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MD Research News

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Drug treatment

Int Ophthalmol. 2014 Jul 25. [Epub ahead of print]

The long-term effect of intravitreal ranibizumab on retinal nerve fiber layer thickness in exudative age-related macular degeneration.

Parlak M, Oner FH, Saatci AO.

Abstract: The aim of this study was to evaluate the long-term effect of intravitreal ranibizumab on the retinal nerve fiber layer (RNFL) in exudative age-related macular degeneration (AMD). Patients with treatment naive neovascular AMD in one eye were enrolled into the study. Following 3 monthly intravitreal ranibizumab injections, the patients were evaluated according to disease activity and re-injections were performed according to "treat and extend" protocol. During the follow-up, peripapillary nerve fiber layer thickness measurements were compared with normal fellow eyes. Forty-four eyes of 11 women and 11 men with the mean age of 66.3 ± 8.8 years (50-80) were enrolled into the study. All patients had completed at least 12 months of follow-up time. Patients received an average of 4.7 (3-11 injections) intravitreal injections. At baseline, no significant difference was observed between two groups for RNFL thickness, which was assessed as quadrants (p = 0.250-0.944) and globally (p = 0.814). In each group, there was a significant RNFL thinning (p = 0.009 and 0.022) after the third month, whereas no significant difference was observed between treated and untreated eyes. Patients were also classified according to the number of injections, and RNFL thickness showed no difference between eyes treated with less or more than five intravitreal injections (p = 0.757-0.973). Although there was no statistically significant difference in RNFL thickness between study and control eyes during 12 months of follow-up, a significant thinning was recorded in both groups compared with baseline values. Cross-sectional images with higher resolutions and precise segmentation opportunities are needed to investigate the hypothesis "VEGF neutralization and inhibition of cell maintenance" in detail.

PMID: 25059401 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2014 Jul 24. doi: 10.1001/jamaophthalmol.2014.2333. [Epub ahead of print]

Cardiovascular Events and Bleeding Risk Associated With Intravitreal Antivascular Endothelial Growth Factor Monoclonal Antibodies: Systematic Review and Meta-analysis.

Thulliez M, Angoulvant D, Le Lez ML, Jonville-Bera AP, Pisella PJ, Gueyffier F, Bejan-Angoulvant T.

Importance: Few data exist regarding the systemic safety of intravitreal antivascular endothelial growth

factor (anti-VEGF) monoclonal antibody (mAb).

Objective: To conduct a systematic review and meta-analysis to evaluate the risk of major cardiovascular and nonocular hemorrhagic events in patients with neovascular age-related macular degeneration (AMD), diabetes mellitus-associated macular edema (DME), or retinal vein occlusions (RVOs) who receive intravitreal anti-VEGF mAbs.

Data Sources: The MEDLINE and Cochrane Central databases were searched for potentially eligible studies.

Study Selection: Randomized clinical trials comparing ranibizumab or bevacizumab with no anti-VEGF treatment, as well as those comparing ranibizumab with bevacizumab in patients with AMD, DME, or RVOs.

Data Extraction and Synthesis: We used a fixed-effects model and report the results as odds ratios (ORs) and 95% CIs.

Main Outcomes and Measures: Primary end points were major cardiovascular and nonocular hemorrhagic events. Secondary end points were all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, venous thromboembolic events (VTEs), and hypertension.

Results: Twenty-one trials that evaluated 9557 patients were retrieved. Anti-VEGF mAbs did not significantly increase the risk of major cardiovascular events (OR, 1.18; 95% CI, 0.81-1.71) or nonocular hemorrhagic events (OR, 1.42; 95% CI, 0.95-2.13) in treatment groups compared with control populations. Bevacizumab did not increase the risk of major cardiovascular events (OR, 0.94; 95% CI, 0.59-1.52) or nonocular hemorrhagic events (OR, 2.56; 95% CI, 0.78-8.38) compared with ranibizumab, but significantly increased VTEs (OR, 3.45; 95% CI, 1.25-9.54). Subgroup analysis showed a significant increase of nonocular hemorrhagic events in patients with AMD in ranibizumab vs control trials (OR, 1.57; 95% CI, 1.01 -2.44). Anti-VEGF mAbs did not significantly increase overall mortality, cardiovascular mortality, stroke, myocardial infarction, VTEs, or hypertension.

Conclusions and Relevance: We showed that intravitreal anti-VEGF-mAbs were not associated with significant increases in major cardiovascular or nonocular hemorrhagic events, but studies and meta-analyses were not powered enough to correctly assess these risks. Increased risks of VTEs with bevacizumab and nonocular hemorrhagic events in older patients with AMD with ranibizumab should be cautiously interpreted because more safety data are needed.

PMID: 25058694 [PubMed - as supplied by publisher]

BMJ Open. 2014 Jul 23;4(7):e005292. doi: 10.1136/bmjopen-2014-005292.

Drug treatment of macular oedema secondary to central retinal vein occlusion: a network meta-analysis.

Ford JA, Shyangdan D, Uthman OA, Lois N, Waugh N.

OBJECTIVE: To indirectly compare aflibercept, bevacizumab, dexamethasone, ranibizumab and triamcinolone for treatment of macular oedema secondary to central retinal vein occlusion using a network meta-analysis (NMA).

DESIGN NMA DATA SOURCES: The following databases were searched from January 2005 to March 2013: MEDLINE, MEDLINE In-process, EMBASE; CDSR, DARE, HTA, NHSEED, CENTRAL; Science Citation Index and Conference Proceedings Citation Index-Science.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES: Only randomised controlled trials assessing patients with macular oedema secondary to central retinal vein occlusion were included. Studies had to report either

proportions of patients gaining ≥3 lines, losing ≥3 lines, or the mean change in best corrected visual acuity. Two authors screened titles and abstracts, extracted data and undertook risk of bias assessment. Bayesian NMA was used to compare the different interventions.

RESULTS: Seven studies, assessing five drugs, were judged to be sufficiently comparable for inclusion in the NMA. For the proportions of patients gaining ≥3 lines, triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg had a higher probability of being more effective than sham and dexamethasone. A smaller proportion of patients treated with triamcinolone 4 mg, ranibizumab 0.5 mg or aflibercept 2 mg lost ≥3 lines of vision compared to those treated with sham. Patients treated with triamcinolone 4 mg, ranibizumab 0.5 mg, bevacizumab 1.25 mg and aflibercept 2 mg had a higher probability of improvement in the mean best corrected visual acuity compared to those treated with sham injections.

CONCLUSIONS: We found no evidence of differences between ranibizumab, aflibercept, bevacizumab and triamcinolone for improving vision. The antivascular endothelial growth factors (VEGFs) are likely to be favoured because they are not associated with steroid-induced cataract formation. Aflibercept may be preferred by clinicians because it might require fewer injections.

PMID: 25056974 [PubMed]

Eur J Ophthalmol. 2014 Jul 18:0. doi: 10.5301/ejo.5000509. [Epub ahead of print]

Effect of anti-VEGF treatment on choroidal thickness over time in patients with neovascular age-related macular degeneration.

McDonnell EC, Heussen FM, Ruiz-Garcia H, Ouyang Y, Narala R, Walsh AC, Sadda SR.

PURPOSE: To evaluate change in subfoveal choroidal thickness (SCT) as measured by spectral-domain optical coherence tomography (SD-OCT) in patients with neovascular age-related macular degeneration (NVAMD) undergoing anti-vascular endothelial growth factor (VEGF) therapy.

METHODS: atients with a diagnosis of NVAMD were retrospectively reviewed to identify those who had at least 12 months of follow-up. The SCT was manually measured from Bruch membrane to the choroid-sclera junction at baseline and last follow-up. Only cases in which the choroid was fully visible were included in quantitative analyses. The SCT measurements were correlated with other characteristics including number and duration of treatments.

RESULTS: Sixty eyes of 47 patients with a follow-up of 23.8 months (SD 7.3) met study inclusion criteria, and 49 eyes of 40 patients received anti-VEGF treatment. Mean age was 83.7 years, and 52% were female. Treated eyes received a mean of 7.8 (SD 7.3) intravitreal anti-VEGF injections. The SCT at baseline was 126.7 μm (SD 50.6) for untreated and 136.2 μm (SD 57.6) for treated eyes. The SCT showed a decrease over time in both groups, with a mean rate of reduction of 6.0 μm (p<0.0002) in treated eyes and 3.6 μm (p = 0.3741) in untreated eyes. However, the change in SCT did not differ between the groups (p = 0.5113), and did not correlate with the number of re-treatments (p = 0.552), visual acuity at baseline (p = 0.618), or change in visual acuity over time (p = 0.429).

CONCLUSIONS: Although choroidal thickness decreased over time in eyes with NVAMD, anti-VEGF therapy did not appear to accelerate or otherwise alter this decline.

PMID: 25044137 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2014 Aug;92(5):e382-7. doi: 10.1111/aos.12356. Epub 2014 Feb 7.

Ultrasound assessment of ocular vascular effects of repeated intravitreal injections of ranibizumab

for wet age-related macular degeneration.

Bonnin P, Pournaras JA, Makowiecka K, Krivosic V, Kedra AW, Le Gargasson JF, Gaudric A, Levy BI, Cohen YS, Tadayoni R, Massin P.

PURPOSE: Determine the effect of repeated intravitreal injections of ranibizumab (0.5 mg; 0.05 ml) on retrobulbar blood flow velocities (BFVs) using ultrasound imaging quantification in twenty patients with exudative age-related macular degeneration treated for 6 months.

METHODS: Visual acuity (ETDRS), central macular thickness (OCT), peak-systolic, end-diastolic and mean-BFVs in central retinal (CRA), temporal posterior ciliary (TPCA) and ophthalmic (OA) arteries were measured before, 2 days, 3 weeks and 6 months after the first injection. Patients were examined monthly and received 1-5 additional injections depending on ophthalmologic examination results.

RESULTS: Six months after the first injection, a significant increase in visual acuity 50.9 ± 25.9 versus 44.4 ± 21.7 ($p < 0.01$) and decrease in mean central macular thickness 267 ± 74 versus 377 ± 115 μm ($p < 0.001$) were observed compared to baseline. Although mean-BFVs decreased by 16%±3% in CRA and 20%±5% in TPCA ($p < 0.001$) 2 days after the first injection, no significant change was seen thereafter. Mean-BFVs in OA decreased by 19%±5% at week 3 ($p < 0.001$). However, the smallest number of injections (two injections) was associated with the longest time interval between the last injection and month 6 (20 weeks) and with the best return to baseline levels for mean-BFVs in CRA, suggesting that ranibizumab had reversible effects on native retinal vascular supply after its discontinuation. Moreover, a significant correlation between the number of injections and percentage of changes in mean-BFVs in CRA was observed at month 6 ($R = 0.74$, $p < 0.001$) unlike TPCA or OA.

CONCLUSION: Ranibizumab could impair the native choroidal and retinal vascular networks, but its effect seems reversible after its discontinuation.

PMID: 25043792 [PubMed - in process]

Ophthalmology. 2014 Jul 21. pii: S0161-6420(14)00513-2. doi: 10.1016/j.ophtha.2014.06.011. [Epub ahead of print]

Monthly Versus As-Needed Ranibizumab Injections in Patients with Retinal Vein Occlusion: The SHORE Study.

Campochiaro PA, Wykoff CC, Singer M, Johnson R, Marcus D, Yau L, Sternberg G.

OBJECTIVE: To compare pro re nata (PRN) and monthly injections of 0.5 mg ranibizumab in retinal vein occlusion (RVO) patients stabilized by monthly injections.

DESIGN: Randomized, open-label, vision-examiner masked, 15-month study.

PARTICIPANTS: Subjects with macular edema secondary to branch or central RVO.

METHODS: Subjects received monthly injections of 0.5 mg ranibizumab for 7 months and those meeting stability criteria between months 7 and 14 were randomized (1:1) to PRN injections versus continued monthly injections. Non-randomized (NR) subjects (never met stability criteria) received monthly injections.

MAIN OUTCOME MEASURES: The primary endpoint was the slope of change in best-corrected visual acuity (BCVA) between months 7 and 15.

RESULTS: There was no significant difference in the slope of change in BCVA between months 7 and 15 in patients treated PRN versus those treated with monthly injections ($P = 0.509$). Mean (± standard deviation) change from baseline BCVA in Early Treatment Diabetic Retinopathy Study letter score at month 15 was 21.0±14.1 in the PRN group ($n = 82$) versus 18.7±14.1 in the monthly group ($n = 80$) and 14.5±14.7 in NR subjects ($n = 13$). The percentage of subjects who achieved BCVA ≥20/40 at month 15 was 76.8% in the

PRN group, 71.3% in the monthly group, and 46.2% in NR subjects. The mean (± standard deviation) change from baseline central subfield thickness was -247.8±207.5 µm in the PRN group, -289.9±177.2 µm in the monthly group, and -93.2±225.2 µm in NR subjects. There were no significant differences in mean BCVA gains or central subfield thickness reductions at month 15 between the PRN and monthly injection groups (all > 0.05).

CONCLUSIONS: After edema resolution from 7 or more monthly ranibizumab injections in RVO subjects, visual outcomes at month 15 were excellent and not significantly different in subjects treated PRN versus those who continued monthly injections.

PMID: 25060610 [PubMed - as supplied by publisher]

Retina. 2014 Jul 24. [Epub ahead of print]

POOR RESPONDERS TO BEVACIZUMAB PHARMACOTHERAPY IN AGE-RELATED MACULAR DEGENERATION AND IN DIABETIC MACULAR EDEMA DEMONSTRATE INCREASED RISK FOR OBSTRUCTIVE SLEEP APNEA.

Nesmith BL, Ihnen M, Schaal S.

PURPOSE: To investigate the risk for obstructive sleep apnea (OSA) in patients with exudative age-related macular degeneration (AMD) or diabetic macular edema with poor response to anti-vascular endothelial growth factor therapy with bevacizumab (Avastin).

METHODS: Age-related macular degeneration group was categorized into nonexudative, exudative, or poor response exudative. Diabetic macular edema group included patients with nonproliferative diabetic retinopathy and cystoid macular edema. Patients were categorized based on the number of intravitreal injections of bevacizumab received. Both groups were compared with age-matched controls. Patients completed a screening questionnaire to assess the risk for OSA, the main outcome measure.

RESULTS: Of 103 patients with AMD, 56 (54.37%) had nonexudative AMD and 47 (45.63%) had exudative AMD, of which 14 (29.79%) had poor response exudative AMD and were at a significantly higher risk of OSA (P < 0.05). Of 30 diabetic macular edema patients with cystoid macular edema, 4 (19%) received 1 injection, 18 (81.82%) received 2 or more consecutive injections, and 16 (72.73%) received 3 or more consecutive injections. Risk for OSA increased significantly with increasing number of injections (P < 0.05).

CONCLUSION: Patients with exudative AMD and diabetic macular edema with poor response to anti-vascular endothelial growth factor therapy have a significantly higher risk of OSA compared with age-matched controls and should be screened to assess the risk of OSA.

PMID: 25062438 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Jul 22. [Epub ahead of print]

Comparison of the efficacy of aflibercept, ranibizumab, and bevacizumab in an RPE/choroid organ culture.

Klettner A, Recber M, Roider J.

PURPOSE: Anti-VEGF treatment is the therapy of choice in age-related macular degeneration and is also applied in diabetic macular edema or retinal vein occlusion. Recently, aflibercept has been approved for therapeutic use. In this study, we investigate the efficacy of aflibercept in comparison with the VEGF-antagonists ranibizumab and bevacizumab in RPE/choroid organ cultures.

METHODS: RPE/choroid organ cultures were prepared from freshly slaughtered pigs' eyes. Organ cultures

were treated with 125 µg/ml aflibercept, ranibizumab, or bevacizumab, and the VEGF content of the supernatant was evaluated over the course of 7 days. Additionally, the minimal concentration of VEGF inhibition was evaluated in organ cultures, measured after 6 h of application.

RESULTS: Aflibercept was able to completely inhibit VEGF detection for 6 h at a minimal concentration of 0.031 µg/ml, in contrast to bevacizumab (3.9 µg/ml) and ranibizumab (0.244 µg/ml). A statistically significant VEGF inhibition compared to control could be found for aflibercept and ranibizumab down to and including 0.031 µg/ml, while bevacizumab was significantly reduced compared to control down to a concentration of 0.244 µg/ml and again at 0.061 µg/ml. Inhibition of VEGF after a single aflibercept application of 125 µg/ml could be found over the course of 7 days, with some VEGF detectable at the 7th day. In contrast, VEGF was detectable after 72 h of ranibizumab treatment and some VEGF could already be found 12 h after bevacizumab treatment.

CONCLUSIONS: In conclusion, aflibercept displays a prolonged VEGF inhibition, confirming its effectiveness but also raising concerns about possible side effects of long-term usage.

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Acta Ophthalmol. 2014 Jul 8. doi: 10.1111/aos.12488. [Epub ahead of print]

Ranibizumab for Branch Retinal Vein Occlusion Associated Macular Edema Study (RABAMES): six-month results of a prospective randomized clinical trial.

Pielen A, Mirshahi A, Feltgen N, Lorenz K, Korb C, Junker B, Schaefer C, Zwiener I, Hattenbach LO; the RABAMES Study Group.

PURPOSE: To compare standard-of-care grid laser photocoagulation versus intravitreal ranibizumab (IVR) versus a combination of both in the treatment of chronic (>3 months) macular oedema secondary to branch retinal vein occlusion.

METHODS: Prospective, randomized, multicentre clinical trial. Thirty patients with a best-corrected visual acuity (BCVA) between 20/320 and 20/40 were randomized 1:1:1 to receive grid laser or three monthly injections of 0.5 mg IVR or both followed by 3 months of observation.

RESULTS: Mean change from baseline BCVA at month 6 was +2 letters [laser; 0.04 logMAR, 95% confidence interval (-0.17; 0.25)], +17 letters [IVR; 0.34 (0.19; 0.5)] and +6 letters [combination; 0.12 (0.01; 0.24)] (IVR versus laser p = 0.02 and IVR versus combination p = 0.02). At month 3, mean improvement in central retinal thickness (CRT) was 90.6 µm (laser) (-18.65; 199.8), 379.5 µm (IVR) (204.2; -554.8), and 248 µm (167.2; -328.8) (combination) (IVR versus laser p = 0.005, laser versus combination p = 0.02). During the observation period, CRT improved in laser [37.6 µm (-66.82; 142.0)], but deteriorated in IVR [-142.4 µm (-247.6; -37.16)] and combination [-171.7 µm (-250.4; -92.96)] (laser versus IVR p = 0.01, laser versus combination p = 0.002) indicating recurrent oedema. Less laser retreatments (at 8 weeks) were required in combination group (2/10) than grid group (7/10).

CONCLUSION: Six-month results suggest that ranibizumab may be superior to grid laser in improving visual acuity. Grid combined with IVR neither enhanced functional and morphological improvement of IVR nor did it prevent or prolong recurrence of oedema. In IVR groups, CRT increased slowly after stopping injections, whereas improvement in visual acuity was sustained, indicating that morphological changes occur prior to functional impairment.

PMID: 25042729 [PubMed - as supplied by publisher]

Retina. 2014 Jul 18. [Epub ahead of print]

COLLATERAL VESSEL PRESENCE IN BRANCH AND CENTRAL RETINAL VEIN OCCLUSIONS AND THEIR IMPACT ON VISUAL ACUITY AND ANATOMICAL GAINS: A Retrospective Analysis.

Singh RP, Lee TJ, Yau L, Rubio RG.

PURPOSE: To evaluate the incidence of collateral vessel formation and to determine their impact on best-corrected visual acuity and central foveal thickness in patients with branch or central retinal vein occlusion (BRVO, CRVO) receiving 0.3 mg or 0.5 mg of ranibizumab, or sham.

METHODS: This retrospective analysis was performed in patients with macular edema secondary to retinal vein occlusion who received 6 monthly intravitreal injections of ranibizumab (0.3 mg or 0.5 mg), or sham, followed by 6 months of as-needed treatment. Collateral vessel presence, change from baseline best-corrected visual acuity, and change from baseline central foveal thickness were assessed at baseline and months 3, 6, 9, and 12.

RESULTS: At month 12, 19.6% of BRVO patients receiving sham/0.5 mg and 16.7% receiving ranibizumab (0.3 mg and 0.5 mg pooled) manifested collaterals at the disk, whereas 48.2% and 47.2% displayed collaterals within the retina, respectively. In CRVO patients, 57.9% and 59.2% of all groups manifested collaterals on the disk, respectively, whereas 12.1% and 15.1% displayed collaterals within the retina. Mean best-corrected visual acuity gain in ranibizumab-treated BRVO and CRVO patients was similar, irrespective of collaterals within the retina (BRVO: $P > 0.05$; CRVO: $P > 0.05$).

CONCLUSION: The location of collaterals differed between retinal vein occlusion subtypes and ranibizumab treatment did not affect collateral vessel incidence. The presence of collaterals did not seem to impact best-corrected visual acuity gains at month 12 in both BRVO and CRVO patients receiving ranibizumab, whereas generally greater central foveal thickness reductions were observed with presence of collaterals in BRVO patients.

PMID: 25046394 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2014 Jul;42(5):409-10. doi: 10.1111/ceo.12380.

Preventing vision loss from advanced age-related macular degeneration.

Fraser-Bell S.

PMID: 25053511 [PubMed - in process]

Optom Vis Sci. 2014 Aug;91(8):816-8. doi: 10.1097/OPX.0000000000000337.

Age-Related Macular Degeneration: What's New and on the Horizon.

Fletcher EL, Chung ST, Downie LE, Guymer RH, Vingrys AJ.

PMID: 25058632 [PubMed - in process]

Other treatment & diagnosis

JAMA Ophthalmol. 2014 Jul 24. doi: 10.1001/jamaophthalmol.2014.1405. [Epub ahead of print]

The ForeSeeHome Device and the HOME Study: A Milestone in the Self-detection of Neovascular Age-Related Macular Degeneration.

Han DP.

PMID: 25058876 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jul 22. pii: IOVS-14-14646. doi: 10.1167/iovs.14-14646. [Epub ahead of print]

Choroid, Haller's and Sattler's layer thickness in intermediate age-related macular degeneration with and without fellow neovascular eyes.

Esmaeelpour M, Ansari-Shahrezaei S, Glittenberg C, Nemetz S, Kraus MF, Hornegger J, Fujimoto JG, Drexler W, Binder S.

Purpose: To analyze choroidal, Sattler's and Haller's layers thickness maps in age-related macular degeneration (AMD) patients consisting of eyes with bilateral large drusen and pigment changes (intermediate AMD), intermediate AMD eyes with neovascular fellow eyes (nAMD) and healthy subjects using 3-dimensional (3D)-1060nm optical coherence tomography (OCT). Methods: Automatically generated choroidal thickness (ChT), retinal thickness, Sattler's and Haller's layer thickness maps were statistically analyzed in 67 subjects consisting of intermediate AMD (n=21), intermediate AMD (n=22) with fellow nAMD eyes (n=22) and healthy eyes (n=24) with no age and axial eye length difference between groups of eyes, P>0.05, ANOVA. Eyes were imaged by a prototype high speed (60.000 A-scans/s) spectral domain 3D-1060nm OCT over a 36x36° field of view. Results: The mean±SD (µm) subfoveal ChT for healthy, bilateral intermediate AMD, unilateral intermediate AMD and their nAMD fellow eyes was 259±95 and 222±98, 149±60 and 171±78, respectively. ChT thickness maps demonstrated significant submacular thinning in unilateral intermediate AMD comparison to healthy and bilateral intermediate AMD eyes (P<0.001, ANOVA, post-hoc P<0.001 and P< 0.05, respectively). Sattler's and Haller's layer were thinnest in intermediate AMDs that presented with nAMD fellow eyes (Kruskal Wallis test P<0.01). For the choroid and its sublayers there was no difference between the intermediate AMD eyes and their fellow nAMD eyes (paired testing, P< 0.05). Conclusion: The 3D-1060nm OCT choroidal imaging visualized significant changes in choroidal, Sattler's and Haller's layer thickness in relation to the progression of AMD. This may be important for the understanding of the choroidopathy in the pathophysiology AMD.

PMID: 25052997 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2014 Jul 22. pii: IOVS-14-14005. doi: 10.1167/iovs.14-14005. [Epub ahead of print]

Simultaneous Investigation of Vascular and Retinal Pigment Epithelial Pathologies of Exudative Macular Diseases by Multi-Functional Optical Coherence Tomography.

Hong YJ, Miura M, Ju MJ, Makita S, Iwasaki T, Yasuno Y.

Purpose: To investigate exudative macular disease, multi-functional optical coherence tomography (MF-OCT) using a 1-µm probe band was developed. The clinical utility of MF-OCT was examined in a descriptive case series.

Methods: Ten eyes of nine subjects with exudative macular disease, including one eye with age-related macular degeneration (AMD), one eye with idiopathic neovascular maculopathy, and eight eyes with polypoidal choroidal vasculopathy (PCV), were investigated. Areas of 6 × 6 mm2 around the pathologic region were scanned with 512 × 1024 depth scans in 6.6 seconds. Structural OCT, Doppler optical coherence angiography (OCA) and cumulative phase retardation images were obtained with a single measurement. Each MF-OCT image visualized the structure, vasculature, and birefringence. Degree of polarization uniformity values were also obtained for selective visualization of the retinal pigment epithelium (RPE). The MF-OCT images were compared with conventional ophthalmic images.

Results: Abnormal vasculatures were observed with Doppler OCA in all eyes and it presented high similarity to indocyanine green angiography in the midphase. The RPE and exudation in the pathologic regions were discriminated in one eye with AMD and five of eight eyes with PCV. Cumulative phase retardation visualized fibrosis scars in two of the PCV cases.

Conclusions: MF-OCT revealed depth-resolved abnormal vasculatures, the integrity of the RPE and choroid, discrimination of the RPE and exudation, and existence of fibrosis scars in exudative macular diseases. Interpretation of MF-OCT examination is well matched with conventional ophthalmic examination. These results suggest MF-OCT can be used as a noninvasive ophthalmic examination tool prior to conventional examinations in clinical routines.

PMID: 25052993 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2014 May;50(5):386-90.

[Progression of flicker perimetry in clinical application].[Article in Chinese]

Yu F, Wang D.

Abstract: Flicker perimetry measures the function of retina by stimulating it using flickering light. It has three test modes:contrast modulation flicker, critical flicker fusion frequency and luminance pedestal flicker. These 3 modes have their own characteristics. Flicker perimetry shows a higher sensitivity than white-white standard automated perimetry in early diagnosis of glaucoma. It also has advantages in the diagnosis for age-related macular degeneration, diabetic retinopathy and other retinal diseases. With further understanding of the flicker perimetry, its clinical application will gradually expand. In this paper, the basic principle and clinical application are reviewed.

PMID: 25052807 [PubMed - in process]

Acta Ophthalmol. 2014 Jul 10. doi: 10.1111/aos.12494. [Epub ahead of print]

Diabetic macular oedema quantified with spectral-domain optical coherence tomography - evaluation of boundary line artefacts and the effect on retinal thickness.

Hodzic-Hadzibegovic D1, Sander BA, Lund-Andersen H.

PURPOSE: To characterize frequency, morphological cause and time-dependent change of boundary line artefacts in optical coherence tomography (OCT) examinations of centre-involved diabetic macular oedema (ciDME) patients who underwent ranibizumab treatment with 1-year follow-up and to evaluate the impact of artefacts on retinal thickness.

METHODS: One hundred and fourteen patients were examined with radial scan protocol by Topcon 3D OCT at baseline, 3 and 12 months. All B scans from all visits were examined for boundary line artefacts (artefacts) and were stratified by morphological element causing artefacts including hard exudates (HE), epiretinal membranes (ERM), optical opacities and serous detachments. Boundary line artefacts were manually corrected and the corrected central subfield thickness (CST) and macular volume were compared with automated values. Data were compared with a repeatability coefficient of 25 μm.

RESULTS: Boundary line artefacts were found in 51.8% of the total 342 OCT examinations and in 25.5% of the total 2052 B scans. Morphological elements that caused artefacts in the total 2052 B scans were HE (10.6%), ERM (10.3%), optical opacities (4.4%), serous detachments (1.7%) and others (1.2%). The number of artefacts due to HE decreased significantly ($p = 0.0005$), and the number of artefacts due to ERM were unchanged ($p = 0.087$) during 12 months. In OCT examinations with artefacts caused by HE, manually corrected CST was statistically significant higher than automated value at baseline and 3 months.

For ERM, manually corrected CST was statistically significant lower than automated value at baseline and 12 months.

CONCLUSION: Boundary line artefacts in OCT examinations of ciDME patients using Topcon 3D OCT occur in 51.8%. In situation of boundary line artefacts in centre 1-mm area every fourth OCT examination has a change in CST beyond 25 µm.

PMID: 25042850 [PubMed - as supplied by publisher]

J Glaucoma. 2014 Jul 22. [Epub ahead of print]

Influence of a New Software Version of the RTVue-100 Optical Coherence Tomograph on Ganglion Cell Complex Segmentation in Various Forms of Age-related Macular Degeneration.

Holló G, Naghizadeh F.

PURPOSE: Previously, we have shown that age-related macular degeneration (AMD) influences glaucoma classification with the ganglion cell complex (GCC) parameters of the RTVue-100 optical coherence tomograph (RTVue-OCT) in nonglaucomatous eyes. Now, we reevaluated the influence of AMD on GCC image segmentation and classification for glaucoma on the same eyes, using a new version of the software.

METHODS: GCC images of nonglaucomatous eyes [30 healthy, 19 with early/intermediate AMD, 16 with subfoveal choroidal neovascularization (CNV), and 19 after intravitreal antiangiogenic treatment of CNV, CNV-anti-VEGF] were reanalyzed with software versions 6.3 (the currently available version) and 6.12 (a version not yet commercially released).

RESULTS: Global loss volume (GLV) was significantly reduced with version 6.12 in all groups (P≤0.0416). Segmentation errors were seen in 2 versus 0 of the normal eyes (P=0.500), 8 versus 0 of the early/intermediate AMD eyes (P=0.0312), 16 versus 6 of the CNV eyes (P=0.0080), and 18 versus 3 of the CNV-anti-VEGF eyes (P=0.0004) with software versions 6.3 and 6.12, respectively. For focal loss volume the distribution of the classification results differed significantly between the software versions in the CNV and CNV-anti-VEGF groups (P=0.0312 and 0.0160, respectively). For both groups more eyes were classified as "within normal limits," and less as "outside normal limits" with software version 6.12 than with version 6.3.

CONCLUSIONS: For nonglaucomatous AMD eyes the frequency of GCC segmentation errors was significantly reduced, GLV was significantly lower (more normal), and the classification for glaucoma was more correct with software version 6.12 than with version 6.3.

PMID: 25055214 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Jul 24. [Epub ahead of print]

Serum cytokines as biomarkers for age-related macular degeneration.

Nassar K, Grisanti S, Elfar E, Lüke J, Lüke M, Grisanti S.

PURPOSE: This study evaluates the potential of serum pro-inflammatory cytokines as AMD biomarkers.

METHODS: Serum samples from 30 age-related macular degeneration (AMD) patients and 15 age-matched controls were examined for 16 inflammatory cytokines using multiplex ELISA. Patients were divided into three subgroups (improvement/no change/deterioration during anti-VEGF treatment) by OCT and funduscopy, and correlated to the cytokine levels.

RESULTS: Serum concentrations of IL-1α, IL-1β, IL-4, IL-5, IL-10, IL-13, and IL-17 were significantly higher

in AMD patients than in controls. None of the co-variables expressed a significant effect on the tested cytokines. Only IL-1a and IL-17 showed a statistically significant difference between groups (improved, unchanged, deteriorated) as determined by one-way ANOVA. Patients with increased macular thickness during treatment showed significantly lower levels of IL-17 compared to improved cases and to unchanged cases ($p = 0.004$, 0.03 respectively, Dunnett's T3 post hoc multiple test). TNF-α was significantly higher in improved cases compared to deteriorated cases ($p = 0.03$, Dunnett's T3 post hoc multiple test). IL-17 was a significant predictor for macular oedema using linear regression ($\beta = -0.888$, $p < 0.05$).

CONCLUSION: Elevation of IL-1α, IL-1β, IL-4, IL-5, IL-10, IL-13, and IL-17 in the serum of AMD patients supports the hypothesis of AMD as an inflammatory disease. Patients with high IL-17 and TNF-α serum levels were more likely to have a favourable course under VEGF therapy. These cytokines may be used as easy-to-obtain biomarkers.

PMID: 25056526 [PubMed - as supplied by publisher]

Photodiagnosis Photodyn Ther. 2005 Mar;2(1):79-90. doi: 10.1016/S1572-1000(05)00006-2.

PDT with TOOKAD(®) studied in the chorioallantoic membrane of fertilized eggs.

Rück A, Böhmler A, Steiner R.

BACKGROUND: The potential application of TOOKAD(®)-PDT for the treatment of blood vessels was investigated. TOOKAD(®) (WST09), a novel palladium-bacteriopheophorbide absorbs light in the near IR with a high quantum yield of intersystem crossing. Our study assessed the efficacy of this drug in inducing vascular damage with a view to its possible use in the treatment of age-related macular degeneration.

METHODS: Vascular damage of TOOKAD(®)-PDT was studied in neovessels of the chorioallantoic membrane of fertilized eggs. Pharmacokinetic investigations were done by video microscopy and laser scanning microscopy. To induce damage vessels were irradiated with 763nm light from a diode laser.

RESULTS: TOOKAD(®) was accumulated in the vessels in the first minutes following injection. TOOKAD (®) fluorescence was seen predominantly in the lumen and not in the vascular endothelial layer. Although fluorescence was very weak it could be attributed to TOOKAD(®) from the fluorescence spectrum in the circulation. Damage assessment was done 24h after application of 763nm light. No significant difference in the degree of damage was observed with different short drug-light intervals (1-10min), but damage increased with the light energy dose. Closure of smaller vessels and vanished capillaries could be achieved by irradiation with 5J/cm(2) and a TOOKAD(®) dose of 33μg/embryo, corresponding to a phototoxic efficacy of 0.0062.

CONCLUSIONS: From the results discussed in this work, TOOKAD(®) could be a potential drug for the PDT of age-related macular degeneration in which the growth of new vessels in the choroids can lead to loss of vision.

PMID: 25048560 [PubMed]

Photodiagnosis Photodyn Ther. 2004 May;1(1):3-7. doi: 10.1016/S1572-1000(04)00003-1.

Photodynamic therapy: from the beginning.

Kessel D.

Abstract: Photodynamic therapy relates to the use of drugs + light for treatment of neoplasia, macular degeneration and atherosclerotic plaque. This field has a long history with recent improvements in drug development and light sources promoting clinical approaches. This summary describes recent progress along with an indication of current lines of research.

PMID: 25048058 [PubMed]

Pathogenesis

Cell Death Dis. 2014 Jul 24;5:e1348. doi: 10.1038/cddis.2014.314.

Vitamin A dimers trigger the protracted death of retinal pigment epithelium cells.

Mihai DM, Washington I.

Abstract: Cellular events responsible for the initiation of major neurodegenerative disorders of the eye leading to blindness, including age-related macular degeneration, Stargardt and Best diseases, are poorly understood. Accumulation of vitamin A dimers, such as N-retinylidene-N-retinylethanolamine (A2E) in the retinal pigment epithelium (RPE), is one of the earliest measurable events preceding retinal degeneration. However, the extent to which these dimers contribute to tissue degeneration is not clear. To determine if A2E could trigger morphological changes associated with the degenerating RPE and subsequent cell death, we evaluated its toxicity to cultured human RPE cells (ARPE-19). We show that A2E triggered the accumulation of debris followed by a protracted death. A2E was up to≈14-fold more toxic than its precursor, retinaldehyde. Measurements reveal that the concentration of A2E in the aged human eye could exceed the concentration of all other retinoids, opening the possibility of A2E-triggered cell death by several reported mechanisms. Findings suggest that accumulation of vitamin A dimers such as A2E in the human eye might be responsible for the formation of ubiquitous RPE debris, an early indication of retinal degeneration, and that preventing or reducing the accumulation of vitamin A dimers is a prudent strategy to prevent blindness.

PMID: 25058422 [PubMed - in process]

Exp Eye Res. 2014 Jul 22. pii: S0014-4835(14)00188-2. doi: 10.1016/j.exer.2014.07.006. [Epub ahead of print]

Blockage of Tissue Factor Ameliorates the Lesion of Laser-induced Choroidal Neovascularization in Mice.

Wang L, Yang Z, Yu Y, Cui C, Guan H, Chen H.

Abstract: Choroidal neovascularization (CNV) occurs as a result of age-related macular degeneration (AMD) and causes severe vision loss among elderly patients. High expression of tissue factor (TF) was found in the retinas of AMD patients. In this study, we used anti-TF monoclonal antibody to test the effect of the TF blockage on experimental CNV induced by laser photocoagulation of retina in mice. Anti-TF monoclonal antibody or vehicle was administered intravitreally at day 1, 2 or 3 after laser application. We found that TF expression increased, and reached the peak at the 3rd week after the after laser application. Anti-TF monoclonal antibody can predominantly decrease the expression of TF, VEGF and F4/80, and reduced the area of CNV. Anti-TF monoclonal antibody also decreased incidence of CNV and leakage area. There were no pathological changes in the liver, heart, brain or kidney tissue. We conclude that TF plays an important role in CNV and anti-TF monoclonal antibody significantly decreases CNV in mouse model and anti-TF monoclonal antibody may have therapeutic potential in AMD.

PMID: 25063201 [PubMed - as supplied by publisher]

Mol Immunol. 2014 Jul 22. pii: S0161-5890(14)00166-7. doi: 10.1016/j.molimm.2014.06.035. [Epub ahead of print]

Humanized cobra venom factor: Structure, activity, and therapeutic efficacy in preclinical disease models.

Vogel CW, Finnegan PW, Fritzinger DC.

Abstract: The complement system is an integral component of both innate and adaptive immunity. However, complement is also a pathogenetic factor in many diseases. The development of agents for therapeutic complement inhibition is the topic of intense investigations by many investigators. We have developed a distinctly different therapeutic approach: complement depletion rather than inhibition. This approach is based on cobra venom factor (CVF), a C3 analog known to be able to safely deplete complement. This manuscript will briefly review the structure and activity of CVF, along with its similarities and differences to C3. Exploiting the knowledge of the structure/function relationship of CVF and C3, we created derivatives of human C3 which display the CVF-like activity of depleting complement, referred to as humanized CVF (hCVF). This review describes the structure and activity of hCVF, including the important property of not cleaving C5. The efficacy of hCVF for therapeutic complement depletion in nine preclinical models diseases with complement pathology is reviewed, including reperfusion injury, age-related macular degeneration (AMD), paroxysmal nocturnal hemoglobinuria (PNH), and immunogenicity of Factor VIII in hemophilia A. Complement depletion is characterized by the absence of toxicity, even after intra-arterial injection into the pulmonary artery of primates. No immunogenicity has been observed.

PMID: 25062833 [PubMed - as supplied by publisher]

Ageing Res Rev. 2014 Jul 22. pii: S1568-1637(14)00067-1. doi: 10.1016/j.arr.2014.07.002. [Epub ahead of print]

Clearance of misfolded and aggregated proteins by aggrephagy and implications for aggregation diseases.

Hyttinen JM, Amadio M, Viiri J, Pascale A, Salminen A, Kaarniranta K.

Abstract: Processing of misfolded proteins is important in order for the cell to maintain its normal functioning and homeostasis. Three systems control the quality of proteins: chaperone-mediated refolding, proteasomal degradation of ubiquitinated proteins, and finally, when the two others fail, aggrephagy, as selective form of autophagy, degrades ubiquitin-labeled aggregated cargos. In this route misfolded proteins gradually form larger aggregates, aggresomes and they eventually become double membrane-wrapped organelles called autophagosomes, which become degraded when they fuse to lysosomes, for reuse by the cell. The stages, the main molecules participating in the process, and the regulation of aggrephagy are discussed here, as is the role of protein aggregation in protein accumulation diseases. In particular, we emphasize that both Alzheimer's disease and age-related macular degeneration, two of the most common pathologies in the aged, are characterized by altered protein clearance and deposits. Based on the hypothesis that manipulations of autophagy may be potentially useful in these and other aggregation-related diseases, we will discuss some promising therapeutic strategies to counteract protein aggregates-induced cellular toxicity.

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Clin Hemorheol Microcirc. 2014 Jul 25. [Epub ahead of print]

Hemorheological parameters and their correlations in OXYS rats: A new model of hyperviscosity syndrome.

Maslov MY, Chernysheva GA, Smol'jakova VI, Aliev OI, Kolosova NG, Plotnikov MB.

Abstract: Rheohaemapheresis aims to normalize major rheological parameters and is used to treat patients with dry age-related macular degeneration (AMD). While effective, this approach is invasive and requires specially trained personnel. Therefore, the search for novel effective compounds with hemorheological properties that can be taken orally to treat AMD is justified. The use of a robust rodent model of AMD with high blood viscosity is crucial to test the efficacy of potential hemorheological drugs to treat this disease.

The objective of this study was to investigate whether OXYS rats, generally used as an animal model of AMD, have hyperviscosity syndrome. The results of this study show that blood viscosity in OXYS rats at low (3-10 s-1) and high (45-300 s-1) shear rates were 14-20% and 7-10% higher than in Wistar rats, while hematocrit and plasma viscosity were not different. Red blood cells (RBCs) in OXYS rats were more prone to aggregation as shown by 39% shorter half-time than in Wistar rats. RBCs were also more rigid in OXYS than in Wistar rats as shown by 21-33% lower index of elongation at the shear stress of 1-7 Pa. These data indicate that OXYS rats have hyperviscosity syndrome as the result of abnormal RBC deformability and aggregation. We propose to use OXYS rats as an animal model for preclinical studies to test compounds with hemorheological properties aimed to treat AMD.

PMID: 25062716 [PubMed - as supplied by publisher]

Mol Immunol. 2014 Jul 19. pii: S0161-5890(14)00153-9. doi: 10.1016/j.molimm.2014.06.022. [Epub ahead of print]

Exploring the potential benefits of vaccinia virus complement control protein in controlling complement activation in pathogenesis of the central nervous system diseases.

Kotwal GJ, Fernando N, Zhou J, Valter K.

Abstract: Aging is a major risk factor for the development of diseases related to the central nervous system (CNS), such as Alzheimer's disease (AD) and age-related macular degeneration (AMD). In both cases, linkage studies and genome-wide association studies found strong links with complement regulatory genes and disease risk. In AD, both CLU and CR1 genes were implicated in the late-onset form of the disease. In AMD, polymorphisms in CFH, CFB and C2 were similarly implicated. The cost of caring for patients with AD or AMD is approaching billions of dollars, and with the baby boomers reaching their 60's, this amount is likely to increase further. Intervention using complement inhibitors for individuals in their early 50s who are at a higher risk of disease development, (testing positive for genetic risk factors), could slow the progression of AD or AMD and possibly prevent the severity of late stage symptoms. Although we have used the vaccinia virus complement control protein (VCP) to elucidate the role of complement in CNS diseases, it has merely been an investigational tool but not the only possible potential therapeutic agent.

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Adv Gerontol. 2014;27(1):87-93.

[Expression of nitric oxide synthases in the retina of OXYS rats during retinopathy development]. [Article in Russian]

[No authors listed]

Abstract: Both the lack and excess generation of nitric oxide (NO) contributes to the pathogenesis of age-related diseases, according to the latest data including age-related macular degeneration (AMD), which is a leading cause of vision loss in people over 65. The mechanisms of the effects of NO are not entirely clear, the information about changes in the expression synthase NO (NOSs) in the retina with age and the development of AMD are limited. We showed previously that the senescence-accelerated OXYS rats strain is an animal model of AMD. The purpose of the present research was to compare the transcriptional activity of genes NOSs: neuronal (nNOS), inducible (iNOS) and endothelial (eNOS) in the retina OXYS and Wistar rats (used as control) by real-time PCR. The study was carried out on animals at the age of 3 and 18 months during the period of manifestation and active progression of AMD-like retinopathy in OXYS rats. We showed that mRNA level of NOSs was not dependent on age in Wistar and OXYS rats. Interstrain differences in the level of eNOS mRNA were not detected, but the level of mRNA of nNOS in the retina of 18-month-old OXYS rats was 2,4 times higher than in age-matched Wistar rats. Regardless of age the level

of iNOS mRNA in OXYS rats was 7 times lower than that in Wistar rats, but the protein content of iNOS in 3 -month-old OXYS rats (ELISA data) was increased. Perhaps such a paradoxical situation reflects a decreased reactivity of the immune system in the OXYS rats.

PMID: 25051763 [PubMed - in process]

JAMA Ophthalmol. 2014 Jul 24. doi: 10.1001/jamaophthalmol.2014.2065. [Epub ahead of print]

Proteomic Landscape of the Human Choroid-Retinal Pigment Epithelial Complex.

Skeie JM, Mahajan VB.

Importance: Differences in geographical protein expression in the human choroid-retinal pigment epithelial (RPE) complex may explain molecular predisposition of regions to ophthalmic diseases such as age-related macular degeneration.

Objective: To characterize the proteome of the human choroid-RPE complex and to identify differentially expressed proteins in specific anatomic regions.

Design, Setting, and Participants: Experimental study of choroid-RPE tissue from 3 nondiseased eyes. The choroid-RPE complex underwent biopsy from beneath the foveal, macular, and peripheral retina. Protein fractions were isolated and subjected to multidimensional liquid chromatography and tandem mass spectrometry. A bioinformatic pipeline matched peptide spectra to the human proteome, assigned gene ontology classification, and identified protein signaling pathways unique to each of the choroid-RPE regions.

Main Outcomes and Measures: Mean number of mass spectra, statistically significant differentially expressed proteins, gene ontology classification, and pathway representation.

Results: We identified a mean of 4403 unique proteins in each of the foveal, macular, and peripheral choroid-RPE tissues. Six hundred seventy-one differentially expressed proteins included previously known risk factors for retinal diseases related to oxidative stress, inflammation, and the complement cascade. Gene ontology analysis showed that unique categories in the foveal and macular regions included immune process proteins as well as protein complexes and plasma membrane proteins. The peripheral region contained unique antioxidant activity proteins. Many proteins had the highest expression in the foveal or macular regions, including inflammation-related proteins HLA-A, HLA-B, and HLA-C antigens; intercellular adhesion molecule 1 (ICAM-1); S100; transcription factor ERG; antioxidant superoxide dismutase 1 (SOD1); chloride intracellular channel 6 ion (CLIC6); activators of the complement cascade C1q, C6, and C8; and complement factor H. Proteins with higher expression in the periphery included bestrophin 1 (BEST1), transcription factor RNA binding motif protein 39 (RBM39), inflammatory mediator macrophage migration inhibitory factor, antioxidant SOD3, ion channel voltage-dependent anion-selective channel protein 3 (VDAC3), and complement inhibitor CD55. The complement activation was among the highest represented pathways ($P < 7.5e-13$).

Conclusions and Relevance: This proteomic data set identifies novel molecular signatures in anatomically sensitive regions of the choroid-RPE complex. The findings give mechanistic insight into choroid-RPE function, reveal important choroid-RPE processes, and prioritize new pathways for therapeutic targeting.

PMID: 25058583 [PubMed - as supplied by publisher]

Exp Eye Res. 2014 Jul 17. pii: S0014-4835(14)00185-7. doi: 10.1016/j.exer.2014.07.003. [Epub ahead of print]

Vinpocetine inhibits amyloid-beta induced activation of NF-κB, NLRP3 inflammasome and cytokine

production in retinal pigment epithelial cells.

Liu RT, Wang A, To E, Gao J, Cao S, Cui JZ, Matsubara JA.

Abstract: Chronic inflammation is a key pathogenic process in age-related macular degeneration (AMD). Amyloid-beta (Aβ) is a constituent of AMD drusen and promotes the activation of NLRP3 inflammasome which facilitates the production of cytokines. We investigated the role of transcription factor NF-κB in the activation of inflammasome in the RPE and the effect of vinpocetine, a dietary supplement with inhibitory effect on NF-κB. ARPE19/NF-κB-luciferase reporter cells treated with Aβ demonstrated enhanced NF-κB activation that was significantly suppressed by vinpocetine. Intraperitoneal injection of vinpocetine (15 mg/kg) inhibited NF-κB nuclear translocation and reduced the expression and activation of NLRP3, caspase-1, IL-1β, IL-18, and TNF-α in the RPE of adult rats that received intraocular Aβ, as measured by retinal immunohistochemistry and Western blot. Cytokine level in the vitreous was assayed using multiplex suspension arrays and revealed significantly lower concentration of MIP-3α, IL-6, IL-1α, IL-1β, and TNF-α in vinpocetine treated animals. These results suggest that the NF-κB pathway is activated by Aβ in the RPE and signals the priming of NLRP3 inflammasome and the expression of pro-inflammatory cytokines including the inflammasome substrates IL-1β and IL-18. NF-κB inhibition may be an effective approach to stem the chronic inflammatory milieu that underlies the development of AMD. Vinpocetine is a potentially useful anti-inflammatory agent that is well-tolerated in long term use.

PMID: 25041941 [PubMed - as supplied by publisher]

J Mol Neurosci. 2014 Jul 20. [Epub ahead of print]

17β-Estradiol Ameliorates Light-Induced Retinal Damage in Sprague-Dawley Rats by Reducing Oxidative Stress.

Wang S, Wang B, Feng Y, Mo M, Du F, Li H, Yu X.

Abstract: Oxidative stress is considered as a major cause of light-induced retinal neurodegeneration. The protective role of 17β-estradiol (βE2) in neurodegenerative disorders is well known, but its underlying mechanism remains unclear. Here, we utilized a light-induced retinal damage model to explore the mechanism by which βE2 exerts its neuroprotective effect. Adult male and female ovariectomized (OVX) rats were exposed to 8,000 lx white light for 12 h to induce retinal light damage. Electroretinogram (ERG) assays and hematoxylin and eosin (H&E) staining revealed that exposure to light for 12 h resulted in functional damage to the rat retina, histological changes, and retinal neuron loss. However, intravitreal injection (IVI) of βE2 significantly rescued this impaired retinal function in both female and male rats. Based on the level of malondialdehyde (MDA) production (a biomarker of oxidative stress), an increase in retinal oxidative stress followed light exposure, and βE2 administration reduced this light-induced oxidative stress. Quantitative reverse-transcriptase (qRT)-PCR indicated that the messenger RNA (mRNA) levels of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (Gpx) were downregulated in female OVX rats but were upregulated in male rats after light exposure, suggesting a gender difference in the regulation of these antioxidant enzyme genes in response to light. However, βE2 administration restored or enhanced the SOD and Gpx expression levels following light exposure. Although the catalase (CAT) expression level was insensitive to light stimulation, βE2 also increased the CAT gene expression level in both female OVX and male rats. Further examination indicated that the antioxidant proteins thioredoxin (Trx) and nuclear factor erythroid 2-related factor 2 (Nrf2) are also involved in βE2-mediated antioxidation and that the cytoprotective protein heme oxygenase-1 (HO-1) plays a key role in the endogenous defense mechanism against light exposure in a βE2-independent manner. Taken together, we provide evidence that βE2 protects against light-induced retinal damage via its antioxidative effect, and its underlying mechanism involves the regulation of the gene expression levels of antioxidant enzymes (SOD, CAT, and Gpx) and proteins (Trx and Nrf2). Our study provides conceptual evidence in support of estrogen replacement therapy for postmenopausal women to reduce the risk of age-related macular degeneration.

PMID: 25038876 [PubMed - as supplied by publisher]

Epidemiology

PLoS One. 2014 Jul 25;9(7):e103466. doi: 10.1371/journal.pone.0103466. eCollection 2014.

Serological Association of Chlamydia pneumoniae Infection with Age-Related Macular Degeneration: A Systematic Review and Meta-Analysis.

Chen X, Jhanji V, Chen C, Chen H.

BACKGROUND: We investigated the serological association of Chlamydia pneumoniae infection with age-related macular degeneration (AMD).

METHODS: A systematic review and meta-analysis was performed. PubMed, Embase, Web of Science and the Association of Research in Vision and Ophthalmology abstracts were searched to identify studies investigating the serological association of Chlamydia pneumoniae infection with age-related macular degeneration. The quality of original studies was assessed using the Newcastle-Ottawa scale. Heterogeneity was explored with meta-regression. The odds ratios (ORs) and standardized mean differences (SMD) of Chlamydia pneumoniae infection between AMD patients and controls were pooled.

RESULTS: In total, 9 studies met the inclusion criteria using the Newcastle-Ottawa scale scores ranging from 4 to 9. There was heterogeneity among studies due to a difference in the study designs and measurement of exposure to Chlamydia pneumoniae infection. The overall OR of Chlamydia pneumoniae infection with AMD was 1.11 (95% confidence interval: 0.78-1.57, P=0.56). The overall SMD of antibody titer between AMD and control was 0.43 (95% confidence interval: -0.12 to 0.99, P=0.13).

CONCLUSIONS: Evidence from the current published literature suggested no statistically significant association between Chlamydia pneumoniae infection and AMD.

PMID: 25062085 [PubMed - as supplied by publisher]

Genetics

Arch Med Res. 2014 Jul 19. pii: S0188-4409(14)00161-1. doi: 10.1016/j.arcmed.2014.07.005. [Epub ahead of print]

Study of Polymorphisms in CX3CR1, PLEKHA1 and VEGF Genes as Risk Factors for Age-related Macular Degeneration in Indian Patients.

Gupta D, Gupta V, Singh V, Chawla S, Parveen F, Agarwal S, Phadke SR.

BACKGROUND AND AIMS: Age-related macular degeneration (AMD) is an important cause of visual impairment in elderly persons. AMD is a multifactorial disease in which both environmental and genetic factors have been implicated. Various single nucleotide polymorphisms (SNPs) have been found to be associated with AMD. This study aimed to investigate the association of polymorphisms in CX3CR1, PLEKHA1 and VEGF genes with AMD in Indian patients.

METHODS: Genotyping for the CX3CR1 T280M (C>T) and V249I (G>A), PLEKHA1 A320T (G>A) &VEGF +674 (C>T) and +936 (C>T) was performed in 121 AMD patients and 100 controls by polymerase chain reaction, restriction fragment length polymorphism (PCR-RFLP) and sequencing method.

RESULTS: The genotype analysis of VEGF gene polymorphisms (+674 and +936) showed a significant association with AMD. Odds ratios for VEGF (+674) and VEGF (+936) were 2.37 and 2.50 with a p value 0.0029 and 0.0358 for the autosomal dominant model. CX3CR1 (T280M and V249I) and PLEKHA1 (A320T) polymorphisms were not found to be associated with AMD. Odds ratios for mutant alleles of T280M and V249I polymorphisms in CX3CR1 gene were 0.95 and 0.83, respectively, compared to the wild-type alleles. Odds ratio for the polymorphism in the PLEKHA1 gene was 0.63.

CONCLUSIONS: The present study suggests that both polymorphisms in VEGF gene are risk factors for AMD in the Indian population. Detection of individuals at risk could lead to strategies for prevention, early diagnosis and management of AMD.

PMID: 25050486 [PubMed - as supplied by publisher]

Diet & lifestyle

Mol Nutr Food Res. 2014 Jul 15. doi: 10.1002/mnfr.201400196. [Epub ahead of print]

Docosahexaenoic Acid Reduces Linoleic Acid-Induced Monocyte Chemoattractant Protein-1 Expression via PPARγ and Nuclear Factor-κB Pathway in Retinal Pigment Epithelial Cells.

Fang IM, Yang CH, Yang CM.

SCOPE: To investigate whether docosahexaenoic acid (DHA) could inhibit linoleic acid (LA)-induced monocyte chemoattractant protein (MCP)-1expression in human retinal pigment epithelial (RPE) cells.

METHODS AND RESULTS: ARPE-19 cells were pretreated with DHA and then exposed to LA. The expression of MCP-1 and PPARγ was examined using RT-PCR and Western blot analysis. LA at 10, 25 or 50 μM induced expression of MCP-1 in ARPE-19 cells in a dose-dependent manner (P< 0.05). DHA at 50 and 100 μM effectively inhibited LA-induced MCP-1 expression and production (P< 0.05) and NF-κB activation. In addition, the culture medium from LA-stimulated ARPE-19 cells could induce tube formation in choroidal endothelial cells (RF6A), whereas 100 μM DHA inhibited tube formation. DHA at 100 μM increased the expression and activity of PPARγ (P< 0.05). Pretreatment with PPARγ inhibitor (GW9662) abolished the inhibitory effect of DHA (100 μM) on LA-induced IκB degradation, p65 translocation and MCP -1 expression in ARPE-19 cells (P< 0.05), as well as tube formation in RF6A.

CONCLUSION: DHA reduced LA-induced MCP-1 expression via a PPARγ- and NF-κB-dependent pathway in ARPE-19 cells. These results suggest the molecular mechanisms underlying the beneficial effects of increased consumption of DHA and reduced consumption of LA on age-related macular degeneration.

PMID: 25044948 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2014 Jun 26;8:1227-32. doi: 10.2147/OPTH.S64048. eCollection 2014.

Factors affecting the use of antioxidant supplements in patients with late AMD.

Yu AL, Paul T, Schaumberger M, Welge-Lussen U.

BACKGROUND: The purpose of this study was to assess the use of oral antioxidant supplements in patients with late age-related macular degeneration (AMD) and to identify influencing factors that may affect the use of such supplements.

METHODS: The study included 47 patients with late AMD. Using a questionnaire, the patients were asked for their demographic, ophthalmologic, and systemic data, their source of recommendation of antioxidant use for AMD, and/or their reasons for nonuse. The demographic, ophthalmologic, and systemic information was correlated with use or nonuse of oral antioxidant supplements for AMD.

RESULTS: Sixty-eight percent (32/47) of patients took antioxidant supplements for AMD and 32% (15/47) of patients did not. There were no statistically significant differences in demographic, ophthalmologic, and systemic parameters between patients with late AMD who used supplements and those who did not. Two thirds of patients with late AMD (66%, 31/47) reported being recommended oral antioxidant supplements for AMD by their ophthalmologist. Patients who did not use antioxidant supplements either did not obtain any recommendation or did not believe in their benefits.

CONCLUSION: This study shows that most patients with late AMD use antioxidant supplements despite the recommendation to do so being missing in the Age-Related Eye Disease Study. Our study emphasizes the importance of seeking further therapeutic options for patients with late AMD.

PMID: 25061269 [PubMed]

Optom Vis Sci. 2014 Jul 24. [Epub ahead of print]

Learning to Read Vertical Text in Peripheral Vision.

Subramanian A, Legge GE, Wagoner GH, Yu D.

PURPOSE: English-language text is almost always written horizontally. Text can be formatted to run vertically, but this is seldom used. Several studies have found that horizontal text can be read faster than vertical text in the central visual field. No studies have investigated the peripheral visual field. Studies have also concluded that training can improve reading speed in the peripheral visual field for horizontal text. We aimed to establish whether the horizontal vertical differences are maintained and if training can improve vertical reading in the peripheral visual field.

METHODS: Eight normally sighted young adults participated in the first study. Rapid serial visual presentation (RSVP) reading speed was measured for horizontal and vertical text in the central visual field and at 10 degrees eccentricity in the upper or lower (horizontal text) and right or left (vertical text) visual fields. Twenty-one normally sighted young adults split equally between two training groups and one control group participated in the second study. Training consisted of RSVP reading using either vertical text in the left visual field or horizontal text in the inferior visual field. Subjects trained daily over 4 days. Pre- and post-horizontal and vertical RSVP reading speeds were carried out for all groups. For the training groups, these measurements were repeated 1 week and 1 month posttraining.

RESULTS: Before training, RSVP reading speeds were faster for horizontal text in the central and peripheral visual fields when compared with vertical text. Training vertical reading improved vertical reading speeds by an average factor of 2.8. There was partial transfer of training to the opposite (right) hemifield. The training effects were retained for up to a month.

CONCLUSIONS: Rapid serial visual presentation training can improve RSVP vertical text reading in peripheral vision. These findings may have implications for patients with macular degeneration or hemianopic field loss.

PMID: 25062130 [PubMed - as supplied by publisher]

Food Chem. 2014 Dec 15;165:300-6. doi: 10.1016/j.foodchem.2014.05.107. Epub 2014 May 27.

Profiling of carotenoids and antioxidant capacity of microalgae from subtropical coastal and brackish waters.

Ahmed F, Fanning K, Netzel M, Turner W, Li Y, Schenk PM.

Abstract: Carotenoids are associated with various health benefits, such as prevention of age-related macular degeneration, cataract, certain cancers, rheumatoid arthritis, muscular dystrophy and cardiovascular problems. As microalgae contain considerable amounts of carotenoids, there is a need to find species with high carotenoid content. Out of hundreds of Australian isolates, 12 microalgal species were screened for carotenoid profiles, carotenoid productivity, and in vitro antioxidant capacity (total phenolic content (TPC) and ORAC). The top four carotenoid producers at 4.68-6.88mg/g dry weight (DW) were Dunaliella salina, Tetraselmis suecica, Isochrysis galbana, and Pavlova salina. TPC was low, with D. salina possessing the highest TPC (1.54mg Gallic Acid Equivalents/g DW) and ORAC (577μmol Trolox

Equivalents/g DW). Results indicate that T. suecica, D. salina, P. salina and I. galbana could be further developed for commercial carotenoid production.

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