAMbase and AMED. Both randomised and prospective non-randomised patient trials were included in the review; results were evaluated in the following classes: "phytotherapy", "acupuncture/acupressure", "biofeedback" and "other alternative treatments". The studies were evaluated by measures of clinical effect, statistical significance (p value and/or confidence interval) and the underlying trial design.

Results: 30 clinical trials were included, including 13 on glaucoma, 5 on cataract and 12 on AMD patients. These trials were based on patient numbers of 6-332, 27-157 and 6-328 patients, respectively. Phytotherapy was applied in 14 trials, including 6 on glaucoma patients (all 6 with a controlled design, and 3 of which reporting statistically significant results); 5 trials were on cataract patients (3 with a controlled design and 2 with a significant result) and 3 on AMD patients (only 1 with a controlled design, with a significant result). Acupuncture/acupressure was investigated in 9 trials, 5 on glaucoma patients (3 with a controlled design, 1 with a significant result); no acupuncture/acupressure trial was found in cataract patients, but 4 trials in AMD patients (none with a controlled design). Biofeedback was studied in 4 trials, all on AMD patients (only one with a controlled design, without statistically significant findings).

Conclusion: Despite its rigorous inclusion criteria, this review identified several clinical trials on complementary and alternative medicine in ophthalmological patients. Phytotherapeutic methods gave significant results in half of the reported controlled trials, whereas there were few significant benefits with acupuncture or acupressure.

PMID: 27459518

Retina. 2016 Aug;36(8):1557-65.

EPIRETINAL MEMBRANE IN NONEXUDATIVE AGE-RELATED MACULAR DEGENERATION: Anatomical Features, Visual Outcomes and Prognostic Factors.

Lee EK, Lee SY, Yu HG.

PURPOSE: To evaluate clinical characteristics, assess surgical outcomes, and determine prognostic factors after vitrectomy for epiretinal membrane (ERM) associated with nonexudative age-related macular degeneration (AMD).

METHODS: This study comprised 171 consecutive patients with idiopathic ERM (n = 132) or nonexudative AMD-associated ERM (AMD-ERM, n = 39) undergoing vitrectomy. Preoperative morphologic characteristics on spectral-domain optical coherence tomography images and postoperative outcomes of the two groups were compared. Factors influencing postoperative best-corrected visual acuity in the AMD-ERM group were also analyzed.

RESULTS: The AMD-ERM group was more likely to have an ERM with a smooth appearance (P = 0.009), a less severe vessel traction score (P = 0.002), a thinner central foveal thickness (P = 0.016), and more photoreceptor disruption than idiopathic ERM group. Mean central foveal thickness improved from 404.92 ± 82.08 and 369.87 ± 68.17 µm at baseline to 339.77 ± 39.27 and 331.72 ± 45.76 µm 1 year after surgery in eyes with idiopathic ERM and AMD-ERM, respectively (all P < 0.001). Mean logarithm of the minimum angle of resolution best-corrected visual acuity improved from 0.30 (20/40) ± 0.21 and 0.32 (20/42) ± 0.18 at baseline to 0.02 (20/21) ± 0.09 and 0.13 (20/27) ± 0.17 1 year after surgery in the idiopathic ERM and AMD-ERM groups, respectively (all P < 0.001). Baseline integrity of the ellipsoid zone line (P = 0.009) and preoperative best-corrected visual acuity (P = 0.024) were significantly correlated with visual outcome in the AMD-ERM group.

CONCLUSION: Morphologic differences between AMD-ERM and idiopathic ERM were identified. Vitrectomy resulted in significant anatomical and visual improvements in eyes with AMD-ERM, but final visual outcome was worse in these eyes than in those with idiopathic ERM.

PMID: 27456023

**Ophthalmologica. 2016 Jul 23. [Epub ahead of print]
Baseline Characteristics of the Fellow Eye in Patients with Neovascular Age-Related Macular Degeneration: Post Hoc Analysis of the VIEW Studies.**

Wolf S, Bandello F, Loewenstein A, Slakter J, Katz T, Sowade O, Korobelnik JF.

PURPOSE: The aim was to describe baseline characteristics of the fellow eye of patients with neovascular age-related macular degeneration (nAMD).

METHODS: A pooled, post hoc analysis of patients with nAMD enrolled in the VIEW studies was carried out. The VIEW studies compared intravitreal aflibercept (monthly or every 2 months after 3 monthly injections) with monthly ranibizumab. Baseline choroidal neovascularization (CNV) status of fellow eyes and baseline best-corrected visual acuity (BCVA) and lens status of all eyes were evaluated. Additional analyses evaluated the presence of drusen and pigment in fellow eyes.

RESULTS: When comparing both eyes, baseline BCVA was worse in 23.8% of fellow eyes and in 75.2% of study eyes. Lens status of fellow eyes and study eyes was similar. Baseline visual acuity of the study eye and that of the fellow eye were not correlated. Most fellow eyes had signs of early AMD, with 34.6% (n = 843) of fellow eyes having evidence of scarring.

CONCLUSIONS: In patients in the VIEW studies, most fellow eyes had evidence of AMD, highlighting the importance of examining both eyes, with close follow-up thereafter, in order to detect and treat CNV earlier as needed.

PMID: 27449643

**Ophthalmology. 2016 Jul 19. [Epub ahead of print]
Evaluation of Geographic Atrophy from Color Photographs and Fundus Autofluorescence Images: Age-Related Eye Disease Study 2 Report Number 11.**

Domalpally A, Danis R, Agrón E, Blodi B, Clemons T, Chew E; Age-Related Eye Disease Study 2 Research Group.

PURPOSE: To compare measurements of area of geographic atrophy (GA) and change in GA area from color photographs and fundus autofluorescence (FAF) images.

DESIGN: The Age-Related Eye Disease Study 2 (AREDS2) was a prospective multicenter randomized clinical trial evaluating progression of dry age-related macular degeneration (AMD) using color photographs at annual visits over a 5-year study period. The FAF images were acquired in a subset of participants who joined the FAF ancillary study at any of the annual visits over the study period.

PARTICIPANTS: The AREDS2 FAF ancillary study included 8070 corresponding color and FAF visits of 2202 participants with variable follow-up.

METHODS: Corresponding color and FAF images were independently evaluated at a central reading center for GA area measurement, lesion growth, and involvement of the macula center.

MAIN OUTCOME MEASURES: Presence, area, growth rate of GA, and involvement of center of macula from color and FAF images.

RESULTS: Hypoautofluorescence was visible in 2048 visits (25.4%). Agreement for the presence of GA between the 2 modalities had a kappa of 0.79, with 23% of visits with hypoautofluorescence not presenting with GA on color photographs. Percentage agreement for GA presence ranged from 43% at baseline to 81% at year 5 with improving agreement over time. The mean difference in GA area between the 2 modalities was 0.5 mm², with larger areas on FAF. Growth rate of GA was 1.45 mm² from color photographs and 1.43 mm² from FAF images. The center of the macula was involved in 51% of color photographs and 56% with FAF images.

CONCLUSIONS: Geographic atrophy may be detected earlier by the use of FAF images, but over the course of the study, the 2 modalities become comparable. Progression of GA area is comparable between color photographs and FAF images, but evaluating involvement of the center of the macula may differ, probably because of macular pigmentation blocking autofluorescence.

PMID: 27448832

**Ophthalmology. 2016 Jul 19.[Epub ahead of print]
Dark Atrophy: An Optical Coherence Tomography Angiography Study.**

Pellegrini M, Acquistapace A, Oldani M, Cereda MG, Giani A, Cozzi M, Staurenghi G.

PURPOSE: To assess the status of choriocapillaris in eyes with macular atrophy secondary to age-related macular degeneration (AMD) (geographic atrophy [GA]) and Stargardt disease (STGD) using optical coherence tomography angiography (OCTA).

DESIGN: Prospective, observational case series.

PARTICIPANTS: A total of 14 patients (20 eyes) affected by GA and 10 patients (20 eyes) affected by STGD.

METHODS: Each patient underwent a complete ophthalmological examination including fundus autofluorescence (FAF), dynamic simultaneous fluorescein angiography (FA) and indocyanine green angiography (ICGA), enhanced-depth imaging optical coherence tomography (EDI-OCT) (HRA+OCT Spectralis, Heidelberg Engineering, Heidelberg, Germany), and OCTA using AngioVue technologies (Optovue Inc, Freemont, CA).

MAIN OUTCOME MEASURES: An evaluation of the status of choriocapillaris in the 2 groups was performed.

RESULTS: Patients' mean age was 75 years for subjects with GA (median, 76 years; range, 63-88 years) and 61 years for STGD (median, 62 years; range, 40-74 years). Atrophy was bilateral in 42% (n = 6) of subjects with GA and 100% (n = 10) of subjects with STGD. In the early frames, FA displayed hyperfluorescence in the atrophic area in 100% (n = 20) of eyes affected by GA and 20% (n = 4) of eyes affected by STGD; dark choroid was present in 0% of GA eyes and 65% of STGD eyes (n = 13). Atrophy in ICGA late frames was hypofluorescent in 20% (n = 4) of GA eyes and 100% (n = 20) of STGD eyes. A ring at atrophy margins was detected in both FA (90%, n = 18) and ICGA (100%, n = 20) in STGD eyes. Mean subfoveal choroidal thickness was 156 μ m (147, 42-362 μ m) for GA eyes and 168 μ m (167, 55-320 μ m) for STGD eyes (P = 0.59). At OCTA evaluation, GA eyes showed persisting, rarefied choriocapillaris in correspondence of retinal pigment epithelium (RPE) atrophy in 80% (n = 16) of cases, whereas eyes affected by STGD had disappearance of this tissue in 100% (n = 20; P < 0.0001).

CONCLUSIONS: Analysis of macular atrophy by OCTA in patients with STGD revealed an extensive loss of choriocapillaris in the central area with persisting tissue at its margins, whereas in those with GA the area of RPE loss showed persistent but rarefied choriocapillaris.

PMID: 27448830

Pathogenesis

**Hum Mol Genet. 2016 Jul 27. [Epub ahead of print]
Lack of P4H-TM in mice results in age-related retinal and renal alterations.**

Leinonen H, Rossi M, Salo AM, et al.

Abstract: Age-related macular degeneration (AMD), affecting the retinal pigment epithelium (RPE), is the leading cause of blindness in middle-aged and older people in developed countries. Genetic and environmental risk factors have been identified, but no effective cure exists. Using a mouse model we show

that a transmembrane prolyl 4-hydroxylase (P4H-TM), which participates in the oxygen-dependent regulation of the hypoxia-inducible factor (HIF), is a potential novel candidate gene for AMD. We show that P4h-tm had its highest expression levels in the mouse RPE and brain, heart, lung, skeletal muscle and kidney. P4h-tm^{-/-} mice were fertile and had a normal life span. Lack of P4h-tm stabilized HIF-1 α in cortical neurons under normoxia, while in hypoxia it increased the expression of certain HIF target genes in tissues with high endogenous P4h-tm expression levels more than in wild-type mice. Renal erythropoietin levels increased in P4h-tm^{-/-} mice with aging, but the resulting $\sim$ 2-fold increase in erythropoietin serum levels did not lead to erythrocytosis. Instead, accumulation of lipid-containing lamellar bodies in renal tubuli was detected in P4h-tm^{-/-} mice with aging, resulting in inflammation and fibrosis, and later glomerular sclerosis and albuminuria. Lack of P4h-tm was associated with retinal thinning, rosette-like infoldings and drusen-like structure accumulation in RPE with aging, as is characteristic of AMD. Photoreceptor recycling was compromised, and electroretinograms revealed functional impairment of the cone pathway in adult P4h-tm^{-/-} mice and cone and rod deficiency in middle-aged mice. P4H-TM is therefore imperative for normal vision, and potentially a novel candidate for age-induced diseases, such as AMD.

Jpn J Ophthalmol. 2016 Jul 25. [Epub ahead of print]

Radiating hemorrhage in exudative age-related macular degeneration.

Kim JH, Chang YS, Kim JW, Lee TG, Kim CG, Lee DW.

PURPOSE: To investigate the characteristics of radiating hemorrhage secondary to exudative age-related macular degeneration (AMD) and its clinical significance.

METHODS: This retrospective, observational case series included 288 eyes of 288 patients who initially presented with submacular hemorrhage secondary to exudative AMD. First, we estimated the incidence of radiating hemorrhage; we then compared the incidence of polypoidal choroidal vasculopathy (PCV) compared with that of the other subtypes of AMD. Optical coherence tomography (OCT) images were analyzed to identify the level of hemorrhage. The extent of submacular hemorrhage was compared between eyes with and without radiating hemorrhage.

RESULTS: Radiating hemorrhage was identified in 41 eyes (14.2 %). In 36 of these eyes, the OCT scanning line included the area of radiating hemorrhage. In 31 of these, OCT showed avulsion of the outer retinal layers, including the outer nuclear layer and photoreceptor layer. The outer plexiform layer and inner retinal layer were relatively well preserved. The extent of submacular hemorrhage was significantly smaller in eyes with radiating hemorrhage (mean 4.2 ± 2.9 disc areas) than in eyes without it (mean 8.3 ± 6.2 disc areas) ($P < 0.001$). In addition, the incidence of radiating hemorrhage was significantly higher in eyes with submacular hemorrhage secondary to PCV (19.4 %) than in those with the other subtypes of AMD (7.5 %; $P = 0.025$).

CONCLUSIONS: Radiating hemorrhage in exudative AMD was found to be a deep retinal hemorrhage generally accompanied with relatively small-sized submacular hemorrhage. The incidence of this type of hemorrhage was higher in PCV than in the other subtypes of AMD.

PMID: 27456843

Exp Mol Pathol. 2016 Jul 24. [Epub ahead of print]

The influence of changes in expression of redox-sensitive genes on the development of retinopathy in rats.

Perepechaeva ML, Kolosova NG, Stefanova NA, Fursova AZ, Grishanova AY.

Abstract: Age-related macular degeneration (AMD) is a complex multifactorial disease of the elderly, with unclear pathogenesis; AMD is the leading cause of blindness. One of the destructive processes in AMD is oxidative stress, which leads to an imbalance in the processes responsible for production and detoxification of reactive oxygen species. The aryl hydrocarbon receptor (AhR) signaling pathway can participate in the

development of oxidative stress, but the main regulator of antioxidant defense is nuclear factor, erythroid derived 2 (Nrf2). AhR-dependent oxidative stress can be attenuated by activation of Nrf2, and defects in the Nrf2 signaling pathway can increase sensitivity of the cell to oxidative stress. Our aim was to determine the role of the pro-oxidant (AhR-dependent) and antioxidant (Nrf2-dependent) systems in the pathogenesis of AMD using rats of OXYS strain and of OXYSb substrain with signs of AMD-like retinopathy of varying severity. We compared the retinal levels of mRNA expression of Nrf2- and AhR-dependent redox-sensitive systems between 1-, 3-, and 12- month-old senescence-accelerated OXYS rats (have been shown to be a valid experimental model of AMD) and the rat substrain OXYSb, which shows low morbidity of AMD. We uncovered interstrain differences in the expression of Nrf2 and Nrf2-dependent genes (glutathione S-reductase [Gsr] and heme oxygenase 1 [Hmox1]), in the expression of AhR-dependent genes (cytochrome P450 1A2 [Cyp1a2] and cytochrome P450 1B1 [Cyp1b1]), and in the NADPH-quinone oxidoreductase (Nqo1) expression, which is controlled by both AhR and Nrf2. Binding of AhR and Nrf2 proteins to the regulatory regions of AhR and Nrf2 genes, respectively, was detected by chromatin immunoprecipitation in the retina of 1-, 3-, and 12-month-old OXYS, OXYSb, and Wistar (control) rats. We compared the strength of DNA-protein interactions of AhR and Nrf2 with regulatory sequences and found that the level of autoupregulation of the AhR gene was higher in the retina of 1-month-old OXYSb rats in comparison with OXYS rats. An imbalance between pro-oxidant (AhR-dependent) and antioxidant (Nrf2-dependent) systems may play a crucial role in the onset and/or progression of AMD.

PMID: 27466007

Case Rep Ophthalmol. 2016 May 19;7(1):243-8.

Long-Term Follow-Up Case of Multiple Retinal Arterial Macroaneurysms Developing Branch Retinal Vein Occlusion following Ruptured Macroaneurysm.

Terubayashi Y, Kida T, Fukumoto M, Sugasawa J, Morishita S, Suzuki H, Ikeda T.

PURPOSE: Retinal arterial macroaneurysm (RAM) has been reported in association with branch retinal vein occlusion (BRVO), and usually BRVO precedes RAM. We present a long-term follow-up case report of unilateral multiple RAMs that developed BRVO following ruptured RAM in the same retinal quadrant.

CASE PRESENTATION: An 80-year-old woman presented with floaters in her right eye in June 2012. Visual acuity (VA) was 20/25 in her right eye with posterior capsular opacity. Her fundus showed the first ruptured RAM at the superotemporal vascular arcade with subinternal limiting membrane and subretinal hemorrhages not involving the macula. These were absorbed gradually with a VA of 20/20. After 2 years, the second RAM at the proximal superotemporal vascular arcade developed and impending BRVO occurred with macular edema at the distal site of the RAM. With the RAM located close to the arteriovenous crossing, her VA was dropped to 20/60. Intravitreal injection of ranibizumab was performed and macular edema was resolved with improved vision of 20/30. Three months later, she realized a sudden vision loss of 2/200. Her posterior pole showed massive pre- and subretinal hemorrhages, and vitrectomy was performed. The source of bleeding was the third RAM's rupture in a different artery. Her vision improved to 20/30. The unaffected eye showed no RAMs.

CONCLUSION: We experienced a long-term follow-up case of multiple RAMs showing different courses. We should cautiously note that BRVO can occur following RAM at the arteriovenous crossing.

PMID: 27462250 PMCID: PMC4943772

Biosens Bioelectron. 2016 Jul 19;86:609-615.[Epub ahead of print]

Quantification of the vascular endothelial growth factor with a bioluminescence resonance energy transfer (BRET) based single molecule biosensor.

Wimmer T, Lorenz B, Stieger K.

Abstract: Neovascular pathologies in the eye like age-related macular degeneration (AMD), the diabetic retinopathie (DR), retinopathie of prematurity (ROP) or the retinal vein occlusion (RVO) are caused through a

hypoxia induced upregulation of the vascular endothelial growth factor (VEGF). So far a correlation of intraocular VEGF concentrations to the impact of the pathologies is limited because of invasive sampling. Therefore, a minimally invasive, repeatable quantification of VEGF levels in the eye is needed to correlate the stage of VEGF induced pathologies as well as the efficacy of anti-VEGF treatment. Here we describe the development of three variants of enhanced BRET2 (eBRET2) based, single molecule biosensors by fusing a Renilla luciferase mutant with enhanced light output (RLuc8) to the N-terminus and a suitable eBRET2 acceptor fluorophore (GFP2) to the C-terminus of a VEGF binding domain, directly fused or separated with two different peptide linkers for the quantification of VEGF in vitro. The VEGF binding domain consists of a single chain variable fragment (scFv) based on ranibizumab in which the light- and the heavy- F(ab) chains were connected with a peptide linker to generate one open reading frame (orf). All three variants generate measureable eBRET2 ratios by transferring energy from the luciferase donor to the GFP2 acceptor, whereas only the directly fused and the proline variant permit VEGF quantification. The directly fused biosensor variant allows the quantification of VEGF with higher sensitivity, compared to the widely used ELISA systems and a wide dynamic quantification range in vitro. Our system demonstrates not only an additional in vitro application on VEGF quantification but also a promising step towards an applicable biosensor in an implantable device able to quantify VEGF reliably after implantation in vivo.

PMID: 27459244

Vision Res. 2016 Jul 27;127:35-48. [Epub ahead of print]

Restoration of visual performance by d-serine in models of inner and outer retinal dysfunction assessed using sweep VEP measurements in the conscious rat and rabbit.

Staubli U, Rangel-Diaz N, Alcantara M, Li YX, Yang JY, Zhang KM, Foster AC.

Abstract: The NMDA subtype of glutamate receptor and its co-agonist d-serine play a key role in synaptic function in the central nervous system (CNS), including visual cortex and retina. In retinal diseases such as glaucoma and macular degeneration, a loss of vision arises from malfunction of retinal cells, resulting in a glutamate hypofunctional state along the visual pathway in the affected parts of the visual field. An effective strategy to remedy this loss of function might be to increase extracellular levels of d-serine and thereby boost synaptic NMDA receptor-mediated visual transmission and/or plasticity to compensate for the impairment. We tested this idea in brain slices of visual cortex exhibiting long-term potentiation, and in rodent models of visual dysfunction caused by retinal insults at a time when the injury had stabilized to look for neuroenhancement effects. An essential aspect of the in vivo studies involved adapting sweep VEP technology to conscious rats and rabbits and combining it with intracortical recording while the animals were actively attending to visual information. Using this technology allowed us to establish complete contrast sensitivity function curves. We found that systemic d-serine dose-dependently rescued the contrast sensitivity impairment in rats with blue light-induced visual dysfunction. In rabbits with inner retinal dysfunction, both systemic and intravitreal routes of d-serine provided a rescue of visual function. In sum, we show that co-agonist stimulation of the NMDA receptor via administration of exogenous d-serine might be an effective therapeutic strategy to enhance visual performance and compensate for the loss of vision resulting from retinal disease.

PMID: 27461280

J Biomol Screen. 2016 Jul 25. [Epub ahead of print]

Rethinking Nuclear Receptors as Potential Therapeutic Targets for Retinal Diseases.

Choudhary M, Malek G.

Abstract: Collectively, retinal diseases, including age-related macular degeneration, retinitis pigmentosa, and diabetic retinopathy, result in severe vision impairment worldwide. The absence and/or limited availability of successful drug therapies for these blinding disorders necessitates further understanding their pathobiology and identifying new targetable signaling pathways. Nuclear receptors are transcription

regulators of many key aspects of human physiology, as well as pathophysiology, with reported roles in development, aging, and disease. Some of the pathways regulated by nuclear receptors include, but are not limited to, angiogenesis, inflammation, and lipid metabolic dysregulation, mechanisms also important in the initiation and development of several retinal diseases. Herein, we present an overview of the biology of three diseases affecting the posterior eye, summarize a growing body of evidence that suggests direct or indirect involvement of nuclear receptors in disease progression, and discuss the therapeutic potential of targeting nuclear receptors for treatment.

PMID: 27455994

Retina. 2016 Jul 28. [Epub ahead of print]

AQUEOUS HUMOR CYTOKINE LEVELS AS BIOMARKERS OF DISEASE SEVERITY IN DIABETIC MACULAR EDEMA.

Hillier RJ, Ojaimi E, Wong DT, Mak MY, Berger AR, Kohly RP, Kertes PJ, Forooghian F, Boyd SR, Eng K, Altomare F, Giavedoni LR, Nisenbaum R, Muni RH.

PURPOSE: To determine whether aqueous cytokine levels correlate with disease severity in diabetic macular edema.

METHODS: A prospective cross-sectional study of 49 adults with diabetes mellitus, centre-involving diabetic macular edema and central subfield macular thickness ≥ 310 μm on spectral domain optical coherence tomography. Clinical examination and aqueous sampling were carried out before an initial injection of ranibizumab. Multiplex immunoassay of sample was carried out for vascular endothelial growth factor, placental growth factor, transforming growth factor beta, intercellular adhesion molecule-1, interleukin (IL)-2, IL-3, IL-6, IL-8, IL-10, IL-17, vascular cell adhesion molecule-1, monocyte chemoattractant protein-1, and epidermal growth factor. Multivariate robust regression models were constructed, and adjusted for age, lens status, or severity of retinopathy, and size of foveal avascular zone.

RESULTS: Spectral domain optical coherence tomography macular volume was an excellent measure of disease severity, correlating strongly with central subfield macular thickness ($P < 0.001$), best-corrected Snellen visual acuity ($P < 0.001$), and baseline diabetic retinopathy severity ($P = 0.01$). Elevated aqueous intercellular adhesion molecule-1 correlated with greater macular volume ($P = 0.002$). No aqueous cytokine, including VEGF, correlated with central subfield macular thickness. There was an association between IL-10 levels and best-corrected Snellen visual acuity ($P = 0.03$).

CONCLUSION: Aqueous intercellular adhesion molecule-1 correlates with disease severity as measured by macular volume on spectral domain optical coherence tomography, and IL-10 is associated with BCVA. Intercellular adhesion molecule-1 may be a clinically useful biomarker for diabetic macular edema severity.

PMID: 27471825

Epidemiology

Am J Public Health. 2016 Jul 26:e1-e6. [Epub ahead of print]

Contribution of the Nurses' Health Study to the Epidemiology of Cataract, Age-Related Macular Degeneration, and Glaucoma.

Kang JH, Wu J, Cho E, Ogata S, Jacques P, Taylor A, Chiu CJ, Wiggs JL, Seddon JM, Hankinson SE, Schaumberg DA, Pasquale LR.

OBJECTIVES: To review the contribution of the Nurses' Health Study (NHS) to understanding the genetic and lifestyle factors that influence the risk of cataract, age-related macular degeneration, and glaucoma.

METHODS: We performed a narrative review of the publications of the NHS between 1976 and 2016.

RESULTS: The NHS has helped to elucidate the roles of genetics, lifestyle factors (e.g., cigarette smoking associated with cataract extraction and age-related macular degeneration), medical conditions (e.g., diabetes associated with cataract extraction and glaucoma), and dietary factors (e.g., greater carotenoid intake and lower glycemic diet associated with lower risk of age-related macular degeneration) in the etiology of degree and progression of lens opacities, cataract extraction, age-related macular degeneration, primary open-angle glaucoma, and exfoliation glaucoma.

CONCLUSIONS: The findings from the NHS, combined with those of other studies, have provided compelling evidence to support public health recommendations for helping to prevent age-related eye diseases: abstinence from cigarette smoking, maintenance of healthy weight and diabetes prevention, and a healthy diet rich in fruits and vegetables. (Am J Public Health. Published online ahead of print July 26, 2016: e1-e6. doi:10.2105/AJPH.2016.303317).

PMID: 27459452

**Klin Monbl Augenheilkd. 2016 Jul 25. [Epub ahead of print]
[Regional Differences in the Care of Patients with Neovascular Age-Related Macular Degeneration, Based on the Non-Interventional OCEAN Study]. [Article in German]**

Ziemssen F, Hufenbach U, Wiedon A, Scheffler M, Bertelmann T.

Background: The main cause of blindness in the elderly in Germany is neovascular age-related macular degeneration (nAMD). In the non-interventional OCEAN study, data were prospectively collected on the routine clinical care of patients treated with the drug ranibizumab.

Patients: As part of an interim analysis within the ongoing study (NCT02194803), stratification was performed by the 17 regions of the German associations of panel physicians and by areas of different population density. Only data were analysed for patients for whom the first treatment with ranibizumab was documented.

Results: A total of 5,606 patients were documented. The present manuscript reviews 2,658 treatment-naïve patients with nAMD, documented by 324 ophthalmologists. Most patients receiving an intravitreal injection were female (60%). The average patient was aged 77.7 ± 8.2 years at study start. The great majority of patients had statutory health insurance (91%). At baseline, fluorescein angiography (FLA) was performed for 72% of patients, while optical coherence tomography (OCT) was carried out for 76%. A combination of both was performed for 54% of patients, varying regionally from 26% (Saxony-Anhalt) to 100% (Berlin). The average waiting time between the first examination and the first injection was 20.0 ± 18.5 days. With different statistical models (ANOVA adjusted, with/without interactions), significant effects on treatment delay were found for district type (population density), federal state and type of specialist.

Conclusion: No major regional differences were observed in the demographic characteristics of the patient population. The main regional disparities in the care of nAMD patients were in the application of diagnostic methods and the waiting times between the first examination and the first drug administration. The regional variations in treatment delays could clearly influence the risk of worse functional outcome.

PMID: 27454304

Genetics

**Biogerontology. 2016 Jul 22. [Epub ahead of print]
Protective role of the apolipoprotein E2 allele in age-related disease traits and survival: evidence from the Long Life Family Study.**

Kulminski AM, Raghavachari N, Arbeev KG, Culminskaya I, Arbeeva L, Wu D, Ukraintseva SV, Christensen K, Yashin AI.

The apolipoprotein E (apoE) is a classic example of a gene exhibiting pleiotropism. We examine potential pleiotropic associations of the apoE2 allele in three biodemographic cohorts of long-living individuals, offspring, and spouses from the Long Life Family Study, and intermediate mechanisms, which can link this allele with age-related phenotypes. We focused on age-related macular degeneration, bronchitis, asthma, pneumonia, stroke, creatinine, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, diseases of heart (HD), cancer, and survival. Our analysis detected favorable associations of the $\epsilon 2$ allele with lower LDL-C levels, lower risks of HD, and better survival. The $\epsilon 2$ allele was associated with LDL-C in each gender and biodemographic cohort, including long-living individuals, offspring, and spouses, resulting in highly significant association in the entire sample ($\beta = -7.1$, $p = 6.6 \times 10^{-44}$). This allele was significantly associated with HD in long-living individuals and offspring (relative risk [RR] = 0.60, $p = 3.1 \times 10^{-6}$) but this association was not mediated by LDL-C. The protective effect on survival was specific for long-living women but it was not explained by LDL-C and HD in the adjusted model (RR = 0.70, $p = 2.1 \times 10^{-2}$). These results show that $\epsilon 2$ allele may favorably influence LDL-C, HD, and survival through three mechanisms. Two of them (HD- and survival-related) are pronounced in the long-living parents and their offspring; the survival-related mechanism is also sensitive to gender. The LDL-C-related mechanism appears to be independent of these factors. Insights into mechanisms linking $\epsilon 2$ allele with age-related phenotypes given biodemographic structure of the population studied may benefit translation of genetic discoveries to health care and personalized medicine.

PMID: 27447179

Clin Ophthalmol. 2016 Jul 4;10:1229-35. eCollection 2016.

Genetics and age-related macular degeneration: a practical review for the clinician.

Schwartz SG, Hampton BM, Kovach JL, Brantley MA Jr.

Age-related macular degeneration is a complex disease, with both genetic and environmental risk factors interacting in unknown ways. Currently, 52 gene variants within 34 loci have been significantly associated with age-related macular degeneration. Two well-studied major genes are complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2). There exist several commercially available tests that are proposed to stratify patients into high-risk and low-risk groups, as well as predict response to nutritional supplementation. However, at present, the bulk of the available peer-reviewed evidence suggests that genetic testing is more useful as a research tool than for clinical management of patients.

PMID: 27445455 PMCID: PMC4938141

Stem cells

Hum Gene Ther. 2016 Jul 27. [Epub ahead of print]

Signaling networks of retinal ganglion cell formation and the potential application of stem cell-based therapy in retinal degenerative diseases.

Wu N, Wang Y, Yang L, Cho KS.

Retinal degenerative diseases such as age-related macular degeneration, retinitis pigmentosa, and glaucoma result in permanent loss of retinal neurons and vision. Stem cell therapy could be a novel treatment strategy to restore visual function. Generation of stem cell-derived retinal neurons for replacement therapy is an ideal approach. Thus, it is crucial to elucidate the molecular mechanisms that regulate the development of retinal progenitor cells and subsequent generation of specific retinal neurons. Here, we summarize recent findings concerning the intrinsic and extrinsic factors that regulate RPC maintenance and differentiation, especially on the transcriptional factors and extrinsic signals. Understanding these mechanisms is critical for designing strategy to generate specific retinal cells such as retinal ganglion cells for replacement treatment of glaucoma and other optic neuropathies.

PMID: 27466076

Diet, lifestyle & low vision

Br J Ophthalmol. 2016 Jul 28.[Epub ahead of print]

Response to AREDS supplements according to genetic factors: survival analysis approach using the eye as the unit of analysis.

Seddon JM, Silver RE, Rosner B.

BACKGROUND/AIMS: The Age-Related Eye Disease Study (AREDS) reported the beneficial impact of antioxidant and zinc supplements on the risk of progression to advanced stages of age-related macular degeneration (AMD). We evaluated the role of genetic variants in modifying the relationship between supplementation and progression to advanced AMD.

METHODS: Among 4124 eyes (2317 subjects with a genetic specimen), 882 progressed from no AMD, early or intermediate AMD to overall advanced disease, including geographic atrophy (GA) and neovascular disease (NV) over the course of the clinical trial. Survival analysis using individual eyes as the unit of analysis was used to assess the effect of supplementation on AMD outcomes, with adjustment for demographic, environmental, ocular and genetic covariates. Interaction effects between supplement groups and individual complement factor H (CFH) Y402H and age-related maculopathy susceptibility 2 (ARMS2) genotypes, and composite genetic risk groups combining the number of risk alleles for both loci, were evaluated for their association with progression.

RESULTS: Among antioxidant and zinc supplement users compared with the placebo group, subjects with a non-risk genotype for CFH (TT) had a lower risk of progression to advanced AMD (HR: 0.55, 95% CI 0.32 to 0.95, $p=0.033$). No significant treatment effect was apparent among subjects who were homozygous for the CFH risk allele (CC). A protective effect was observed among high-risk ARMS2 (TT) carriers (HR: 0.52, 95% CI 0.33 to 0.82, $p=0.005$). Similar results were seen for the NV subtype but not GA.

CONCLUSIONS: The effectiveness of antioxidant and zinc supplementation appears to differ by genotype. Further study is needed to determine the biological basis for this interaction.

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Olive Oil Consumption and Age-Related Macular Degeneration: The Alienor Study.

Cougnard-Grégoire A, Merle BM, Korobelnik JF, Rougier MB, Delyfer MN, Le Goff M, Samieri C, Dartigues JF, Delcourt C.

BACKGROUND: Olive oil provides a mixture of lipids and antioxidant nutrients which may help preventing age-related diseases such as age-related macular degeneration (AMD). However, little is known about the associations between olive oil consumption and the risk of AMD.

OBJECTIVE: To examine associations between olive oil use and AMD prevalence in elderly subjects.

METHODS: Alienor (Antioxydants, Lipides Essentiels, Nutrition et maladies OculaiRes) is a population-based study on eye diseases performed in elderly residents of Bordeaux (France). In 1999-2000, frequencies of consumption of main categories of dietary fats used were collected. In 2006-2008, AMD was graded from non mydriatic retinal photographs into three exclusive stages: no AMD, early AMD, and late AMD. Two categories of preferred dietary fat used (olive oil, n-3 rich oils, n-6 rich oils, mixed oils, butter and margarine) were defined: "no use" and "regular use" (using fat for spreading and/or cooking and/or dressing). Associations of AMD with each fat use were estimated using Generalized Estimating Equation logistic regressions models.

RESULTS: Our study included 654 subjects (1269 eyes) with complete data ($n = 268$ eyes with early AMD and $n = 56$ with late AMD). After adjustment for potential confounders, regular use of olive oil was significantly associated with a decreased risk of late AMD (odds ratio [OR] = 0.44, 95% confidence interval

[CI]: 0.21;0.91). In contrast, regular use of olive oil was not significantly associated with early AMD (OR = 0.84, 95%CI: 0.59;1.21). No associations were found between regular consumption of n-3 rich oils, n-6 rich oils, mixed oils, butter and margarine and AMD, whatever the stage.

CONCLUSIONS: This study suggests a protective effect of olive oil consumption for late AMD in this elderly community-dwelling population. Characterization of the mediating nutrients deserves further research.

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Association of Vision Impairment and Major Eye Diseases With Mobility and Independence in a Chinese Population.

Fenwick EK, Ong PG, Man RE, Cheng CY, Sabanayagam C, Wong TY, Lamoureux EL.

IMPORTANCE: Mobility limitations arising from vision impairment (VI) can result in loss of independence and reduced quality of life. However, few data are available on the association between VI and mobility limitations at a population-based level, particularly in Asian populations.

OBJECTIVE: To assess the association of VI and major eye diseases with mobility and independence (M&I) in a Chinese population.

DESIGN, SETTING, AND PARTICIPANTS: The Singapore Chinese Eye Study (February 9, 2009, to December 19, 2011) was a population-based, cross-sectional study of 3353 persons aged 40 to 80 years of Chinese ethnicity. Patients underwent visual acuity testing, and sociodemographic and medical data were collected from standardized questionnaires. Data analysis for this study was performed October 2015 to April 2016.

EXPOSURES: Presenting bilateral visual acuity (categorized as none, moderate, or severe VI) and major eye diseases (cataract, uncorrected refractive error, glaucoma, age-related macular degeneration, and diabetic retinopathy).

MAIN OUTCOMES AND MEASURES: Patients answered questions on the M&I scale of the Impact of Vision Impairment questionnaire, validated using Rasch analysis. The composite M&I score (score range, -4.47 to 7.48 logits; higher scores indicate better M&I) and 11 individual item scores were the main outcomes. The association between bilateral VI and eye conditions and the composite and individual M&I item scores was assessed using linear regression models.

RESULTS: Of the 3353 patients, the mean (SD) age was 59.7 (9.9) years, and 1662 (49.6%) were male. The mean (SD) presenting visual acuity values in the better and worse eyes were 0.20 (0.21) and 0.39 (0.42) logMAR, respectively. A total of 1432 patients (42.7%) and 114 patients (3.4%) had moderate and severe bilateral VI, respectively. Mobility and independence systematically worsened as the severity of bilateral VI increased. There was a clinically meaningful reduction in M&I (20%; β , -1.44; 95% CI, -1.75 to -1.13) and all 11 M&I tasks in patients with severe bilateral VI compared with no VI. Glaucoma (13%; β , -0.94; 95% CI, -1.82 to -0.06) and cataract (6%; β , -0.43; 95% CI, -0.65 to -0.22) were independently associated with worse M&I, with patients with glaucoma particularly concerned about avoiding falling or tripping.

CONCLUSIONS AND RELEVANCE: Bilateral VI in this population was associated with substantial decrements in M&I, with glaucoma and cataract independently associated with worse M&I. Although these associations do not prove that preventing bilateral VI will improve M&I in this population, the results suggest that such interventions could be of tremendous value from this perspective.

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Patient knowledge concerning age-related macular degeneration: an AMD questionnaire.

Burgmüller M, Cakmak N, Weingessel B, Vécsei C, Vécsei-Marlovits PV.

BACKGROUND: Age-related macular degeneration (AMD) is a disease with rising prevalence. This study evaluates patients' knowledge and the need for more patient information.

METHODS: 271 patients with AMD were asked to complete a questionnaire concerning their knowledge about AMD. 150 patients were interviewed by a physician and 121 patients completed the questionnaire on their own.

RESULTS: 79.4 % of patients had previous knowledge about AMD. Most patients, 97.3 %, got their information from physicians. 58 % of patients find their knowledge concerning AMD adequate. Only 23.9 % knew about aid organizations for patients with visual impairments.

DISCUSSION: Though the majority of patients had good knowledge concerning AMD, there was a large percentage of patients who seemed to lack information. Physicians should actively ask their patients if they have any questions related to their disease. Medial focus on AMD and information about aid organizations could help patients to cope with their disease.

CONCLUSION: A large number of patients seemed to need additional information. We suggest that ophthalmologists provide general information concerning AMD to their patients every 3 to 5 years. Information about aid organizations specializing in visual impairment could also be provided. Well-informed patients would be better able to follow their physician's instructions and would have a better understanding of their disease, particularly for the sake of therapy.

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Lutein acts via multiple antioxidant pathways in the photo-stressed retina.

Kamoshita M, Toda E, Osada H, Narimatsu T, Kobayashi S, Tsubota K, Ozawa Y.

Lutein slows the progression of age-related macular degeneration (AMD), a leading cause of blindness in ageing societies. However, the underlying mechanisms remain elusive. Here, we evaluated lutein's effects on light-induced AMD-related pathological events. Balb/c mice exposed to light (2000 lux, 3 h) showed tight junction disruption in the retinal pigment epithelium (RPE) at 12 h, as detected by zona occludens-1 immunostaining. Substantial disruption remained 48 h after light exposure in the vehicle-treated group; however, this was ameliorated in the mice treated with intraperitoneal lutein at 12 h, suggesting that lutein promoted tight junction repair. In the photo-stressed RPE and the neighbouring choroid tissue, lutein suppressed reactive oxygen species and increased superoxide dismutase (SOD) activity at 24 h, and produced sustained increases in sod1 and sod2 mRNA levels at 48 h. SOD activity was induced by lutein in an RPE cell line, ARPE19. We also found that lutein suppressed upregulation of macrophage-related markers, f4/80 and mcp-1, in the RPE-choroid tissue at 18 h. In ARPE19, lutein reduced mcp-1 mRNA levels. These findings indicated that lutein promoted tight junction repair and suppressed inflammation in photo-stressed mice, reducing local oxidative stress by direct scavenging and most likely by induction of endogenous antioxidant enzymes.

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