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Drug treatment

Ophthalmology. 2016 Apr 20. [Epub ahead of print]

Five-Year Outcomes with Anti-Vascular Endothelial Growth Factor Treatment of Neovascular Age-Related Macular Degeneration: The Comparison of Age-Related Macular Degeneration Treatments Trials.

Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Maguire MG, Martin DF, Ying GS, Jaffe GJ, Daniel E, Grunwald JE, Toth CA, Ferris FL 3rd, Fine SL.

PURPOSE: To describe outcomes 5 years after initiating treatment with bevacizumab or ranibizumab for neovascular age-related macular degeneration (AMD).

DESIGN: Cohort study.

PARTICIPANTS: Patients enrolled in the Comparison of AMD Treatments Trials.

METHODS: Patients were assigned randomly to ranibizumab or bevacizumab and to 1 of 3 dosing regimens. After 2 years, patients were released from the clinical trial protocol. At 5 years, patients were recalled for examination.

MAIN OUTCOME MEASURES: Visual acuity (VA) and morphologic retinal features.

RESULTS: Visual acuity was obtained for 647 of 914 (71%) living patients with average follow-up of 5.5 years. The mean number of examinations for AMD care after the clinical trial ended was 25.3, and the mean number of treatments was 15.4. Most patients (60%) were treated 1 time or more with a drug other than their assigned drug. At the 5-year visit, 50% of eyes had VA of 20/40 or better and 20% had VA of 20/200 or worse. Mean change in VA was -3 letters from baseline and -11 letters from 2 years. Among 467 eyes with fluorescein angiography, mean total lesion area was 12.9 mm², a mean of 4.8 mm² larger than at 2 years. Geographic atrophy was present in 213 of 515 (41%) gradable eyes and was subfoveal in 85 eyes (17%). Among 555 eyes with spectral-domain optical coherence tomography, 83% had fluid (61% intraretinal, 38% subretinal, and 36% sub-retinal pigment epithelium). Mean foveal total thickness was 278 µm, a decrease of 182 µm from baseline and 20 µm from 2 years. The retina was abnormally thin (<120 µm) in 36% of eyes. Between 2 and 5 years, the group originally assigned to ranibizumab for 2 years lost more VA than the bevacizumab group (-4 letters; P = 0.008). Otherwise, there were no statistically significant differences in VA or morphologic outcomes between drug or regimen groups.

CONCLUSIONS: Vision gains during the first 2 years were not maintained at 5 years. However, 50% of eyes had VA of 20/40 or better, confirming anti-vascular endothelial growth factor therapy as a major long-term therapeutic advance for neovascular AMD.

PMID: 27156698 [PubMed - as supplied by publisher]

Ophthalmology. 2016 May 4. [Epub ahead of print]

Morphology and Visual Acuity in Aflibercept and Ranibizumab Therapy for Neovascular Age-Related Macular Degeneration in the VIEW Trials.

Waldstein SM, Simader C, Staurenghi G, Chong NV, Mitchell P, Jaffe GJ, Lu C, Katz TA, Schmidt-Erfurth U.

PURPOSE: To compare the efficacy of intravitreal aflibercept and ranibizumab on the exudative activity of neovascular age-related macular degeneration (nAMD) using optical coherence tomography (OCT) and to correlate morphologic findings with visual acuity (VA) outcomes.

DESIGN: Post hoc analysis of the prospective VIEW trials.

PARTICIPANTS: Data of 1815 patients randomized to 0.5 mg ranibizumab every 4 weeks (Q4wks), 2 mg aflibercept Q4wks, or 2 mg aflibercept every 8 weeks (Q8wks).

METHODS: Standardized OCT evaluation was performed by masked reading centers for the presence of intraretinal cystoid fluid (IRC), subretinal fluid (SRF), and pigment epithelial detachment (PED). Rates of feature resolution were compared between drugs and regimen. Associations between morphologic features and VA were analyzed using multivariate modeling.

MAIN OUTCOME MEASURES: Resolution rates of IRC, SRF, and PED, and associations between morphology and VA.

RESULTS: At baseline, the proportions of eyes with IRC, SRF, and PED were balanced between the aflibercept and ranibizumab groups. At week 12, IRC resolved in 50% of eyes with both agents. Subretinal fluid resolved in 70% of pooled aflibercept-treated eyes and in 59% of ranibizumab-treated eyes, and PED resolved in 29% and 24% of pooled aflibercept-treated eyes and ranibizumab-treated eyes, respectively. At week 52, IRC resolved in 57% (aflibercept Q4wks), 50% (aflibercept Q8wks), and 52% (ranibizumab) of patients; SRF resolved in 75% (both aflibercept Q4wks/Q8wks) and 66% (ranibizumab) of patients; and PED resolved in 40% (aflibercept Q4wks), 34% (aflibercept Q8wks), and 28% (ranibizumab) of patients. During fixed dosing (weeks 12-52) all exudative features showed synchronized fluctuations after treatment-free visits in the Q8wks aflibercept regimen. During pro re nata dosing (weeks 52-96), greater proportions of patients showed recurrent fluid in all treatment arms. Presence of IRC was generally associated with lower VA at baseline, which translated into poorer final VA outcomes.

CONCLUSIONS: Fluid resolution in all compartments was consistently greater for aflibercept Q4wks than for aflibercept Q8wks and ranibizumab. At week 52, Q8wks aflibercept-treated eyes were, on average, as dry as or drier than with ranibizumab despite the extended treatment interval. Independent of agent or regimen, preexisting morphologic features of the retina at baseline markedly influenced VA outcomes.

PMID: 27157149 [PubMed - as supplied by publisher]

J Pharm Pract. 2016 May 10. [Epub ahead of print]

Aflibercept: A Review of Its Use in the Management of Diabetic Eye Complications.

Akiyode O, Major J, Ojo A.

Abstract: Aflibercept is the most recently approved vascular endothelial growth factor (anti-VEGF) inhibitor for the management of diabetic macular edema and diabetic retinopathy. The purpose of this article is to review the efficacy and safety of aflibercept in the management of diabetic eye complications and to describe its place in therapy. Anti-VEGF agents have been noted in clinical trials to be superior to laser photocoagulation, the standard therapy ($P < .0001$, $P \leq .0085$, respectively). Aflibercept has been comparatively studied with other anti-VEGF agents, namely, bevacizumab and ranibizumab, and noted to

be equally efficacious and safe in patients with mild visual acuity loss ($P > .50$). However, in the treatment of patients with diabetic macular edema having moderate to severe visual acuity loss, aflibercept outperformed the other 2 anti-VEGF agents (aflibercept vs bevacizumab, $P < .001$; aflibercept vs ranibizumab, $P = .003$). However, additional studies are needed to fully appreciate the long-term safety and efficacy of aflibercept and the anti-VEGF therapy class.

PMID: 27166390 [PubMed - as supplied by publisher]

Int Ophthalmol. 2016 May 12. [Epub ahead of print]

Comparison of early dexamethasone retreatment versus standard dexamethasone regimen combined with PRN ranibizumab in diabetic macular edema.

Arikan Yorgun M, Toklu Y, Mutlu M.

Abstract: The purpose of the study is to evaluate the efficacy and safety of as-needed dexamethasone (DEX) retreatment compared with standard DEX retreatment combined with PRN ranibizumab injections among patients with persistent diabetic macular edema (DME). Twenty-eight patients with persistent macular edema having recurrence earlier than 6 months after initial DEX implantation were included in this retrospective study. Group I consisted of 13 patients retreated using monthly PRN ranibizumab injections combined with standard 6-monthly DEX implantation; Group II consisted of 15 patients retreated with DEX implantation earlier than 6 months on an "as-needed" basis. There was no significant difference between the groups with regarding to age, gender, HbA1C levels, duration of diabetes, duration of macular edema, baseline central macular thickness (CMT), best-corrected visual acuity (BCVA), and intraocular pressure (IOP) values ($p > 0.05$). The mean follow-up time of the whole study population was 10.13 ± 1.75 months (range 9-15). The mean CMT values were significantly decreased in both groups compared to baseline values except for the 6th-month CMT in Group I ($p < 0.05$). The mean logMAR BCVA values were not statistically different between groups during the follow-up compared to baseline BCVA values ($p > 0.05$). However, a significant change in mean BCVA from baseline was seen at 4th, 6th, and 9th months in Group II ($p \leq 0.05$). The mean number of total intravitreal treatments was 3.50 ± 0.77 in Group I and 2.53 ± 0.51 in Group II ($p = 0.001$). During the follow-up period, one patient in Group I and five patients in Group II had increased IOP (≥ 25 mmHg). Early DEX retreatment improved vision with superior anatomical improvement at 6th month and with fewer intravitreal treatments in eyes with DME. However, improvement in visual acuity is similar with standard DEX retreatment combined with PRN ranibizumab group.

PMID: 27173834 [PubMed - as supplied by publisher]

Mol Pharm. 2016 May 12. [Epub ahead of print]

An anti-VEGF polysiRNA polyplex for the treatment of choroidal neovascularization.

Lee J, Ryoo NK, Han H, Hong HK, Park JY, Park SJ, Kim YK, Sim C, Kim K, Woo SJ, Park KH, Kim H.

Abstract: Choroidal neovascularization (CNV) is a major cause of severe vision loss in patients with age-related macular degeneration (AMD). Present ocular siRNA delivery technology is limited due to poor delivery through the retina to choroid, where CNV originates. Our goal was to develop an optimized nano-sized polyRNAi-based therapeutic delivery system to the sub-retinal space. We developed it by siRNA multimerization (polysiRNA) followed by coating with branched polyethylenimine and hyaluronic acid, and then evaluated its efficacy in vitro and in vivo. The polysiRNA polyplex showed a narrow size distribution (260.7 ± 43.27 nm) and negative charge (-4.98 ± 0.47 mV) owing to the hyaluronic acid outer layer. In vitro uptake of the polysiRNA polyplex by human ARPE cells was discovered, and the direct inhibition of VEGF mRNA translation was confirmed in B16F10 cells. The intravitreally administered polysiRNA polyplex overcame both the vitreous and retina barriers in vivo and reached the sub-retinal space efficiently.

Intravitreal injection of polysiRNA polyplex was not toxic to the retina in histopathology. Furthermore, intravitreal injections of the polysiRNA polyplex at both 1 and 7 days after laser photocoagulation inhibited laser induced choroidal neovascularization, compared to the control ($p < 0.05$). These results suggest that anti-VEGF polysiRNA polyplexes show great potential in delivering multimeric RNAi-based therapeutics to treat retinal or choroidal disorders.

PMID: 27173745 [PubMed - as supplied by publisher]

Cytokine. 2016 May 7;83:210-216. [Epub ahead of print]

Ranibizumab interacts with the VEGF-A/VEGFR-2 signaling pathway in human RPE cells at different levels.

Ranjbar M, Brinkmann MP, Tura A, Rudolf M, Miura Y, Grisanti S.

Abstract: Vascular endothelial growth factor (VEGF) secreted by the retinal pigment epithelium (RPE) plays an important role in ocular homeostasis, but also in diseases, most notably age-related macular degeneration (AMD). To date, anti-VEGF drugs like ranibizumab have been shown to be most effective in treating these pathologic conditions. However, clinical trials suggest that the RPE could degenerate and perish through anti-VEGF treatment. Herein, we evaluated possible pathways and outcomes of the interaction between ranibizumab and human RPE cells (ARPE-19). Results indicate that ranibizumab affects the VEGF-A metabolism in RPE cells from an extra- as well as intracellular site. The drug is taken up into the cells, with the VEGF receptor 2 (VEGFR-2) being involved, and decreases VEGF-A protein levels within the cells as well as extracellularly. Oxidative stress plays a key role in various inflammatory disorders of the eye. Our results suggest that oxidative stress inhibits RPE cell proliferation. This anti-proliferative effect on RPE cells is significantly enhanced through ranibizumab, which does not inhibit RPE cell proliferation substantially in absence of relevant oxidative stress. Therefore, we emphasize that anti-VEGF treatment should be selected carefully in AMD patients with preexistent extensive RPE atrophy.

PMID: 27163716 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2016 Apr 18;9(4):551-5. Collection 2016.

6-weekly bevacizumab versus 4-weekly ranibizumab for neovascular age-related macular degeneration: a 2-year outcome.

Chiam PJ, Ho VW, Hickley NM, Kotamarthi V.

AIM: To compare visual acuity and central macular thickness (CMT) changes in neovascular age related macular degeneration patients treated with either 6 weekly bevacizumab regimen or 4 weekly ranibizumab on an as required basis.

METHODS: Patients made an informed choice between bevacizumab 1.25 mg or ranibizumab 0.5 mg. The selected treatment was administered in the first 3 visits. Bevacizumab patients were followed-up 6 weekly and ranibizumab 4 weekly. Retreatment criteria was based on the reduction of >5 letters in the best-corrected visual acuity (BCVA), the presence of retinal fluid on optical coherence tomography (OCT) or new retinal haemorrhage.

RESULTS: Visual acuity at 2y bevacizumab patients gained 7.0 letters and ranibizumab 9.2 ($P = 0.31$, 95% CI -6.4 to 2.0). At 2y 86% of bevacizumab and 94% ranibizumab patients had not lost 15 letters or more ($P = 0.13$). Mean CMT decreased at 2y bevacizumab by 146 μm , ranibizumab 160 μm ($P = 0.72$). Mean number of injections was at 2y bevacizumab 11.9, ranibizumab 10.3 ($P = 0.023$).

CONCLUSION: Bevacizumab 6 weekly on an as required basis was not demonstrably non-inferior to

ranibizumab 4 weekly pro re nata (prn) in terms of BCVA and change in CMT. In the bevacizumab group, one more injection was required in the second year compared to the ranibizumab group.

PMID: 27162727 [PubMed] PMCID: PMC4853350

Middle East Afr J Ophthalmol. 2016 Apr-Jun;23(2):222-4.

Anti-Vascular Endothelial Growth Factor Treatment for Proliferative Macular Telangiectasia Type 2.

Alkin Z, Yilmaz I, Ozkaya A, Yazici AT.

Abstract: Idiopathic macular telangiectasia type 2 (IMT 2), is the most common type of a heterogeneous group of disorders, characterized by telangiectatic alterations of the juxtafoveal capillary network. Vision loss is due to retinal atrophy and subretinal neovascularization (SRN). Here, we report the outcomes of intravitreal anti-vascular endothelial growth factor injections, bevacizumab or ranibizumab, in four cases with proliferative IMT 2. Baseline best corrected visual acuity (VA) ranged from 20/50 to 20/100. Follow-up time ranged from 12 months to 24 months. One of four patients received one injection, two patients received three injections, and one patient received seven injections. VA improved in three eyes (≥ 1 line improvement) and decreased in one eye (≥ 1 line decrease) over time. Final acuity ranged from 20/30 to 20/100. There were no cases of leakage after the cessation of treatment. SRN, which is a complication of IMT 2, should be recognized and treated accordingly.

PMID: 27162458 [PubMed - in process] PMCID: PMC4845624

Am J Ophthalmol. 2016 May 6. [Epub ahead of print]

Clinical Efficacy and Safety of Ranibizumab versus Dexamethasone for Central Retinal Vein Occlusion (COMRADE C): A European Label Study.

Hoerauf H, Feltgen N, Weiss C, Paulus EM, Schmitz-Valckenberg S, Pielen A, Puri P, Berk H, Eter N, Wiedemann P, Lang GE, Rehak M, Wolf A, Bertelmann T, Hattenbach LO; COMRADE-C Study Group.

PURPOSE: To compare the efficacy and safety of the European labels of ranibizumab 0.5mg versus dexamethasone 0.7mg in patients with macular edema secondary to central retinal vein occlusion (CRVO).

DESIGN: Phase IIIb, multicenter, double-masked, randomized clinical trial. **METHODS:** Patients were randomized (1:1) to receive either monthly ranibizumab followed by PRN-treatment (n=124) or one sustained-release dexamethasone implant followed by PRN sham injections (n=119). Main outcomes were mean average change in best-corrected visual acuity (BCVA) from baseline to month 1 through month 6, mean change in BCVA and adverse events (AEs).

RESULTS: 185/243 (76.1%) patients completed the study. No difference was observed in BCVA between ranibizumab and dexamethasone at months 1 and 2. From month 3 to month 6, there was significant difference in BCVA gains in favour of ranibizumab. At month 6, mean average BCVA gain was significantly higher with ranibizumab than dexamethasone (12.86 vs 2.96 letters; difference 9.91 letters, 95%CI:[6.51-13.30]; $P < 0.0001$). Mean injection number of ranibizumab was 4.52. Ocular AEs were reported in more patients in the dexamethasone than in the ranibizumab group (86.6% vs 55.6%).

CONCLUSIONS: Using the European labels, similar efficacy was observed for ranibizumab and dexamethasone at months 1 and 2. However, ranibizumab maintained its efficacy throughout the study whereas dexamethasone declined from month 3 onwards. The main limitation of the study was that dexamethasone patients received only a single treatment during the 6-month study. In clinical practice, dexamethasone retreatment may be required earlier than 6 months. Safety findings were similar to those previously reported.

PMID: 27163237 [PubMed - as supplied by publisher]

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Int J Ophthalmol. 2016 Mar 18;9(3):424-30. eCollection 2016.

Bevacizumab for neovascular age-related macular degeneration in Chinese patients in a clinical setting.

Ng DS, Kwok AK, Tong JM, Chan CW, Li WW.

AIM: To determine the outcome of non-investigational treatment with intravitreal bevacizumab (IVB) in neovascular age-related macular degeneration (AMD) patients.

METHODS: Retrospective chart review of 81 eyes with neovascular AMD followed-up for at least 12mo and received 3-monthly loading IVB injections. Re-treat was based upon the individual clinician's judgment. Best -corrected visual acuity (BCVA) and optical coherence tomography measurements of central foveal thickness outcomes were evaluated at 12, 24mo.

RESULTS: Eighty-one eyes (of 75 patients) completed 12mo of follow-up and 44 eyes (of 41 patients) completed 24mo of follow-up. The mean baseline logMAR BCVA significantly improved from 0.94 ± 0.69 to 0.85 ± 0.68 at 12mo ($P < 0.001$) and from 0.91 ± 0.65 to 0.85 ± 0.60 ($P = 0.004$) at 24mo. The proportion of eyes that lost < 15 logMAR letters at 12mo was 90.1% and at 24mo was 81.8%. IVB was effective in improving visual acuity in both treatment naïve and previous photodynamic therapy (PDT)-treated subgroups. Treatment naïve patients required significantly fewer injections than patients with prior PDT. Multiple regression analysis identified that poorer baseline visual acuity was associated with greater improvement in visual acuity ($P = 0.015$).

CONCLUSION: Fewer injections in clinical practice may result in suboptimal visual outcomes compared with clinical trials of IVB in neovascular AMD patients. Poor baseline visual acuity and prior PDT treatment may also improve vision after IVB. The safety and durability of effect was maintained at 24mo.

PMID: 27158614 [PubMed] PMCID: PMC4844047

J Fr Ophtalmol. 2016 May 4. [Epub ahead of print]

[Extemporaneous withdrawal with a mini-spike filter: A low infection risk technique for drawing up bevacizumab for intravitreal injection]. [Article in French]

Le Rouic JF, Breger D, Peronnet P, Hermouet-Leclair E, Alphandari A, Pousset-Decré C, Badat I, Becquet F.

PURPOSE: To describe a technique for extemporaneously drawing up bevacizumab for intravitreal injection (IVT) and report the rate of post-injection endophthalmitis.

PATIENTS AND METHODS: Retrospective monocentric analysis (January 2010-December 2014) of all IVT of bevacizumab drawn up with the following technique: in the operating room (class ISO 7) through a mini-spike with an integrated bacteria retentive air filter. The surgeon was wearing sterile gloves and a mask. The assisting nurse wore a mask. The bevacizumab vial was discarded at the end of each session.

RESULTS: Six thousand two hundred and thirty-six bevacizumab injections were performed. One case of endophthalmitis was noted (0.016%). During the same period, 4 cases of endophthalmitis were found after IVT of other drugs (4/32,992; 0.012%. $P = 0.8$).

CONCLUSION: Intravitreal injection of bevacizumab after extemporaneous withdrawal through a mini-spike filter is a simple and safe technique. The risk of postoperative endophthalmitis is very low. This simple technique facilitates access to compounded bevacizumab.

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Other treatment & diagnosis

Prog Retin Eye Res. 2016 May 9. [Epub ahead of print]

Differentiating drusen: Drusen and drusen-like appearances associated with ageing, age-related macular degeneration, inherited eye disease and other pathological processes.

Khan KN, Mahroo OA, Khan R, Mohamed MD, McKibbin M, Bird A, Michaelides M, Tufail A, Moore AT.

Abstract: Drusen are discussed frequently in the context of their association with age-related macular degeneration (AMD). Some types may, however, be regarded as a normal consequence of ageing; others may be observed in young age groups. They also occur in a number of inherited disorders and some systemic conditions. Whilst drusen are classically located external (scleral) to the retinal pigment epithelium, accumulations of material internal (vitreal) to this layer can display a drusen-like appearance, having been variously termed pseudodrusen or subretinal drusenoid deposits. This review first briefly presents an overview of drusen biogenesis and subclinical deposit. The (frequently overlapping) subtypes of clinically detectable deposit, seen usually in the context of ageing or AMD, are then described in more detail, together with appearance on imaging modalities: these include hard and soft drusen, cuticular drusen, reticular pseudodrusen and "ghost drusen". Eye disorders other than AMD which may exhibit drusen or drusen-like features are subsequently discussed: these include monogenic conditions as well as conditions with undefined inheritance, the latter including some types of early onset drusen such as large colloid drusen. A number of systemic conditions in which drusen-like deposits may be seen are also considered. Throughout this review, high resolution images are presented for most of the conditions discussed, particularly the rarer ones, providing a useful reference library for images of the range of conditions associated with drusen-like appearances. In the final section, some common themes are highlighted, as well as a brief discussion of some future avenues for research.

PMID: 27173377 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2647-2656.

Quantitative Analysis of Outer Retinal Tubulation in Age-Related Macular Degeneration From Spectral-Domain Optical Coherence Tomography and Histology.

Litts KM, Ach T, Hammack KM, Sloan KR, Zhang Y, Freund KB, Curcio CA.

PURPOSE: To assess outer retinal tubulation (ORT) morphology from spectral-domain optical coherence tomography (SD-OCT) volumes and donor eye histology, analyze ORT reflectivity, and estimate the number of cones surviving in ORT.

METHODS: In SD-OCT volumes from nine patients with advanced AMD, ORT was analyzed en face and in B-scans. The hyperreflective ORT border in cross-section was delineated and surface area calculated. Reflectivity was compared between ORT types (Closed, Open, Forming, and Branching). A flatmount retina from a donor with neovascular AMD was labeled to visualize the external limiting membrane that delimits ORT and allow measurements of cross-sectional cone area, center-to-center cone spacing, and cone density. The number of cones surviving in ORT was estimated.

RESULTS: By en face SD-OCT, ORT varies in complexity and shape. Outer retinal tubulation networks almost always contain Closed cross-sections. Spectral-domain OCT volumes containing almost exclusively Closed ORTs showed no significant direction-dependent differences in hyperreflective ORT border intensity. The surface areas of partial ORT assessed by SD-OCT volumes ranged from 0.16 to 1.76 mm². From the flatmount retina, the average cross-sectional area of cone inner segments was 49.1 ± 7.9 μm². The average cone spacing was 7.5 ± 0.6 μm. Outer retinal tubulation cone density was 20,351 cones/mm². The estimated number of cones in ORT in a macula ranged from 26,399 to 186,833 cones, which is 6% to

44% of the cones present in a healthy macula.

CONCLUSIONS: These first estimates for cone density and number of cones surviving in ORT suggest that ORT formation considerably distorts the photoreceptor mosaic. Results provide additional insight into the reflectivity characteristics and number of ORT cones observable in living patients by SD-OCT, as cones persist and disease progresses.

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Am J Ophthalmol. 2016 May 6. [Epub ahead of print]

Correlation of partial outer retinal thickness with scotopic and mesopic fundus-controlled perimetry in patients with reticular drusen.

Steinberg JS, Saßmannshausen M, Fleckenstein M, Fimmers R, Oishi A, Holz FG, Schmitz-Valckenberg S.

PURPOSE: To correlate partial outer retinal thickness with scotopic and mesopic fundus-controlled perimetry in patients with reticular drusen (RDR).

DESIGN: Observational case series with controls of similar age **METHODS:** Twenty eyes from 18 patients with RDR (mean age 75.8 years) and 20 eyes from 20 healthy controls (mean age 75.5 years) were included. Scotopic and mesopic fundus-controlled perimetry was performed in patients. The localized partial outer retinal thickness at the site of test stimuli was determined as the distance between the outer border of the outer plexiform layer and the inner border of the ellipsoid zone and topographically corrected according to measurements in controls.

RESULTS: The mean partial outer retinal thickness in patients was 65.8µm over areas with RDR and 76.4µm ($p<0.0001$) over non-affected retinal areas. Mesopic and scotopic sensitivity were reduced corresponding to areas with RDR (mean scotopic 12.8dB and mean mesopic 17.2dB) as compared to non-affected retinal areas (18.2dB and 18.4dB) ($p<0.001$, $p=0.001$). On average a reduction of partial outer retinal thickness by 1µm was associated with a decrease of scotopic function of 0.96dB.

CONCLUSIONS: The extent of outer retinal thinning in the presence of RDR is spatially associated with the extent of impairment in scotopic retinal function, indicating a direct structural-functional correlation of structural changes to loss of rod function. High-resolution retinal imaging in combination with scotopic fundus-controlled perimetry allows for a more refined structure-function correlation in diseases with a presumed higher vulnerability of rod compared with cone function.

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Expert Rev Med Devices. 2016 May 13. [Epub ahead of print]

Optical coherence tomography angiography: a non-invasive tool to image end-arterial system.

Agrawal R, Xin W, Keane PA, Chhablani J, Agarwal A.

Abstract: Optical coherence tomography angiography (OCTA) is a relatively novel technology for in vivo imaging of vascular network. It uses moving erythrocytes as contrasting mechanism and avoids the use of intravenous dyes. A depth-resolved 3-dimensional image set can be generated within seconds using the technique of OCTA. Therefore, it possesses a great potential for widespread application in ophthalmic angiography. Herein we discuss the most common technologies behind OCTA and the scope of future technical improvement. We provide a perspective on advantages and disadvantages of OCTA over conventional fluorescein angiography and indocyanine green angiography. Lastly, current literature on the clinical application of OCTA in common ocular diseases including neovascular age-related macular

degeneration, diabetic retinopathy, retinal artery and vein occlusion, and glaucoma are reviewed.

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Anticancer Agents Med Chem. 2016 May 13. [Epub ahead of print]

New Approaches to Photodynamic Therapy from Type I, II and III to Type IV Using One or More Photons.

Scherer KM, Bisby RH, Botchway SW, Parker AW.

Abstract: Photodynamic therapy (PDT) is an alternative cancer treatment to conventional surgery, radiotherapy and chemotherapy. It is based on activating a drug with light that triggers the generation of cytotoxic species that promote tumour cell killing. At present, PDT is mainly used in the treatment of wet age-related macular degeneration, for precancerous conditions of the skin (e.g. actinic keratosis) and in the palliative care of advanced cancers, for instance of the bladder or the oesophagus. PDT is still not used as a first line cancer treatment, which is surprising given the first clinical trials by Dougherty's group dating back to the 1970's. PDT has significant advantages over surgery or radiation therapy for low lying tumours due to better cosmetic outcome and localised treatment for the patients. However, despite these advantages and significant developments in optical technology that has enabled light penetration to deeper lying tumours, in excess of 5 cm, a lack of phase III clinical trials has slowed down the uptake of PDT by the healthcare sector as a frontline treatment in cancer. However research continues to demonstrate the potential benefits of PDT and the need to stimulate funding and uptake of clinical studies using next generation photosensitizers offering advanced targeted delivery, improved photodynamic dose combined with modern light delivery technologies. This review surveys the available PDT treatments and emerging novel developments in the field with a particular focus on two-photon techniques that are anticipated to improve the effectiveness of PDT in tissues at depth and on next generation drugs that work without the need of the presence of oxygen for photosensitization making them effective where hypoxia has taken hold.

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Pathogenesis

PLoS One. 2016 May 12;11(5):e0154397.

High-Density Lipoprotein Function in Exudative Age-Related Macular Degeneration.

Pertl L, Kern S, Weger M, Hausberger S, Trieb M, Gasser-Steiner V, Haas A, Scharnagl H, Heinemann A, Marsche G.

PURPOSE: High-density lipoproteins (HDL) have long been implicated in the pathogenesis of age-related macular degeneration (AMD). However, conflicting results have been reported with regard to the associations of AMD with HDL-cholesterol levels. The present study is the first to assess HDL composition and metrics of HDL function in patients with exudative AMD and control patients.

METHODS: Blood samples were collected from 29 patients with exudative AMD and 26 age-matched control patients. Major HDL associated apolipoproteins were determined in apoB-depleted serum by immunoturbidimetry or ELISA, HDL-associated lipids were quantified enzymatically. To get an integrated measure of HDL quantity and quality, we assessed several metrics of HDL function, including cholesterol efflux capacity, anti-oxidative and anti-inflammatory activities using apoB-depleted serum from study participants.

RESULTS: In our study, we observed that the HDL associated acute phase protein serum amyloid A (SAA)

was significantly increased in AMD patients ($p < 0.01$), whereas all other assessed apolipoproteins including ApoA-I, apoA-II, apoC-II, apoC-III and apoE as well as major HDL associated lipids were not altered. HDL efflux capacity, anti-oxidative capacity and arylesterase activity were not different in AMD patients when compared with the control group. The ability of apoB-depleted serum to inhibit monocyte NF- κ B expression was significantly improved in AMD patients (mean difference (MD) -5.6, $p < 0.01$). Moreover, lipoprotein-associated phospholipase A2 activity, a marker of vascular inflammation, was decreased in AMD subjects (MD -24.1, $p < 0.01$).

CONCLUSIONS: The investigated metrics of HDL composition and HDL function were not associated with exudative AMD in this study, despite an increased content of HDL associated SAA in AMD patients. Unexpectedly, anti-inflammatory activity of apoB-depleted serum was even increased in our study. Our data suggest that the investigated parameters of serum HDL function showed no significant association with exudative AMD. However, we cannot exclude that alterations in locally produced HDL may be part of the AMD pathogenesis.

PMID: 27171197 [PubMed - as supplied by publisher]

Medicina (Kaunas). 2016;52(2):99-103. Epub 2016 Feb 22.

N-carboxymethyllysine as a biomarker for coronary artery disease and age-related macular degeneration.

Stanislovaitienė D, Žaliūnienė D, Steponavičiūtė R, Žemaitienė R, Gustienė O, Žaliūnas R.

BACKGROUND AND OBJECTIVE: An association between coronary artery disease (CAD) and age-related macular degeneration (ARMD) has long been postulated, but exact mechanisms remain unclear. The global prevalence of CAD and ARMD increases and early biomarkers for early diagnosis of these diseases are necessary. The aim of this study was to investigate the plasma level of oxidative stress biomarker CML in patients with and without angiographic findings of atherosclerosis in the coronary arteries (CADath+ and CADath-, respectively) and to assess if there was an association of CAD with ARMD.

MATERIALS AND METHODS: The study enrolled 233 subjects. Based on cardiologic and ophthalmologic examinations, the patients were divided into four subgroups: CADath+ARMD+, CADath+ARMD-, CADath-ARMD+, and CADath-ARMD-. The enzyme-linked immunosorbent assay was used for the measurement of plasma CML levels. Serum lipid levels were determined by an automatic analyzer using conventional enzymatic methods.

RESULTS: CADath+ patients had higher CML concentration compared to CADath- subjects (1.04 ± 0.6 vs. 0.83 ± 0.4 ng/mL, $P < 0.001$). The highest mean CML level (1.12 ± 0.7 ng/mL) was found in CADath+ARMD+ patients. The mean plasma CML concentration was higher in subjects with any of the analyzed diseases compared to CADath-ARMD- subjects. A significant positive association of CADath+ (OR=2.50, 95% CI 1.60-3.90, $P=0.0001$), ARMD (OR=2.08, 95% CI 1.40-3.11, $P=0.0001$) and both analyzed diseases (OR=4.67, 95% CI 2.29-9.53, $P=0.0001$) with an increased level of plasma CML in a logistic regression model adjusting by age was identified.

CONCLUSIONS: The level of CML, an oxidative stress biomarker, reflects the presence of atherosclerosis in coronary arteries and shows a possible link between ARMD and CADath+ via oxidative status.

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Serum vascular endothelial growth factor receptor-2 and adropin levels in age-related macular degeneration.

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Örnek N, Örnek K, Aydın S, Yılmaz M, Ölmez Y.

AIM: To investigate the serum levels of vascular endothelial growth factor receptor-2 (VEGFR-2) and adropin in age-related macular degeneration (AMD) patients.

METHODS: Ninety-eight AMD patients were included in the study. Seventy-eight age- and sex-matched healthy volunteers were recruited as the control group. Fundus fluorescein angiography and optical coherence tomography were performed to assess the posterior segment details. Serum VEGFR-2 and adropin levels were measured using enzyme-linked immunosorbent assays and compared between the study groups.

RESULTS: AMD group had significantly increased foveal retinal thickness, serum LDL and HDL levels and significantly decreased subfoveal choroidal thickness ($P = 0.01, 0.047, 0.025$ and <0.001 , respectively). Serum VEGFR-2 level revealed a significant decrease in AMD patients compared to controls (26.48 ± 6.44 vs 30.42 ± 7.92 ng/mL, $P < 0.001$). There was an insignificant increase in serum adropin level in AMD patients (6.17 ± 3.19 vs 5.79 ± 2.71 ng/mL, $P = 0.4$). Serum level of VEGFR-2 in AMD patients had a significant negative correlation with foveal retinal thickness ($r = -0.226$, $P = 0.025$) and a significant positive correlation with subfoveal choroidal thickness ($r = 0.2$, $P = 0.048$).

CONCLUSION: The current study demonstrated that the decreased serum VEGFR-2 level may be considered in the development of AMD. Adropin does not seem to play a role in the pathogenesis of AMD.

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Invest Ophthalmol Vis Sci. 2016 May 1;57(6):2586-97.

The Urokinase Receptor-Derived Peptide UPARANT Mitigates Angiogenesis in a Mouse Model of Laser-Induced Choroidal Neovascularization.

Cammalleri M, Dal Monte M, Locri F, Lista L, Aronsson M, Kvanta A, Rusciano D, De Rosa M, Pavone V, André H, Bagnoli P.

PURPOSE: A mouse model of age-related macular degeneration (AMD) was used to investigate the anti-angiogenic and anti-inflammatory role of UPARANT in laser-induced choroidal neovascularization (CNV).

METHODS: Choroidal neovascularization was induced by laser photocoagulation, and UPARANT was intravitreally injected. Some experiments were also performed after either intravitreal injection of anti-VEGF drugs or systemic administration of UPARANT. Immunohistochemistry using CD31 antibodies was used to evaluate the area of CNV. Evans blue dye extravasation was quantitatively assessed. Transcripts of markers of outer blood retinal barrier were measured by quantitative RT-PCR, also used to evaluate angiogenesis and inflammation markers. Western blot was used to determine levels of transcription factors encoding genes involved in angiogenesis and inflammation. Levels of urokinase-type plasminogen activator (uPA), its receptor (uPAR), and formyl peptide receptors (FPRs) were determined at the transcript and the protein level.

RESULTS: Intravitreal UPARANT reduced the CNV area and the leakage from the choroid. The uPA/uPAR/FPR system was upregulated in CNV, but was not influenced by UPARANT. UPARANT recovered laser-induced upregulation of transcription factors encoding angiogenic and inflammatory markers. Accordingly, angiogenic and inflammatory factors were also reduced. UPARANT as compared to anti-VEGF drugs displayed similar effects on CNV area.

CONCLUSIONS: UPARANT mitigates laser-induced CNV by inhibiting angiogenesis and inflammation through an action on transcription factors encoding angiogenesis and inflammatory genes. The finding that UPARANT is effective against CNV may help to establish uPAR and its membrane partners as putative targets in the treatment of AMD.

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Brain derived neurotrophic factor keeps pattern electroretinogram from dropping after superior colliculus lesion in mice.

Yang BB, Yang X, Ding HY.

AIM: To determine if brain-derived neurotrophic factor (BDNF) could offer protection to retinal ganglion cells following a superior colliculus (SC) lesion in mice using pattern electroretinogram (PERG) and optical coherence tomography (OCT) as a measures of ganglion cell response and retinal health.

METHODS: Seven C57BL/6J mice with BDNF protection were tested with PERG and OCT before and after SC lesions.

RESULTS: Compared with baseline PERG, the amplitude of PERG decreased 11.7% after SC lesions, but not significantly ($P>0.05$). Through fast Fourier transform (FFT) analysis of the PERGs before and after SC lesions, it was found that dominant frequency of PERGs stayed unchanged, suggesting that the ganglion cells of the retina remained relatively healthy inspite of damage to the ends of the ganglion cell axons. Also, OCT showed no changes in retinal thickness after lesions.

CONCLUSION: It was concluded that BDNF is essential component of normal retina and helps retina keeping normal function. While retina lack of BDNF, ex vivo resource of BDNF provides protection to the sick retina. It implies that BDNF is a kind therapeutic neurotrophic factor to retina neurodegeneration diseases, such as glaucoma, age related macular degeneration.

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Effect of cytokeratin 17 on retinal pigment epithelium degeneration and choroidal neovascularization.

Shen Y, Zhuang P, Xiao T, Chiou GC.

AIM: To study the effects of cytokeratin 17 (CK17) on sodium iodate (NaIO₃) induced rat retinal pigment epithelium (RPE) degeneration, laser induced rat choroidal neovascularization (CNV), and oxidative stress of human retinal pigment epithelium cells (ARPE-19) and human umbilical vein endothelial cell (HUVEC).

METHODS: Thirty 8-week-old male Brown Norway rats were randomly divided into 3 groups, 10 rats in control group treated with solvent alone; 10 rats in NaIO₃ group treated with solvent and 35 mg/kg NaIO₃ injection through hypoglossal vein and 10 rats in CK17+NaIO₃ group treated with 1% CK17 eye drop 3 times a day for 1wk before and 4wk after NaIO₃ injection. RPE function was measured with c-wave of electroretinogram (ERG). Another 20 rats were randomly divided into 2 groups. Of them 10 rats in CK17 group were anesthetized to receive Nd:YAG laser and given 1% CK17 eye drop before same as above; 10 rats in control were received Nd:YAG and treated with solvent. The development of choroidal neovascularization (CNV) was determined by fundus fluorescein angiography (FFA) performed on 4wk after laser. Methylthiazoly tetrazolium (MTT) assay was used to study effect of CK17 on various oxidants induced injury in ARPE-19 and HUVEC in vitro.

RESULTS: Four weeks after NaIO₃ injection, the c-wave amplitude of ERG was 0.393 ± 0.02 V in the control group, 0.184 ± 0.018 V in NaIO₃ group and 0.3 ± 0.01 V in CK17+NaIO₃ group. There was a significant reversal of the c-wave by CK17 as compared to NaIO₃ group ($P<0.01$). Four weeks after laser, the size of the CNV lesion was 2.57 ± 0.27 mm² in control group and 1.64 ± 0.08 mm² in CK17 group. The lesion size significantly diminished in CK17 group ($P<0.01$). The in vitro results showed CK17 also reversed the various oxidants induced injuries in ARPE-19 at the dose of 100 µg/mL and enhanced the injury in HUVECs at different concentrations.

CONCLUSION: CK17 can significantly protect RPE from NaIO₃ induced degeneration in vivo and in vitro and also could reverse the various oxidants induced injuries in vitro. It inhibits the development of CNV in rat model, interfered with vascular endothelial cell proliferation in vitro.

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Epidemiology

Prog Retin Eye Res. 2016 May 5. [Epub ahead of print]

Risk factors and biomarkers of age-related macular degeneration.

Lambert NG, Singh MK, ElShelmani H, Mansergh FC, Wride MA, Padilla M, Keegan D, Hogg RE, Ambati BK.

Abstract: A biomarker can be a substance or structure measured in body parts, fluids or products that can affect or predict disease incidence. As age-related macular degeneration (AMD) is the leading cause of blindness in the developed world, much research and effort has been invested in the identification of different biomarkers to predict disease incidence, identify at risk individuals, elucidate causative pathophysiological etiologies, guide screening, monitoring and treatment parameters, and predict disease outcomes. To date, a host of genetic, environmental, proteomic, and cellular targets have been identified as both risk factors and potential biomarkers for AMD. Despite this, their use has been confined to research settings and has not yet crossed into the clinical arena. A greater understanding of these factors and their use as potential biomarkers for AMD can guide future research and clinical practice. This article will discuss known risk factors and novel, potential biomarkers of AMD in addition to their application in both academic and clinical settings.

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Am J Ophthalmol. 2016 May 6. [Epub ahead of print]

Oral Bisphosphonates and Risk of Wet Age-Related Macular Degeneration.

Mammo Z, Guo M, Maberley D, Matsubara J, Etminan M.

PURPOSE: To examine the risk of age related macular degeneration (AMD) with oral bisphosphonates.

DESIGN: Three study designs were used. 1) disproportionality analysis; 2) case-control study; 3) Self-controlled case series (SCCS).

METHODS: Setting: 1) Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) Database; 2) Two patient cohorts from British Columbia, Canada.

STUDY POPULATION: 1) All reports of AMD to the FDA with oral bisphosphonates; 2) Patients with wet AMD in British Columbia (2009-2013) and one million controls (2000-2007).

INTERVENTION: Oral bisphosphonates.

MAIN OUTCOME MEASURES: 1) Reports of AMD to the FDA; 2) First diagnosis of wet AMD verified by a retina specialist in British Columbia.

RESULTS: In the disproportionality analysis there were 133 cases of AMD reported with alendronate, 20 with ibandronate, and 14 with risedronate. The reported odds ratios (RORs) for alendronate, ibandronate and risedronate were 3.82 (2.94-4.96), 2.40 (1.49-3.86) and 2.87 (1.58-5.19) respectively. In the case-control analysis there were 6,367 cases and 6370 corresponding controls. The adjusted OR for wet AMD

among regular users of bisphosphonates in the one, two and three years prior to the index date were 1.27 (95%CI: 1.14-1.41), 1.41 (95%CI: 1.25- 1.59) and 1.61 (95%CI:1.40- 1.86) respectively. In the SCCS analysis there were 198 cases of wet AMD on continuous bisphosphonate therapy. The RR for wet AMD for continuous bisphosphonate use was 1.99 (95% CI:1.41-2.79). We did not have information on intravenous bisphosphonates.

CONCLUSIONS: Continuous users of oral bisphosphonates are at a higher risk of developing wet AMD. Given the observational nature of this study and limitation of the data, future studies are needed to confirm these findings.

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Coronary Artery Disease and Reticular Macular Disease, a Subphenotype of Early Age-Related Macular Degeneration.

Cymerman RM, Skolnick AH, Cole WJ, Nabati C, Curcio CA, Smith RT.

PURPOSE: Reticular macular disease (RMD) is the highest risk form of early age-related macular degeneration and also specifically confers decreased longevity. However, because RMD requires advanced retinal imaging for adequate detection of its characteristic subretinal drusenoid deposits (SDD), it has not yet been completely studied with respect to coronary artery disease (CAD), the leading cause of death in the developed world. Because CAD appears in middle age, our purpose was to screen patients aged 45-80 years, documented either with or without CAD, to determine if CAD is associated with RMD.

DESIGN: A prospective cohort study of patients with documented CAD status and no known retinal disease in a clinical practice setting at one institution. **Subjects and Controls:** A number of 76 eyes from 38 consecutive patients (23 with documented CAD, 15 controls documented without CAD; 47.4% female; mean age 66.7 years).

METHODS: Patients were imaged with near-infrared reflectance/spectral domain optical coherence tomography and assessed in masked fashion by two graders for the presence of SDD lesions of RMD and soft drusen.

MAIN OUTCOME MEASURES: Presence or absence of RMD/SDD and soft drusen.

RESULTS: RMD was more frequent in patients with CAD versus those without (Relative Risk [RR] = 2.1, CI = 1.08-3.95, P = 0.03). There was no association of CAD with soft drusen.

CONCLUSIONS: A specific relationship between CAD and RMD suggests common systemic causes for both and warrants further study.

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Med Sci Monit. 2016 May 9;22:1566-70.

Long-Term Changes in Subfoveal Choroidal Thickness After Cataract Surgery.

Yilmaz T, Karci AA, Yilmaz İ, Yilmaz A, Yıldırım Y, Sakalar YB.

BACKGROUND: Cataract surgery is associated with the development of late-onset age-related macular degeneration (AMD). The pathogenic mechanism is still not fully established. The purpose of this study was to evaluate the possible changes in central macula thickness (CMT) and subfoveal choroid thickness (SCT) after uneventful cataract surgery.

MATERIAL AND METHODS: A total of 65 eyes of 65 patients who underwent phacoemulsification and intracapsular lens implantation were included in this prospective study. Patients had not undergone previous ocular surgery and had no other ocular abnormality. CMT and SCT were measured at baseline and postoperatively at week 1 and months 1, 3, 6 and 12 via spectral domain optical coherence tomography (SD-OCT).

RESULTS: CMT was 252.4 ± 27.6 μm (mean $\pm$ SD) preoperatively, then 253.5 ± 29.8 , 256.1 ± 28.7 , 257.4 ± 27.2 , 253.18 ± 23.7 , and 252.8 ± 21.7 μm at postoperative week 1 and postoperative months 1, 3, 6, and 12, respectively. There were insignificant changes in CMT, and it returned to baseline at six months after surgery (all $p > 0.05$). SCT was 237.4 ± 21.6 μm preoperatively, and 240.5 ± 24.8 , 241.2 ± 25.7 , 242.7 ± 26.3 , 243.1 ± 24.2 , and 244.2 ± 21.4 μm at postoperative week 1 and postoperative months 1, 3, 6, and 12, respectively. Although there was an increase in SCT during follow-up, the difference between preoperative and postoperative values was not significant ($p > 0.05$).

CONCLUSIONS: Uncomplicated phacoemulsification induces subclinical changes in CMT, probably due to the inflammatory insult of surgery, and CMT returns to baseline value. There were slight, insignificant increases in choroid thickness during follow-up, and this did not return to baseline during follow-up. Changes in the choroid after cataract surgery may provide clues to the development of late-onset AMD.

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Nippon Ganka Gakkai Zasshi. 2016 Mar;120(3):163-88; discussion 189.

[Age-related Macular Degeneration in the Japanese]. [Article in Japanese]

Yoshimura N.

Abstract: Age-related macular degeneration (AMD) in the Japanese often shows different clinical features from those described in Caucasians. For example, we often observe choroidal neovascularization (CNV) in elderly patients without drusen in the fundus. The high incidence of polypoidal choroidal vasculopathy (PCV) in AMD among Japanese is well-known. The reason why such differences occur in clinical manifestations of AMD has been one of my main interests. In this review article, I will discuss the characteristics of AMD in the Japanese population, as found in our recent study. I. Prevalence and clinical characteristics of AMD in the Japanese population. Cohort studies are important to determine the prevalence and incidence of diseases. In Japan, cohort studies began to be carried out rather late compared with Western countries. Although good cohort studies from Japan are reported in the literature, the size of the cohorts was not sufficiently large to determine the prevalence of AMD. However, a recent meta-analysis of Asian cohorts has shown that the prevalence of late AMD in Asians is not different from that reported in Caucasians. On the other hand, the prevalence of early AMD appears lower in the Japanese than in Caucasians. Recently, we have published the results of the Nagahama Cohort study. In this cohort study, we found a high prevalence of drusen. It seems that the incidence of dry AMD is likely to increase among Japanese. In Japan, most retina specialists classify AMD into three categories: typical AMD, PCV, and retinal angiomatous proliferation (RAP). However, there are no definite diagnostic criteria to distinguish between the three conditions. To compare the clinical features of Japanese and Western cases of AMD, and to determine the incidence of the three types of AMD, we exchanged data about 100 consecutive cases between Kyoto University and Centre d'Ophtalmologie de Paris, France. Interestingly, the diagnoses made by the two institutes were not always in agreement. We also found more cases of PCV among the Japanese than among the French. II. PCV. About 50% of exudative AMD cases in the Japanese population are PCV. Because of its peculiar angiographic findings, PCV has long been considered to be a distinct clinical entity different from the usual exudative AMD. Also, there have been serious discussions on the nature of PCV. In our analyses, about 20% of PCV cases show rather large lesion sizes that exceed the vascular arcade. Scar formation in the macula and compromised vision are frequent findings in such cases. The occurrence of PCV in the inferior staphyloma or in angioid streaks shows heterogeneity in PCV. These findings suggest that PCV may be a finding on indocyanine green angiography rather than a distinct clinical

entity. Spectral domain OCT examination shows that the branching vascular network of PCV is located between the retinal pigment epithelium and Bruch's membrane. In cases with retinal pigment epithelial detachment, CNV from the branching vascular network was found to extend along the roof of the detached retinal pigment epithelium. Such findings show that the branching vascular network of PCV is type 1 CNV. Complement factor H (CFH) and age-related maculopathy 2 (ARMS2)/High temperature requirement 1 (HTRA1) located on chromosome 10 (10q26) are well-established disease susceptible genes of AMD. In the Japanese, the prevalence of CFH Y402H gene polymorphism is low and ARMS2/HTRA1 plays a more important role in the development of AMD. In ARMS2 A69S polymorphism, a large deletion/insertion (443del1/54ins) that is reported in Caucasians was also found in Japanese. Thus, the genetic background of Caucasian and Japanese AMD is quite similar, as is also the case with exudative AMD and PCV. Our findings show that PCV is not a distinct clinical entity but is a subtype of exudative AMD. III. Exudative AMD with choroidal vascular hyperpermeability. Choroidal vascular hyperpermeability observed in central serous chorioretinopathy can be found in about 20% to 30% of exudative AMD cases in Japanese. Such cases often show a thick choroid, lack of drusen, and rather good visual prognosis with slow progression of the disease. Recently, "pachychoroid neovascularopathy" has been described by a group from New York. Such cases of AMD with choroidal vascular hyperpermeability, a thick choroid, and lack of drusen appears to belong to pachychoroid neovascularopathy. We studied the risk allele frequencies of CFH I62V and ARMS2 A69S gene polymorphisms in three groups : usual exudative AMD, pachychoroid neovascularopathy, and normal controls. Interestingly, cases of pachychoroid neovascularopathy show different gene polymorphisms of CFH I62V and ARMS2 A69S from the usual cases of exudative AMD and a more similar pattern to normal controls. Therefore, the possible mechanisms of the CNV development in such cases may differ from the classic well-documented drusen-dependent pathways. IV. Atrophic AMD in Japanese. Data from the Nagahama Cohort study show an increasing prevalence of drusen in Japanese. Recently, more extensive information on drusen has become available and the redefinition of drusen is currently in progress. In particular, the importance of reticular pseudodrusen (RPD) is more widely appreciated. This type of drusen is often found in Japanese AMD. Although the nature and location of RPD are still debatable, many investigators believe that this type of drusen is located under the sensory retina rather than under Bruch's membrane. In our analyses, RPD was found in 18.4% of late AMD cases in Japanese. It was more common in eyes with RAP or atrophic AMD and was seldom found in PCV. ARMS2 A69S gene polymorphism was found more frequently in cases of exudative AMD with RPD, than in cases of exudative AMD without RPD. Eyes with RPD show a thin choroid and diminished vascular densities of choroidal vessels.

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Genetics

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Genetic factors associated with the development of age-related macular degeneration.

Sergejeva O, Botov R, Liutkevičienė R, Kriaučiūnienė L.

Abstract: Age-related macular degeneration (AMD) affects the macula and is the leading cause of significant and irreversible central visual loss. It is the most common cause of visual loss in people aged more than 60 years. This disease affects 2.5 million individuals in Europe. AMD is caused by both environmental and genetic factors. Numerous risk factors have been reported, but the pathogenesis of AMD is complex and fairly understood. Age, female gender, obesity, race, education status, family history, hyperopia, iris color, cigarette smoking, previous cataract surgery, history of cardiovascular and cerebrovascular disease, diabetes, sunlight exposure and many other factors have been shown to be associated with AMD development. Scientific evidence shows that genes may play a role in the development of nearly 3 out of 4 cases of this devastating eye disease. The genes that have been shown to be associated with AMD are genes encoding complement system components such as CFH, C2, C3, CFB,

and other.

PMID: 27170480 [PubMed - in process]

Stem cells

Nippon Ganka Gakkai Zasshi. 2016 Mar;120(3):210-24; discussion 225.

[Retinal Cell Therapy Using iPS Cells]. [Article in Japanese]

Takahashi M.

Abstract: Progress in basic research, starting with the work on neural stem cells in the middle 1990's to embryonic stem (ES) cells and induced pluripotent stem (iPS) cells at present, will lead the cell therapy (regenerative medicine) of various organs, including the central nervous system to a big medical field in the future. The author's group transplanted iPS cell-derived retinal pigment epithelial (RPE) cell sheets to the eye of a patient with exudative age-related macular degeneration (AMD) in 2014 as a clinical research. Replacement of the RPE with the patient's own iPS cell-derived young healthy cell sheet will be one new radical treatment of AMD that is caused by cellular senescence of RPE cells. Since it was the first clinical study using iPS cell-derived cells, the primary endpoint was safety judged by the outcome one year after surgery. The safety of the cell sheet has been confirmed by repeated tumorigenicity tests using immunodeficient mice, as well as purity of the cells, karyotype and genetic analysis. It is, however, also necessary to prove the safety by clinical studies. Following this start, a good strategy considering cost and benefit is needed to make regenerative medicine a standard treatment in the future. Scientifically, the best choice is the autologous RPE cell sheet, but autologous cell are expensive and sheet transplantation involves a risky part of surgical procedure. We should consider human leukocyte antigen (HLA) matched allogeneic transplantation using the HLA 6 loci homozygous iPS cell stock that Prof. Yamanaka of Kyoto University is working on. As the required forms of donor cells will be different depending on types and stages of the target diseases, regenerative medicine will be accomplished in a totally different manner from the present small molecule drugs. Proof of concept (POC) of photoreceptor transplantation in mouse is close to being accomplished using iPS cell-derived photoreceptor cells. The shortest possible course for treatment is now being investigated in preclinical research. Among the mixture of rod and cone photoreceptors in the donor cells, the percentage of cone photoreceptors is still low. Donor cells with more cone photoreceptors will be needed. If that will work well, photoreceptor transplantation will be the first example of neural network reconstruction in the central nervous system. These efforts will reach to variety of retinal cell transplantations in the future.

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Diet, lifestyle & low vision

Clin Exp Optom. 2016 May 7. [Epub ahead of print]

Ocular disease and driving.

Wood JM, Black AA.

Abstract: As the driving population ages, the number of drivers with visual impairment resulting from ocular disease will increase given the age-related prevalence of ocular disease. The increase in visual impairment in the driving population has a number of implications for driving outcomes. This review summarises current research regarding the impact of common ocular diseases on driving ability and safety, with particular focus on cataract, glaucoma, age-related macular degeneration, hemianopia and diabetic retinopathy. The evidence considered includes self-reported driving outcomes, driving performance (on-road and simulator-

based) and various motor vehicle crash indices. Collectively, this review demonstrates that driving ability and safety are negatively affected by ocular disease; however, further research is needed in this area. Older drivers with ocular disease need to be aware of the negative consequences of their ocular condition and in the case where treatment options are available, encouraged to seek these earlier for optimum driving safety and quality of life benefits.

PMID: 27156178 [PubMed - as supplied by publisher]

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