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Drug treatment

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Incidence and Growth of Geographic Atrophy during 5 Years of Comparison of Age-Related Macular Degeneration Treatments Trials.

Grunwald JE, Pistilli M, Daniel E, Ying GS, Pan W, Jaffe GJ, Toth CA, Hagstrom SA, Maguire MG, Martin DF; Comparison of Age-Related Macular Degeneration Treatments Trials Research Group.

PURPOSE: To estimate the incidence, size, and growth rate of geographic atrophy (GA) during 5 years of follow-up among participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

DESIGN: Cohort within a clinical trial.

PARTICIPANTS: Participants included in CATT.

METHODS: A total of 1185 CATT participants were randomly assigned to ranibizumab or bevacizumab treatment and to 3 treatment regimens. Participants were released from protocol treatment at 2 years and examined at approximately 5 years (N = 647). Two masked graders assessed the presence and size of GA in digital color photographs (CPs) and fluorescein angiograms (FAs) taken at baseline and years 1, 2, and 5. Cox proportional hazard models were used to identify risk factors for incidence of GA. Annual change in the square root of the total area of GA was the measure of growth. Multivariate linear mixed models including baseline demographic, treatment, and ocular characteristics on CP/FA and optical coherence tomography (OCT) as candidate risk factors were used to estimate adjusted growth rates, standard errors (SEs), and 95% confidence intervals (CIs).

MAIN OUTCOME MEASURES: Geographic atrophy incidence and growth rate.

RESULTS: Among the 1011 participants who did not have GA at baseline and had follow-up images gradable for GA, the cumulative incidence was 12% at 1 year, 17% at 2 years, and 38% at 5 years. At baseline, older age, hypercholesterolemia, worse visual acuity, larger choroidal neovascularization (CNV) area, retinal angiomatous proliferation (RAP) lesion, GA in the fellow eye, and intraretinal fluid were associated with a higher risk of incident GA. Thicker subretinal tissue complex and presence of subretinal fluid were associated with less GA development. The overall GA growth rate was 0.33 mm/year (SE, 0.02 mm/year). Eyes treated with ranibizumab in the first 2 years of the clinical trial had a higher growth rate than eyes treated with bevacizumab (adjusted growth rate, 0.38 vs. 0.28 mm/year; P = 0.009). Geographic atrophy in the fellow eye, hemorrhage, and absence of sub-retinal pigment epithelium fluid at baseline were associated with a higher growth rate.

CONCLUSIONS: Development of GA is common 5 years after initiating therapy. Several risk factors identified at 2 years of follow-up persist at 5 years of follow-up.

PMID: 28079023 PMCID: PMC5234734

Arq Bras Oftalmol. 2016 Nov-Dec;79(6):384-389.

Efficacy of aflibercept on exudative age-related macular degeneration in patients exhibiting complete ranibizumab resistance and tachyphylaxis.

Gokce G, Durukan AH, Koylu MT, Kucukevcilioglu M.

PURPOSE: The present study compared the efficacy of aflibercept for neovascular age-related macular degeneration (NV-AMD) in patients with complete ranibizumab resistance and tachyphylaxis.

METHODS: Forty-four eyes of 38 neovascular age-related macular degeneration patients were evaluated. Eyes were divided into a complete resistance group (n=23 eyes) and tachyphylaxis group (n=21 eyes).

RESULTS: After three injections, eight (38.1%) patients in the tachyphylaxis group and nine (39.1%) in the complete resistance group presented with macular dryness. After the first injection of aflibercept, the mean visual acuity improved significantly in the tachyphylaxis group (p=0.018) but remained unchanged in the complete resistance group (p=0.37). There was a non-significant trend towards improved mean visual acuity in both groups after the second and third injections relative to the acuity at the final visit for ranibizumab treatment. In the tachyphylaxis group, the presence of subfoveal pigmented epithelium detachment (PED) decreased significantly after intravitreal aflibercept treatment.

CONCLUSIONS: Although treatment with aflibercept yielded generally positive anatomical results in both groups, no significant increase in visual acuity was achieved.

PMID: 28076566

Eye (Lond). 2017 Jan 20.[Epub ahead of print]

The incidence and risk factors for the development of vitreomacular interface abnormality in diabetic macular edema treated with intravitreal injection of anti-VEGF.

Chang CK, Cheng CK, Peng CH.

Purpose: To report the incidence and associated factors for the development of vitreomacular interface abnormality (VMIA) in patients with diabetic macular edema (DME) who received intravitreal injection (IVI) of anti-VEGF (Bevacizumab and Ranibizumab) treatment.

Methods: A retrospective observational study. Patients with DME followed at least 6 months were reviewed. Baseline best-corrected visual acuity (BCVA), central retinal thickness (CRT) and final BCVA, CRT in eyes with and without VMIA were compared. Multiple logistic regression was also used to investigate the risk factors of VMIA formation in patients with DME treated by anti-VEGF.

Results: A total of 201 eyes in 142 patients met the inclusion criteria of the study. VMIA developed in 44 eyes (21.89%) of patients during a mean follow-up period of 40.84 months. The estimated mean incidence of VMIA formation was 6.43% per year. Poor baseline BCVA was found to be a risk factor for VMIA development (P=0.001, odds ratio=5.299, 95% confidence interval: 1.972 to 14.238). There was no difference between eyes with and without VMIA formation in improving BCVA (P=0.557) and lowering the macular edema (eyes without VMIA formation: -107.72±171.91 μm; eyes with VMIA formation: -155.02±212.27 μm, P=0.133).

Conclusions: This study revealed the incidence of VMIA formation in IVI anti-VEGF treated DME eyes was 6.43%. Poor baseline BCVA was found to be a risk factor for VMIA formation. Both eyes with and without VMIA development had favorable response to anti-VEGF treatment.Eye advance online publication, 20 January 2017; doi:10.1038/eye.2016.317.

PMID: 28106889

Retina. 2017 Jan 13. [Epub ahead of print]

NATURAL COURSE OF PATIENTS DISCONTINUING TREATMENT FOR AGE-RELATED MACULAR DEGENERATION AND FACTORS ASSOCIATED WITH VISUAL PROGNOSIS.

Kim JH, Chang YS, Kim JW.

PURPOSE: To evaluate the 24-month natural course of visual changes in patients discontinuing treatment despite persistent or recurrent fluid and factors predictive of visual prognosis.

METHODS: This retrospective, observational study included 35 patients (35 eyes) who initially received anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration (AMD), but discontinued treatment despite persistent or recurrent fluid. The best-corrected visual acuity (BCVA) at treatment discontinuation was determined and compared with the 24-month BCVA, which was then compared between polypoidal choroidal vasculopathy and other neovascular age-related macular degeneration subtypes. Baseline characteristics predictive of visual outcome and the degree of visual change were also analyzed.

RESULTS: The mean number of anti-vascular endothelial growth factor injections before treatment discontinuation was 4.0 ± 1.6. The mean logarithm of minimal angle of resolution of BCVA at treatment discontinuation and that at 24 months were 1.02 ± 0.20 (Snellen equivalents = 20/209) and 1.60 ± 0.56 (20/796), respectively ($P < 0.001$). The 24-month BCVA was not different between polypoidal choroidal vasculopathy and other neovascular age-related macular degeneration subtypes ($P = 0.803$). The type of fluid (intraretinal fluid vs. no intraretinal fluid) was predictive of 24-month BCVA ($P = 0.004$) and the degree of changes in BCVA ($P = 0.043$).

CONCLUSION: Marked deterioration in visual acuity was noted in patients discontinuing treatment, regardless of neovascular age-related macular degeneration subtypes. The presence of intraretinal fluid was associated with worse visual prognosis, suggesting that patients with intraretinal fluid should be strongly warned about their poor prognosis before they decide to discontinue treatment.

PMID: 28092343

Retina. 2017 Jan 18. [Epub ahead of print]

SYSTEMIC PHARMACOKINETICS AND PHARMACODYNAMICS OF INTRAVITREAL AFLIBERCEPT, BEVACIZUMAB, AND RANIBIZUMAB.

Avery RL, Castellarin AA, Steinle NC, Dhoot DS, Pieramici DJ, See R, Couvillion S, Nasir MA, Rabena MD, Maia M, Van Everen S, Le K, Hanley WD.

PURPOSE: To evaluate the systemic pharmacokinetics (PKs) of aflibercept, bevacizumab, and ranibizumab in patients with neovascular age-related macular degeneration (AMD), diabetic macular edema (DME), or retinal vein occlusion (RVO).

METHODS: Prospective, open-label, nonrandomized clinical trial of patients with AMD, DME, or RVO who were antivascular endothelial growth factor (VEGF) naïve or had not received anti-VEGF for ≥4 months. Patients received 3 monthly intravitreal injections of aflibercept 2.0 mg, bevacizumab 1.25 mg, or ranibizumab (0.5 mg for AMD/RVO, 0.3 mg for DME). The main outcome measures were serum PKs and plasma free-VEGF concentrations after the first and third injections.

RESULTS: A total of 151 patients were included. In AMD/DME/RVO, systemic exposure to each drug was highest with bevacizumab, then aflibercept, and lowest with ranibizumab. Ranibizumab cleared from the bloodstream more quickly than bevacizumab or aflibercept. Aflibercept treatment resulted in the greatest reductions in plasma free-VEGF relative to baseline levels, whereas ranibizumab treatment resulted in the smallest decreases in plasma free-VEGF.

CONCLUSION: The three anti-VEGF treatments examined in this analysis demonstrated notable

differences in systemic PKs. Generally, the reduction in plasma free-VEGF levels correlated with elevated levels of circulating anti-VEGF agents, with the reduction in free-VEGF levels greatest with aflibercept and least with ranibizumab.This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

PMID: 28106709

Arq Bras Oftalmol. 2016 Nov-Dec;79(6):373-375.

Influence of the epiretinal membrane on ranibizumab therapy outcomes in patients with diabetic macular edema.

Ercalik NY, Imamoglu S, Kumral ET, Yenerel NM, Bardak H, Bardak Y.

PURPOSE: To investigate the influence of the epiretinal membrane (ERM) on intravitreal ranibizumab (IVR) therapy for diabetic macular edema (DME).

METHODS: This retrospective study included 56 eyes of 48 patients with DME divided into two groups: the DME with ERM (study) and only DME (control) groups. Changes in the central macular thickness (CMT) and best-corrected visual acuity (BCVA) were evaluated.

RESULTS: In the study group, although the CMT was significantly reduced following the first injection ($p<0.001$), BCVA did not improve significantly ($p=0.296$). However, after the first injection, the control group exhibited both a significant decrease in CMT ($p<0.001$) and improvement in BCVA ($p<0.001$). However, the improvement in BCVA in the control group was not significantly different from the outcome of the study group.

CONCLUSIONS: We observed a negative short-term influence of the ERM on IVR treatment for DME.

PMID: 28076563

PLoS One. 2017 Jan 13;12(1):e0170271. eCollection 2017.

Assessment of Corneal Sensation, Innervation and Retinal Nerve Fiber Layer in Patients Treated with Multiple Intravitreal Ranibizumab Injections.

Bitirgen G, Belviranli S, Malik RA, Kerimoglu H, Satirtav G, Zengin N.

PURPOSE: To evaluate the effects of repeated intravitreal ranibizumab injections on corneal sensitivity, corneal sub-basal nerve plexus (SBNP) and peripapillary retinal nerve fiber layer (RNFL) thickness in patients with neovascular age-related macular degeneration (AMD).

METHODS: Sixty-six eyes of 33 patients who had received unilateral repeated intravitreal ranibizumab injections (0.5 mg/0.05 ml) for the treatment of AMD and 25 eyes of 25 healthy subjects were included in the study. Central corneal sensation was measured using the contact Cochet-Bonnet esthesiometer. The laser scanning in vivo corneal confocal microscope was used to determine corneal SBNP parameters. The peripapillary RNFL thickness was assessed with spectral-domain optical coherence tomography. Data obtained from the ranibizumab-injected eyes were compared with those of the fellow non-treated eyes and the eyes of the healthy control subjects.

RESULTS: The mean number of ranibizumab injections per eye was 8.9±5.0 (range 3-20). There were no statistically significant differences in the central corneal sensitivity threshold and corneal SBNP parameters between the ranibizumab-injected eyes and the fellow untreated eyes or between those with neovascular AMD and the healthy control group ($P>0.05$ for all). The average peripapillary RNFL thickness of the

treated eyes did not differ significantly to the fellow eyes (P = 0.237), and the eyes of healthy control subjects (P = 0.918). There were no significant correlations between the number of ranibizumab injections and any of the study parameters.

CONCLUSIONS: Multiple intravitreal injections of ranibizumab seem to have no harmful effects on corneal sensitivity, innervation and peripapillary RNFL thickness in patients with AMD.

PMID: 28085965

Acta Ophthalmol. 2017 Jan 13. [Epub ahead of print]

Response of vascular pigment epithelium detachment due to age-related macular degeneration to monthly treatment with ranibizumab: the prospective, multicentre RECOVER study.

Clemens CR, Wolf A, Alten F, Milojcic C, Heiduschka P, Eter N.

PURPOSE: To assess the effects of monthly intravitreal ranibizumab injections in patients with vascularized pigment epithelium detachment (vPED) secondary to age-related macular degeneration (AMD).

METHODS: A total of 40 patients were prospectively observed and treated monthly with 0.5 mg ranibizumab injections (ClinicalTrials.gov Ident. NCT00976222). Inclusion criterion was a treatment-naïve vPED lesion with a minimum height of ≥200 µm. Best-corrected visual acuity (BCVA) and spectral-domain optical coherence tomography (SD-OCT) were evaluated at all visits. Fluorescein angiography and indocyanine green angiography were performed at baseline and quarterly. Lesions were differentiated between serous vascular PED (svPED, group A, 29 patients) and fibrovascular PED (fPED, group B, 11 patients). Primary outcome was the effectivity of continuous monthly treatment during a 12-month period as measured in change in BCVA. Secondary outcomes were change in PED height and PED greatest linear diameter (GLD). Further secondary outcomes were the presence of subretinal fluid and prognostic markers of an impending retinal pigment epithelium (RPE) tear: PED lesion height and diameter, ratio of choroidal neovascularization (CNV) size to PED size, hyperreflective lines in near-infrared images, microrips and subretinal cleft.

RESULTS: Mean BCVA was 56.9 ± 11.5 letters (A: 55.4 ± 10.8; B: 59.1 ± 13.4) at baseline and 55.1 ± 15.9 (A: 53.7 ± 17.0; B: 58.9 ± 12.7) at 12-month follow-up. Excluding the RPE tear patients, the svPED group showed an increase in BCVA from 56.1 ± 10.3 at baseline to 62.4 ± 10.2 at 12-month follow-up (p = 0.048). Best-corrected visual acuity in patient who developed a RPE tear was 55.8 ± 12.5 at baseline and 37.1 ± 14.9 at 12-month follow-up. The mean change in PED height was -242.1 µm ± 285.5 (A: -427.3 µm ± 299.7; B: -51.6 µm ± 99.5). The mean decrease in PED GLD was -471.8 µm ± 727.6 (A: -738.9 µm ± 788.2; B: -10.4 µm ± 185.6). In group A, 10 patients developed a RPE tear (25%) after a mean of 3.6 injections. No tear was documented in group B. Lesion height, ratio of CNV size to PED size and presence of hyperreflective lines differed significantly between patients with and without RPE tear development.

CONCLUSION: Serous vascular PED lesions showed an improvement regarding BCVA and morphologic characteristics unless an RPE tear occurred. In fPED lesions, a functional and morphological stabilization was observed. Monthly ranibizumab injections are an effective treatment regarding the resorption of subretinal fluid in vPED due to AMD. Patients should be screened for the presence of morphologic risk factors for RPE tear development before and during treatment.

PMID: 28084038

Exp Ther Med. 2016 Dec;12(6):3923-3926. Epub 2016 Nov 8.

Effect of anti-VEGF drugs combined with photodynamic therapy in the treatment of age-related macular degeneration.

Dong Y, Wan G, Yan P, Chen Y, Wang W, Peng G.

Abstract: We analyzed the effects of anti-vascular endothelial growth factor (VEGF) drugs combined with photodynamic therapy (PDT) in the treatment of age-related macular degeneration (AMD). Ninety-six cases (192 eyes) of AMD were included in this study and randomly divided into the observation group and control group (n=48 cases per group). The control group was administered the treatment of Lucentis intravitreal injection alone and the observation group was administered Lucentis combined with PDT. The therapeutic effects were compared. The best corrected visual acuity of patients in the two groups increased gradually after treatment. Patients in the observation group had a significantly higher visual acuity when compared to the control group 1 and 6 months post-operation. The differences were statistically significant (P<0.05). The proportion of patients with vision improvement in the observation group was higher than that in the control group from 1 to 6 months; differences were statistically significant (P<0.05). Through detection by color Doppler ultrasound within 6 months after treatment, we observed that the peak systolic velocity and arterial end diastolic velocity of retrobulbar optic nerve bitemporal PCA of the observation group were higher than those of the control group. The values of arterial resistance index and pulsatility index of the observation group were lower than those of control group. The differences were statistically significant (P<0.05). Six months after treatment, the value of central foveal thickness of the observation group was lower than that of the control group, the value of mean sensitivity of visual field parameter 10° and 4° was higher in the observation group than in the control group, and the absolute value of mean defects in the observation group were lower than that of the control group. In summary, the differences were statistically significant (P<0.05). Anti-VEGF drugs combined with PDT can optimize the overall vision of patients with AMD, improve hemodynamic parameters and reduce visual field defects.

PMID: 28105123

Graefes Arch Clin Exp Ophthalmol. 2017 Jan 19. [Epub ahead of print]

Efficacy and safety of a fixed bimonthly ranibizumab treatment regimen in eyes with neovascular age-related macular degeneration: results from the RABIMO trial.

Feltgen N, Bertelmann T, Bretag M, Pfeiffer S, Hilgers R, Callizo J, Goldammer L, Bemme S, Hoerauf H.

PURPOSE: To evaluate prospectively the efficacy and safety of a fixed bimonthly ranibizumab treatment regimen (RABIMO) in eyes with neovascular age-related macular degeneration (nAMD) and to compare these results with a pro re nata (PRN) treatment scheme.

METHODS: This was a 12-month, phase IV, single center, randomised, non-inferiority study. Following three initial monthly injections, patients were randomised to receive either ranibizumab bimonthly (RABIMO group) or ranibizumab PRN (PRN group) (n = 20 each). Main outcome measures were best-corrected visual acuity (BCVA), central retinal thickness (CRT), number of injections, and adverse events (AEs).

RESULTS: BCVA [median (interquartile range, IQR)] increased significantly in both groups after 12 months [RABIMO group +8.5 (14); PRN group +6.5 (16) ETDRS letters] when compared to baseline (p < 0.0001; p = 0.0085). At month 12, the RABIMO treatment regimen was non-inferior to the PRN scheme (ΔBCVA = 3.5 ETDRS letters; p < 0.0001). CRT was significantly reduced in both groups after the 12-month study period (p < 0.0001 each), with no significant difference between groups (p = 0.6772). Number of overall injections [median (IQR)] was 8 (0) in the RABIMO versus 4 (5) in the PRN group (p = 0.0037). Three patients in the RABIMO group received one additional unscheduled injection. We observed no significant differences between groups in the number of patients with reported SAEs/AEs (RABIMO group n = 6/15; PRN group n = 7/13) (p = 0.7357/p = 0.4902).

CONCLUSIONS: We found no evidence of significant functional or anatomical differences between the RABIMO and PRN treatment regimens. However, the RABIMO group's number of injections was twice as high as the PRN group's (protocol-driven). In light of potential side effects, the fixed bimonthly treatment regimen might not be advisable for routine clinical care, but it might be a worthwhile treatment option if monthly monitoring is not possible. Eudra-CT number: 2009-017324-11.

PMID: 28102456

BMC Ophthalmol. 2017 Jan 19;17(1):7.

Demographics of patients receiving Intravitreal anti-VEGF treatment in real-world practice: healthcare research data versus randomized controlled trials.

Ziemssen F, Feltgen N, Holz FG, Guthoff R, Ringwald A, Bertelmann T, Wiedon A7, Korb C; OCEAN study group.

BACKGROUND: While randomized controlled trials (RCTs) are based on strict inclusion/exclusion criteria, non-interventional studies (NISs) might provide additional information to guide management in patients more representative to the real-world setting. The aim of this study was to compare baseline characteristics of patients receiving intravitreal treatment in the NIS OCEAN with those from published RCTs.

METHODS: The ongoing OCEAN study enrolled patients treated with ranibizumab for neovascular age-related macular degeneration (nAMD), diabetic macular oedema (DME) or branch/central retinal vein occlusion (B/CRVO). Baseline patient characteristics were compared by indication within the OCEAN cohort. Furthermore, the characteristics were set in reference to those of published RCTs in the same indications. Confidence intervals (CIs) were calculated and assessed for statistically significant differences as indicated by non-overlapping CIs.

RESULTS: Patient characteristics in the NIS OCEAN were evaluated for 3,614 patients with nAMD, 1,211 with DME, 204 with BRVO and 121 with CRVO. Between these groups, significant differences in mean age, gender distributions, and mean baseline VA were seen, reflecting known differences between the indications. Compared to the patient characteristics of published RCTs (trials selected by literature search: nAMD: 13 RCTs, DME: 9, RVO: 5), the OCEAN patients' mean age was significantly higher in every indication. The gender distributions across the trials were comparable, with only few differences between OCEAN and the RCTs. Regarding the mean baseline VA, notable differences were found in nAMD and in DME, with VA significantly higher in some RCTs and lower in others.

CONCLUSIONS: The described differences underline the complementarity of NISs and RCTs. OCEAN covers a broader spectrum and more variability of patients than do RCTs. As baseline values may have impact on the treatment response (ceiling effect), there is an ongoing need for research in all patient subgroups. Country-specific assessments of patient populations can better reflect the real-world situation. NISs can deliver insights that RCTs may not, as NISs can include non-typical patients, patients with comorbidities, a broader age spectrum and patients of various disease stages.

PMID: 28103831

Retina. 2017 Jan 16. [Epub ahead of print]

HOW VITREOMACULAR INTERFACE MODIFIES THE EFFICACY OF ANTI-VEGF THERAPY FOR MYOPIC CHOROIDAL NEOVASCULARIZATION.

Iacono P, Battaglia Parodi M, Iuliano L, Bandello F.

PURPOSE: To evaluate the efficacy of intravitreal ranibizumab in the treatment of myopic choroidal neovascularization (mCNV) complicated by vitreoretinal interface alterations.

METHODS: Thirty-two patients affected by mCNV and concurrent vitreoretinal interface disorders, including macular epiretinal membrane (18 patients), lamellar macular hole (4 patients), full-thickness macular hole (1 patient), broad/focal vitreomacular traction (3 patients), broad/focal vitreomacular adhesion (4 patients), and myopic foveoschisis (2 patients), were enrolled in a prospective study. After a comprehensive ophthalmologic examination, including best-corrected visual acuity (BCVA), fluorescein angiography, and spectral-domain optical coherence tomography, each patient received a first intravitreal ranibizumab. Further re-treatments were performed in the presence of choroidal neovascularization activity (new hemorrhages, leakage on fluorescein angiography, intraretinal/subretinal fluid on spectral-domain optical coherence tomography, visual acuity loss of five letters). Main outcome measure was the change in the

BCVA and in the central foveal thickness. Data were compared with the historical control group with uncomplicated mCNV.

RESULTS: The median BCVA in the epiretinal membrane-myopic choroidal neovascularization subgroup showed a stabilization from the baseline value of 0.30 logarithm of minimal angle resolution (20/40) to 0.40 (20/50, P: 0.49) at the last visit (30 ± 13 months). Median BCVA significantly improved from 0.30 (20/40) to 0.10 (20/25, P: 0.0005) in the mCNV group and was better than the epiretinal membrane-myopic choroidal neovascularization subgroup (0.008). Central foveal thickness reduced significantly within both groups, with no difference between the groups at the final examination. Considering the vitreoretinal alterations with lower prevalence, BCVA stabilization was registered after a follow-up of 28.9 ± 13 months, with a median BCVA of 0.3 logarithm of minimal angle resolution (20/40) at the baseline and at the final examination. A nonstatistically significant reduction in the median central foveal thickness was registered at the final examination (P: 0.12).

CONCLUSION: The data show that ranibizumab is effective in controlling mCNV activity when associated with vitreoretinal interface alterations. However, a visual recovery was observed only in patients with uncomplicated mCNV.

PMID: 28098725

Retin Cases Brief Rep. 2016 Dec 19. [Epub ahead of print]

LONG-TERM FOLLOW-UP OF RETINAL PIGMENT EPITHELIUM RESTORATION AFTER A TRIPLE TEAR.

Zahid S, Dolz Marco R, Freund KB.

PURPOSE: To demonstrate longitudinal multimodal imaging findings in a case of neovascular age-related macular degeneration presenting with multiple retinal pigment epithelium (RPE) tears showing progressive RPE restoration.

METHODS: Observational clinical case report.

RESULTS: A 79-year-old woman diagnosed with neovascular age-related macular degeneration developed 3 consecutive RPE tears in her right eye during the course of treatment with intravitreal anti-vascular endothelial growth factor therapy. The RPE tears initially appeared hypoautofluorescent on fundus autofluorescence. Spectral domain optical coherence tomography showed contractile folds of the RPE with adjacent subretinal fluid and overlying ellipsoid zone disruption. Over an 8-year follow-up period, the RPE defects progressively resolved with a return of patchy fundus autofluorescence. Eye-tracked spectral domain optical coherence tomography showed gradual restoration of the RPE band defects over an enlarging Type 1 neovascular lesion.

CONCLUSION: Some RPE tears may show observable remodeling and restoration over time. These changes may be followed longitudinally with multimodal imaging, including eye-tracked spectral domain optical coherence tomography and fundus autofluorescence.

PMID: 28098621

Clin Ophthalmol. 2016 Dec 23;11:95. eCollection 2017.

Erratum: Macular morphology and response to ranibizumab treatment in patients with wet age-related macular degeneration [Corrigendum].[No authors listed]

Abstract: [This corrects the article on p. 1117 in vol. 10, PMID: 27366051.].

Erratum for

Macular morphology and response to ranibizumab treatment in patients with wet age-related macular degeneration. [Clin Ophthalmol. 2016]

PMID: 28096652

Acta Ophthalmol. 2017 Jan 13. [Epub ahead of print]

Comparison between the short-term outcomes of bevacizumab and ziv-aflibercept in the treatment of primary diabetic macular oedema.

Ashraf M, El Kayal H, Souka AA.

PMID: 28084003

Eye (Lond). 2017 Jan 20. [Epub ahead of print]

Neovascular age-related macular degeneration: is it worthwhile treating an eye with poor visual acuity, if the visual acuity of the fellow eye is good?

Rasmussen A, Fuchs J, Hansen LH, Larsen M, Sander B, Lund-Andersen H.

PMID: 28106891

Other treatment & diagnosis

Int J Retina Vitreous. 2017 Jan 9;3:1. eCollection 2017.

The potential of spectral domain optical coherence tomography imaging based retinal biomarkers.

Phadikar P, Saxena S, Ruia S, Lai TY, Meyer CH, Eliott D.

BACKGROUND: Biomarker", a merged word of "biological marker", refers to a broad subcategory of medical signs that objectively indicate the state of health, and well-being of an individual. Biomarkers hold great promise for personalized medicine as information gained from diagnostic or progression markers can be used to tailor treatment to the individual for highly effective intervention in the disease process. Optical coherence tomography (OCT) has proved useful in identifying various biomarkers in ocular and systemic diseases.

MAIN BODY: Spectral domain optical coherence tomography imaging-based biomarkers provide a valuable tool for detecting the earlier stages of the disease, tracking progression, and monitoring treatment response. The aim of this review article is to analyze various OCT based imaging biomarkers and their potential to be considered as surrogate endpoints for diabetic retinopathy, age related macular degeneration, retinitis pigmentosa and vitreomacular interface disorder. These OCT based surrogate markers have been classified as retinal structural alterations (macular central subfield thickness and cube average thickness); retinal ultrastructural alterations (disruption of external limiting membrane and ellipsoid zone, thinning of retinal nerve fiber layer and ganglion cell layer); intraretinal microangiopathic changes; choroidal surrogate endpoints; and vitreoretinal interface endpoints.

CONCLUSION: OCT technology is changing very quickly and throughout this review there are some of the multiple possibilities that OCT based imaging biomarkers will be more useful in the near future for diagnosis, prognosticating disease progression and as endpoint in clinical trials.

PMID: 28078103 PMCID: PMC5220620

Int Ophthalmol. 2017 Jan 21. [Epub ahead of print]

Performance characteristics of multicolor versus blue light and infrared imaging in the identification of reticular pseudodrusen.

Badal J, Biarnés M, Monés J.

PURPOSE: To describe the appearance of reticular pseudodrusen on multicolor imaging and to evaluate its diagnostic accuracy as compared with the two modalities that may be considered the current reference standard, blue light and infrared imaging.

METHODS: Retrospective study in which all multicolor images (constructed from images acquired at 486 nm-blue, 518 nm-green and 815 nm-infrared) of 45 consecutive patients visited in a single center was reviewed. Inclusion criteria involved the presence of >1 reticular pseudodrusen on a 30° × 30° image centered on the fovea as seen with the blue light channel derived from the multicolor imaging. Three experienced observers, masked to each other's results with other imaging modalities, independently classified the number of reticular pseudodrusen with each modality.

RESULTS: The median interobserver agreement (kappa) was 0.58 using blue light; 0.65 using infrared; and 0.64 using multicolor images. Multicolor and infrared modalities identified a higher number of reticular pseudodrusen than blue light modality in all fields for all observers ($p < 0.0001$). Results were not different when multicolor and infrared were compared ($p \geq 0.27$).

CONCLUSIONS: These results suggest that multicolor and infrared are more sensitive and reproducible than blue light in the identification of RPD. Multicolor did not appear to add a significant value to infrared in the evaluation of RDP. Clinicians using infrared do not need to incorporate multicolor for the identification and quantification of RPD.

PMID: 28108901

Ophthalmologica. 2017 Jan 12. [Epub ahead of print]

The Journey of "Geographic Atrophy" through Past, Present, and Future.

Schmitz-Valckenberg S.

Abstract: "Geographic atrophy" is a concise term that has been firmly established for the description of the end-stage manifestation of nonexudative age-related macular degeneration (AMD). "Geographic lesions" resembling sharply demarcated continents on a map have been originally described in the German literature in 1854 (landkartenartiger/inselförmiger Zungenfratt) for a manifestation later called "geographic tongue" in English. In 1970, Gass was the first to describe "geographic areas of atrophy" in "senile macular choroidal degeneration." Within a decade, the disease itself was named "geographic atrophy." Today, various meanings of the term are used in parallel both in research and in routine clinical care. Currently, we are on the verge of better understanding the different forms of atrophy development, manifestation, and progression in AMD, which will pave the way for a more rational approach to their nomenclature and classification.

MID: 28076857

J Control Release. 2017 Jan 10. [Epub ahead of print]

Polymeric micelles for ocular drug delivery: From structural frameworks to recent preclinical studies.

Mandal A, Bisht R, Rupenthal ID, Mitra AK.

Abstract: Effective intraocular drug delivery poses a major challenge due to the presence of various

elimination mechanisms and physiological barriers that result in low ocular bioavailability after topical application. Over the past decades, polymeric micelles have emerged as one of the most promising drug delivery platforms for the management of ocular diseases affecting the anterior (dry eye syndrome) and posterior (age-related macular degeneration, diabetic retinopathy and glaucoma) segments of the eye. Promising preclinical efficacy results from both in-vitro and in-vivo animal studies have led to their steady progression through clinical trials. The mucoadhesive nature of these polymeric micelles results in enhanced contact with the ocular surface while their small size allows better tissue penetration. Most importantly, being highly water soluble, these polymeric micelles generate clear aqueous solutions which allows easy application in the form of eye drops without any vision interference. Enhanced stability, larger cargo capacity, non-toxicity, ease of surface modification and controlled drug release are additional advantages with polymeric micelles. Finally, simple and cost effective fabrication techniques render their industrial acceptance relatively high. This review summarizes structural frameworks, methods of preparation, physicochemical properties, patented inventions and recent advances of these micelles as effective carriers for ocular drug delivery highlighting their performance in preclinical studies.

PMID: 28087407

Case Rep Ophthalmol. 2016 Nov 25;7(3):256-264.

Effects of Disseminated Mycobacterial Infection on Age-Related Macular Degeneration.

Collett G, Lopez N, Lopez PF.

Abstract: Our patient, in the 7th decade of life, presented with worsening blurry vision over 3 weeks. The pertinent history included nonexudative age-related macular degeneration, recent pulmonary mycobacterial infection, and autoimmune pancreatitis. The patient had decreased visual acuity in both eyes; the remaining findings of our examination were relatively benign. The diagnosis of bilateral exudative age-related macular degeneration was aided by ocular imaging. Not only were exudative changes confirmed, but one modality suggested an underlying occult choroiditis, which presumably fueled a local inflammatory drive leading to evolution of the disease. Given the choroiditis developed in the setting of a recent Mycobacterium chelonae infection, dissemination of the organism must be considered a potential culprit. Additionally, a chronic inflammatory state perhaps played a simultaneous immunologic role. We feel the proposed pathogenic mechanism outlined sufficiently accounts for the rare event, that is, development of subacute bilateral exudative maculopathy. The patient responded well to bilateral intravitreal aflibercept injections. After 1 month, visual acuity was found to be near baseline and ocular imaging showed significant resolution of the exudative changes. An additional follow-up 3 months after confirmed similar stability. This case required thorough investigation of seemingly unrelated components within the patient's history. We stress the importance of obtaining appropriate documentation from fellow health care teams when suspicious clinical presentations arise. During our investigation, we identified cryptic retinal lesions by way of angiography - leading us to recommend usage of such methods in complex cases. We also summarize the implemented aflibercept course and the favorable response to such treatment.

PMID: 28101043

Retina. 2017 Jan 10. [Epub ahead of print]

OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY CHANGES IN EARLY TYPE 3 NEOVASCULARIZATION AFTER ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT.

Miere A, Querques G, Semoun O, Amoroso F, Zambrowski O, Chapron T, Capuano V, Souied EH.

PURPOSE: To investigate the morphologic changes on optical coherence tomography angiography (OCTA) of treatment-naive Type 3 neovascularization secondary to exudative age-related macular degeneration after 1 year of anti-vascular endothelial growth factor therapy.

METHODS: Consecutive patients diagnosed with treatment-naive early-stage Type 3 neovascularization were enrolled in this retrospective study. All patients underwent color fundus photographs/MultiColor (Heidelberg Engineering) imaging, fluorescein angiography, indocyanine green angiography, structural spectral domain OCT, and OCTA Optovue RTVue XR Avanti (Optovue) at baseline, and repeated OCTA and structural spectral domain OCT at Month 12. Qualitative analysis of the 3 × 3 OCTA examinations at baseline and Month 12 was then compared, to assess changes after anti-vascular endothelial growth factor therapy.

RESULTS: A total of 15 treatment-naive eyes of 15 consecutive patients were included in the analysis. At 12-month follow-up after pro-re-data anti-vascular endothelial growth factor therapy (5.75 ± 1.48 injections of ranibizumab, and injections of 6.33 ± 1.21 of aflibercept), OCTA demonstrated persistence of the deep capillary plexus abnormalities in 13/15 eyes. In the outer retina and choriocapillaris, the initial lesion became undetectable in 7/15 cases, accompanied by choriocapillaris atrophy. The abnormal vascular complex persisted in the form of a tuft-shaped lesion in the outer retinal segmentation in 9/15 eyes, which in the choriocapillaris segmentation was associated with sub-retinal pigment epithelium neovascularization in 8 cases.

CONCLUSION: Optical coherence tomography angiography showed that the tuft-shaped abnormal outer retinal lesion, frequently associated with a small clew-like flow signal in the choriocapillaris, after 1 year of anti-vascular endothelial growth factor therapy, either becomes undetectable or develops sub-retinal pigment epithelium neovascularization.

PMID: 28079756

Biomed Opt Express. 2016 Dec 16;8(1):281-297. eCollection 2017.

Multi-surface segmentation of OCT images with AMD using sparse high order potentials.

Oliveira J, Pereira S, Gonçalves L, Ferreira M, Silva CA.

Abstract: In age-related macular degeneration (AMD), the quantification of drusen is important because it is correlated with the evolution of the disease to an advanced stage. Therefore, we propose an algorithm based on a multi-surface framework for the segmentation of the limiting boundaries of drusen: the inner boundary of the retinal pigment epithelium + drusen complex (IRPEDC) and the Bruch's membrane (BM). Several segmentation methods have been considerably successful in segmenting retinal layers of healthy retinas in optical coherence tomography (OCT) images. These methods are successful because they incorporate prior information and regularization. Nonetheless, these factors tend to hinder the segmentation for diseased retinas. The proposed algorithm takes into account the presence of drusen and geographic atrophy (GA) related to AMD by excluding prior information and regularization just valid for healthy regions. However, even with this algorithm, prior information and regularization still cause the oversmoothing of drusen in some locations. Thus, we propose the integration of local shape prior in the form of a sparse high order potentials (SHOPs) into the algorithm to reduce the oversmoothing of drusen. The proposed algorithm was evaluated in a public database. The mean unsigned errors, relative to the average of two experts, for the inner limiting membrane (ILM), IRPEDC and BM were 2.94±2.69, 5.53±5.66 and 4.00±4.00 µm, respectively. Drusen areas measurements were evaluated, relative to the average of two expert graders, by the mean absolute area difference and overlap ratio, which were 1579.7 ± 2106.8 µm2 and 0.78 ± 0.11, respectively.

PMID: 28101418

Pathogenesis

Aging Cell. 2017 Jan 13. [Epub ahead of print]

The amino acid transporter SLC36A4 regulates the amino acid pool in retinal pigmented epithelial

cells and mediates the mechanistic target of rapamycin, complex 1 signaling.

Shang P, Valapala M, Grebe R, Hose S, Ghosh S, Bhutto IA, Handa JT, Lutty GA, Lu L, Wan J, Qian J, Sergeev Y, Puertollano R, Zigler JS Jr, Xu GT, Sinha D.

Abstract: The dry (nonneovascular) form of age-related macular degeneration (AMD), a leading cause of blindness in the elderly, has few, if any, treatment options at present. It is characterized by early accumulation of cellular waste products in the retinal pigmented epithelium (RPE); rejuvenating impaired lysosome function in RPE is a well-justified target for treatment. It is now clear that amino acids and vacuolar-type H+ -ATPase (V-ATPase) regulate the mechanistic target of rapamycin, complex 1 (mTORC1) signaling in lysosomes. Here, we provide evidence for the first time that the amino acid transporter SLC36A4/proton-dependent amino acid transporter (PAT4) regulates the amino acid pool in the lysosomes of RPE. In Cryba1 (gene encoding βA3/A1-crystallin) KO (knockout) mice, where PAT4 and amino acid levels are increased in the RPE, the transcription factors EB (TFEB) and E3 (TFE3) are retained in the cytoplasm, even after 24 h of fasting. Consequently, genes in the coordinated lysosomal expression and regulation (CLEAR) network are not activated, and lysosomal function remains low. As these mice age, expression of RPE65 and lecithin retinol acyltransferase (LRAT), two vital visual cycle proteins, decreases in the RPE. A defective visual cycle would possibly slow down the regeneration of new photoreceptor outer segments (POS). Further, photoreceptor degeneration also becomes obvious during aging, reminiscent of human dry AMD disease. Electron microscopy shows basal laminar deposits in Bruch's membrane, a hallmark of development of AMD. For dry AMD patients, targeting PAT4/V-ATPase in the lysosomes of RPE cells may be an effective means of preventing or delaying disease progression.

PMID: 28083894

PLoS One. 2017 Jan 20;12(1):e0169865. eCollection 2017.

Neuropilin 1 Involvement in Choroidal and Retinal Neovascularisation.

Fernández-Robredo P, Selvam S, Powner MB, Sim DA, Fruttiger M.

PURPOSE: Inhibiting VEGF is the gold standard treatment for neovascular age-related macular degeneration (AMD). It is also effective in preventing retinal oedema and neovascularisation (NV) in diabetic retinopathy (DR) and retinal vein occlusions (RVO). Neuropilin 1 (Nrp1) is a co-receptor for VEGF and many other growth factors, and therefore a possible alternative drug target in intra ocular neovascular disease. Here we assessed choroidal and retinal NV in an inducible, endothelial specific knock out model for Nrp1.

METHODS: Crossing Nrp1 floxed mice with Pdgfb-CreERT2 mice produced tamoxifen-inducible, endothelial specific Nrp1 knock out mice (Nrp1ΔEC) and Cre-negative, control littermates. Cre-recombinase activity was confirmed in the Ai3(RCL-EYFP) reporter strain. Animals were subjected to laser-induced CNV (532 nm) and spectral domain-optical coherence tomography (SD-OCT) was performed immediately after laser and at day 7. Fluorescein angiography (FA) evaluated leakage and postmortem lectin staining in flat mounted RPE/choroid complexes was also used to measure CNV. Furthermore, retinal neovascularisation in the oxygen induced retinopathy (OIR) model was assessed by immunohistochemistry in retinal flatmounts.

RESULTS: In vivo FA, OCT and post-mortem lectin staining showed a statistically significant reduction in leakage ($p<0.05$), CNV volume ($p<0.05$) and CNV area ($p<0.05$) in the Nrp1ΔEC mice compared to their Cre-negative littermates. Also the OIR model showed reduced retinal NV in the mutant animals compared to wild types ($p<0.001$).

CONCLUSION: We have demonstrated reduced choroidal and retinal NV in animals that lack endothelial Nrp1, confirming a role of Nrp1 in those processes. Therefore, Nrp1 may be a promising drug target for neovascular diseases in the eye.

PMID: 28107458

J Biol Chem. 2017 Jan 19. [Epub ahead of print]

microRNA-processing Enzymes Are Essential for Survival and Function of Mature Retinal Pigmented Epithelial Cells in Mice.

Sundermeier TR, Sakami S, Sahu B, Howell SJ, Gao S, Dong Z, Golczak M, Maeda A, Palczewski K.

Abstract: Age-related macular degeneration (AMD) is a major cause of irreversible vision loss. The neovascular or "wet" form of AMD can be treated to a varying degree with anti-angiogenic drugs, but geographic atrophy (GA) is an advanced stage of the more prevalent "dry" form of AMD for which there is no effective treatment. Development of GA has been linked to loss of the microRNA (miRNA)-processing enzyme DICER1 in the mature retinal pigmented epithelium (RPE). This loss results in the accumulation of toxic transcripts of Alu transposable elements which activate the NLRP3 inflammasome and additional downstream pathways that compromise the integrity and function of the RPE. However, it remains unclear whether the loss of miRNA processing and subsequent gene regulation in the RPE due to DICER1 deficiency also contributes to RPE cell death. To clarify the role of miRNAs in RPE cells, we used two different mature RPE cell-specific Cre recombinase drivers to inactivate either Dicer1 or DiGeorge syndrome critical region 8 (Dgcr8), thus removing RPE miRNA regulatory activity in mice by disrupting two independent and essential steps of miRNA biogenesis. In contrast with prior studies, we found that loss of each factor independently led to strikingly similar defects in the survival and function of the RPE and retina. These results suggest that the loss of miRNAs also contributes to RPE cell death and loss of visual function and could affect the pathology of dry AMD.

PMID: 28104803

Biomed Pharmacother. 2017 Jan 16;88:124-133. [Epub ahead of print]

Hesperetin protects against H2O2-triggered oxidative damage via upregulation of the Keap1-Nrf2/HO-1 signal pathway in ARPE-19 cells.

Zhu C, Dong Y, Liu H, Ren H, Cui Z.

Abstract: Age-related macular degeneration (AMD) is an irreversible vision loss disease that primarily results from oxidative stress that causes oxidative damage to the retinal pigment epithelial (RPE) cells. Hesperetin (Hesp) is a common flavanone glycoside compound that has been demonstrated to exhibit a variety of biological and pharmacological properties that include anti-inflammatory and antioxidant properties. The aim of this study is to explore the ability of Hesp to attenuate oxidative damage in hydrogen peroxide (H2O2)-stimulated ARPE-19 cells. The results indicated that Hesp treatment not only increased cell survival but also decreased reactive oxygen species (ROS) generation, whereas these roles were effectively enhanced the superoxide dismutase (SOD) and glutathione (GSH) levels, and reduced malondialdehyde (MDA) formation. Importantly, the level of heme oxygenase-1 (HO-1) expression was increased by Hesp exposure, which resulted in a decrease after the transfection of cells with Nrf2-siRNA. Additionally, further results revealed that Hesp treatment significantly elevated Keap-1 protein expression, Nrf2 nuclear translocation and ARE activities. These observations indicated that Hesp treatment effectively protected against H2O2-induced oxidative damage in ARPE-19 cells by inhibiting cell apoptosis, ROS overproduction and MDA formation as well as enhancing the SOD and GSH levels. The underlying mechanisms may be related to the activation of the Keap1-Nrf2/HO-1 signal pathway, which may provide biological evidence to further encourage the investigation of the protective effect of Hesp in AMD disease.

PMID: 28103505

Sci Transl Med. 2017 Jan 18;9(373).

Tyrosine kinase blocking collagen IV-derived peptide suppresses ocular neovascularization and vascular leakage.

Lima E Silva R, Kanan Y, Mirando AC, Kim J, Shmueli RB, Lorenc VE, Fortmann SD, Sciamanna J, Pandey NB, Green JJ, Popel AS, Campochiaro PA.

Abstract: Vascular endothelial growth factor (VEGF)-neutralizing proteins provide benefit in several retinal and choroidal vascular diseases, but some patients still experience suboptimal outcomes, and the need for frequent intraocular injections is a barrier to good outcomes. A mimetic peptide derived from collagen IV, AXT107, suppressed subretinal neovascularization (NV) in two mouse models predictive of effects in neovascular age-related macular degeneration (NVAMD) and inhibited retinal NV in a model predictive of effects in ischemic retinopathies. A combination of AXT107 and the current treatment aflibercept suppressed subretinal NV better than either agent alone. Furthermore, AXT107 caused regression of choroidal NV. AXT107 reduced the VEGF-induced vascular leakage that underlies macular edema in ischemic retinopathies and NVAMD. In rabbit eyes, which are closer to the size of human eyes, intraocular injection of AXT107 significantly reduced VEGF-induced vascular leakage by 86% at 1 month and 70% at 2 months; aflibercept significantly reduced leakage by 69% at 1 month and did not reduce leakage at 2 months, demonstrating the longer effectiveness of AXT107. AXT107 reduced ligand-induced phosphorylation of multiple receptors: VEGFR2, c-Met, and PDGFRβ. Optimal signaling through these receptors requires complex formation with β3 integrin, which was reduced by AXT107 binding to αvβ3 AXT107 also reduced total VEGFR2 levels by increasing internalization, ubiquitination, and degradation. This biomimetic peptide is a sustained, multitargeted therapy that may provide advantages over intraocular injections of specific VEGF-neutralizing proteins.

PMID: 28100839

Ophthalmologica. 2017 Jan 17. [Epub ahead of print]

Behaviour of CD11b-Positive Cells in an Animal Model of Laser-Induced Choroidal Neovascularisation.

Li L, Heiduschka P, Alex AF, Niekämper D, Eter N.

BACKGROUND/AIM: Immune cells, e.g. microglial cells of the retina, appear to be involved in pathological processes in neovascular age-related macular degeneration. Therefore, the purpose of this study was to immunohistochemically check the expression of various factors and cytokines by CD11b-positive (CD11b+) immune cells in an animal model of choroidal neovascularisation (CNV).

METHODS: We used the animal model of laser-induced CNV in mice. Eyes were isolated at 1, 4, 7, and 14 days after laser treatment. Cryosections were prepared and checked immunohistochemically for the presence of different growth factors and cytokines on microglial cells and other immune cells identified by CD11b immunoreactivity.

RESULTS: We found that the number of CD11b+ cells at the laser spots increased dramatically 4 days after laser treatment, the majority of them entering the laser spot most probably by migration. CD11b+ cells in the laser spot were positive for a variety of pro-angiogenic factors, such as PDGF-β, FGF-1, FGF-2, and TGF-β1. They were also positive for some inflammatory cytokines, in particular TNF-α, IL-6, and CXCL1. In non-treated retinas, CD11b+ cells showed almost no immunoreactivity for these proteins.

CONCLUSION: Microglial cells, macrophages, and other CD11b+ cells may promote the neovascularisation in the laser spot and show a moderate inflammatory behaviour. Immunoreactivity for most of these molecules was found to decrease during the time of observation. Modulation of immune cell activity may thus be a tool to reduce the extent of CNV.

PMID: 28092911

Epidemiology

Br J Ophthalmol. 2017 Jan 20. pii: bjophthalmol-2016-309729. [Epub ahead of print]

Five-year progression of unilateral age-related macular degeneration to bilateral involvement: the Three Continent AMD Consortium report.

Joachim N, Colijn JM, Kifley A, Lee KE, Buitendijk GH, Klein BE, Myers CE, Meuer SM, Tan AG, Holliday EG, Attia J, Liew G, Iyengar SK, de Jong PT, Hofman A, Vingerling JR, Mitchell P, Klaver CC, Klein R, Wang JJ.

PURPOSE: To assess the 5-year progression from unilateral to bilateral age-related macular degeneration (AMD) and associated risk factors.

DESIGN: Pooled data analyses of three prospective population-based cohorts, the Blue Mountains Eye Study, Beaver Dam Eye Study and Rotterdam Study.

METHODS: Retinal photography and interview with comprehensive questionnaires were conducted at each visit of three studies. AMD was assessed following the modified Wisconsin AMD grading protocol. Progression to bilateral any (early and late) or late AMD was assessed among participants with unilateral involvement only. Factors associated with the progression were assessed using logistic regression models while simultaneously adjusting for other significant risk factors.

RESULTS: In any 5-year duration, 19-28% of unilateral any AMD cases became bilateral and 27-68% of unilateral late AMD became bilateral. Factors associated with the progression to bilateral involvement of any AMD were age (per year increase, adjusted OR 1.07), carrying risk alleles of the complement factor H and age-related maculopathy susceptibility 2 genes (compared with none, OR 1.76 for 1 risk allele and OR 3.34 for 2+ risk alleles), smoking (compared with non-smokers, OR 1.64 for past and OR 1.67 for current smokers), and the presence of large drusen area or retinal pigmentary abnormalities in the first eye.

CONCLUSION: One in four to one in five unilateral any AMD cases, and up to one in two unilateral late AMD cases, progressed to bilateral in 5 years. Known AMD risk factors, including smoking, are significantly associated with the progression to bilateral involvement.

PMID: 28108569

Ophthalmology. 2017 Jan 12. [Epub ahead of print]

Peripheral Retinal Changes Associated with Age-Related Macular Degeneration in the Age-Related Eye Disease Study 2: Age-Related Eye Disease Study 2 Report Number 12 by the Age-Related Eye Disease Study 2 Optos PEripheral RetinA (OPERA) Study Research Group.

Writing Committee for the OPTOS PEripheral RetinA (OPERA) study (Ancillary Study of Age-Related Eye Disease Study 2), Domalpally A, Clemons TE, Danis RP, Sadda SR, Cukras CA, Toth CA, Friberg TR, Chew EY.

PURPOSE: To compare rates of peripheral retinal changes in Age-Related Eye Disease Study 2 (AREDS2) participants with at least intermediate age-related macular degeneration (AMD) with control subjects without intermediate age-related changes (large drusen).

DESIGN: Cross-sectional evaluation of clinic-based patients enrolled in AREDS2 and a prospective study.

PARTICIPANTS: Participants from prospective studies.

METHODS: The 200° pseudocolor and fundus autofluorescence (FAF) images were captured on the Optos 200 Tx Ultrawide-field device (Optos, Dunfermline, Scotland) by centering on the fovea and then steering superiorly and inferiorly. The montaged images were graded at a reading center with the images divided into 3 zones (zone 1 [posterior pole], zone 2 [midperiphery], and zone 3 [far periphery]) to document the

presence of peripheral lesions.

MAIN OUTCOME MEASURES: Peripheral retinal lesions: drusen, hypopigmentary/hyperpigmentary changes, reticular pseudodrusen, senile reticular pigmentary changes, cobblestone degeneration, and FAF abnormalities.

RESULTS: A total of 484 (951 eyes) AREDS2 participants with AMD (cases) and 89 (163 eyes) controls without AMD had gradable color and FAF images. In zones 2 and 3, neovascularization and geographic atrophy (GA) were present, ranging from 0.4% to 6% in eyes of cases, respectively, and GA was present in 1% of eyes of controls. Drusen were detected in 97%, 78%, and 64% of eyes of cases and 48%, 21%, and 9% of eyes of controls in zones 2 and 3 superior and 3 inferior, respectively ($P < 0.001$ for all). Peripheral reticular pseudodrusen were seen in 15%. Senile reticular pigmentary change was the predominant peripheral change seen in 48% of cases and 16% of controls in zone 2 ($P < 0.001$). Nonreticular pigment changes were less frequent in the periphery than in the posterior pole (46% vs. 76%) and negligible in controls.

CONCLUSIONS: Peripheral retinal changes are more prevalent in eyes with AMD than in control eyes. Drusen are seen in a majority of eyes with AMD in both the mid and far periphery, whereas pigment changes and features of advanced AMD are less frequent. Age-related macular degeneration may be more than a "macular" condition but one that involves the entire retina. Future longitudinal studies of peripheral changes in AMD and their impact on visual function may contribute to understanding AMD pathogenesis.

PMID: 28089680

Biomed Res Int. 2016;2016:8212063. Epub 2016 Dec 14.

Relation between Age-Related Macular Degeneration and Cardiovascular Events and Mortality: A Systematic Review and Meta-Analysis.

Wang J, Xue Y, Thapa S, Wang L, Tang J, Ji K.

Abstract: Data on the association between age-related macular degeneration (AMD) and cardiovascular disease and mortality are conflicting. The purpose of this report is to conduct a systematic review to better understand the role of AMD as a risk factor for CVD events and mortality. We searched Medline (Ovid) and Embase (Ovid) for trials published from 1980 to 2015. We included 20 cohort studies that reported relative risks with 95% confidence intervals for the association of AMD and cardiovascular events and mortality, involving 29,964,334 participants. In a random-effects model, the adjusted RR (95% confidence interval [CI]) associated with AMD was 1.08 (1.00-1.117) for all-cause mortality (8 studies) and 1.18 (0.98-1.43) for cardiovascular disease mortality (5 studies). The pooled RR (95% CI) was 1.17 (0.94-1.45) for coronary heart disease (CHD; 3 studies) and 1.13 (0.93-1.36) for stroke (8 studies). Findings from this systematic review support that AMD is associated with increased risk of all-cause mortality. The evidence that AMD predicts incident CVD events or CVD mortality remains inclusive and warrants further study in the future.

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Chin Med J (Engl). 2017 20th Jan;130(2):155-159.

Awareness of Age-related Macular Degeneration and Its Risk Factors among Beijing Residents in China.

Zhang CX, Zhang GM, Ma N, Xia S, Yang JY, Chen YX.

BACKGROUND: Age-related macular degeneration (AMD) is a major cause of irreversible blindness, and awareness of this disease is important in the prevention of blindness. However, lack of public awareness of AMD was shown in previous studies, and there was no report of AMD awareness in the Mainland of China. Therefore, the aim of our study was to assess the awareness of AMD and its risk factors among Beijing

residents in China.

METHODS: A cross-sectional, computer-assisted, telephone investigation was conducted to measure the awareness of AMD among Beijing residents. All the contacts of potential respondents were randomly generated by computer. Only those above 18 years of age and willing to participate in the study were included. The questionnaire for the study was modified from the AMD Alliance International Global Report. Pearson's Chi-square test and binary logistic regression analysis were used to identify the factors that affected the knowledge of AMD.

RESULTS: Among 385 Beijing residents who agreed to participate, the awareness of AMD was 6.8%, far below than that of cataract and glaucoma. Participants who were above 30 years of age (odds ratio [OR] 6.17, confidence interval [CI] 1.44-26.57), with experience of health-related work (OR 8.11, CI 3.25-20.27), and whose relatives/friends or themselves suffering from AMD (OR 32.18, CI 11.29-91.68) had better AMD awareness. Among those familiar with AMD, only 35% of them identified smoking as a risk factor, and only 23.1% of the residents believed that smoking could lead to blindness.

CONCLUSIONS: The sample of Chinese population had limited knowledge of AMD. Educational programs need to be carried out to raise public awareness of AMD.

PMID: 28091406

Genetics

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Age-related macular degeneration associated polymorphism rs10490924 in ARMS2 results in deficiency of a complement activator.

Micklisch S, Lin Y, Jacob S, et al

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. The polymorphism rs10490924 in the ARMS2 gene is highly associated with AMD and linked to an indel mutation (del443ins54), the latter inducing mRNA instability. At present, the function of the ARMS2 protein, the exact cellular sources in the retina and the biological consequences of the rs10490924 polymorphism are unclear.

METHODS: Recombinant ARMS2 was expressed in Pichia pastoris, and protein functions were studied regarding cell surface binding and complement activation in human serum using fluoresence-activated cell sorting (FACS) as well as laser scanning microscopy (LSM). Biolayer interferometry defined protein interactions. Furthermore, endogenous ARMS2 gene expression was studied in human blood derived monocytes and in human induced pluripotent stem cell-derived microglia (iPSdM) by PCR and LSM. The ARMS2 protein was localized in human genotyped retinal sections and in purified monocytes derived from AMD patients without the ARMS2 risk variant by LSM. ARMS2 expression in monocytes under oxidative stress was determined by Western blot analysis.

RESULTS: Here, we demonstrate for the first time that ARMS2 functions as surface complement regulator. Recombinant ARMS2 binds to human apoptotic and necrotic cells and initiates complement activation by recruiting the complement activator properdin. ARMS2-properdin complexes augment C3b surface opsonization for phagocytosis. We also demonstrate for the first time expression of ARMS2 in human monocytes especially under oxidative stress and in microglia cells of the human retina. The ARMS2 protein is absent in monocytes and also in microglia cells, derived from patients homozygous for the ARMS2 AMD risk variant (rs10490924).

CONCLUSIONS: ARMS2 is likely involved in complement-mediated clearance of cellular debris. As AMD patients present with accumulated proteins and lipids on Bruch's membrane, ARMS2 protein deficiency due to the genetic risk variant might be involved in drusen formation.

PMID: 28086806 PMCID: PMC5234120

BMC Genet. 2016 Dec 22;17(Suppl 3):153.

Genes of susceptibility to early neurodegenerative changes in the rat retina and brain: analysis by means of congenic strains.

Korbolina EE, Zhdankina AA, Fursova AZ, Kozhevnikova OS, Kolosova NG.

BACKGROUND: There has been considerable interest in discovery of the genetic architecture of complex traits, particularly age-related neurodegenerative disorders. To predict disease risk and to understand its genetic basis in humans, it is necessary to study animal models. Our previous research on the accelerated-senescence OXYS strain has revealed two quantitative trait loci (QTLs) on rat chromosome 1 that are associated with early cataract and/or retinopathy as well as with behavioral abnormalities. Each locus was partially mapped within the introgressed segments in a certain congenic strain: WAG/OXYS-1.1 or WAG/OXYS-1.2. Retinal transcriptome profiling of 20-day-old congenic and OXYS rats by high-throughput RNA sequencing uncovered relevant candidate genes and pathways. Nonetheless, the question remained open whether the same genetic components simultaneously have effects on various manifestations of the accelerated-senescence phenotype in OXYS rats. The present study was designed to analyze the genes of susceptibility to early neurodegenerative processes taking place in the OXYS rat retina and brain and to assess their potential functional clustering. The study was based on the findings from recent publications (including mapping of quantitative trait loci) and on comparative phenotyping of congenic rat strains.

RESULTS: The backcrossing of Wistar Albino Glaxo (WAG) and OXYS strains to generate the congenics resulted in two congenic strains with high susceptibility to cataract and retinopathy but with no obvious signs of Alzheimer's disease-like brain pathology that are specific for OXYS rats. Thus, the genes of susceptibility to brain neurodegeneration were not introgressed into the congenic strains or there is a strong effect of the genetic background on the disease phenotype. Moreover, the progression of retinopathy with age was relatively less severe in the WAG background compared to the OXYS background. A comparative analysis of previously defined QTLs and congenic segments led to identification of candidate genes with a suspected effect on brain neurodegeneration including the genes showing differential expression in the congenic strains.

CONCLUSION: Overall, our findings suggest that the cause of the cataract and the cause of retinopathy phenotypes in OXYS rats may be genetically linked to each other within the introgressed segments in the WAG/OXYS-1.1 and/or WAG/OXYS-1.2 congenic strains.

PMID: 28105932

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Association of the DNA repair SMUG1 rs3087404 polymorphism and its interaction with high sensitivity C-reactive protein for age-related macular degeneration in Iranian patients.

Bonyadi M, Mehdizadeh F, Jabbarpoor Bonyadi MH, Soheilian M, Javadzadeh A, Yaseri M.

BACKGROUND: Age-related macular degeneration (AMD) is a complex disease and recently the role of DNA repairing genes in its susceptibility has been studied. It has been hypothesized that polymorphism in DNA repair system genes reduce the capacity to repair DNA damages which may lead to a greater susceptibility to AMD. C-reactive protein (CRP) production is shown to enhance inflammatory processes by increasing oxidative stress and inducing DNA damage. We planned to evaluate the possible association of SMUG1 variants and their possible interaction with high sensitivity CRP levels in AMD.

MATERIALS AND METHODS: We included 500 case-control samples consisting of 279 advanced type AMD patients and 221 genetically unrelated healthy controls enrolled for evaluation. Extracted-DNA samples were amplified to obtain fragments including the polymorphic region SMUG1 rs3087404. We calculated relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S) to clarify possible interaction of different genotypes and CRP levels for AMD.

RESULTS: The distribution of the genotypes were not significantly different in the AMD patients compared to that of controls (p = 0.849). The allele frequency for SMUG1 was not different between study groups. No difference of SMUG1 polymorphism between case and control groups was evident in higher CRP levels (CRP>3mg/dl) compared with lower CRP levels. SMUG1/CRP synergy indices calculated as RERI = -0.12 and AP = -0.18 while S was not calculable.

CONCLUSIONS: Our study showed that c.-31A/G-SMUG1 genotypes/alleles do not have any association with the occurrence or severity of advanced type AMD. There was no interaction of CRP levels and SMUG1 genotypes in AMD susceptibility.

PMID: 28095127

Ophthalmic Genet. 2017 Jan 17:1-6. [Epub ahead of print]

Association of combined cigarette smoking and ARMS2/LOC387715 A69S polymorphisms with age-related macular degeneration: A meta-analysis.

Jabbarpoor Bonyadi MH, Yaseri M, Bonyadi M, Soheilian M, Nikkhah H.

PURPOSE: The age-related maculopathy susceptibility2 (ARMS2)/LOC387715 A69S (rs10490924) polymorphism and cigarette smoking have been shown to have significant association with AMD. In this meta-analysis we used the results of available association studies of combined ARMS2/LOC387715 genotypes and cigarette smoking with AMD to estimate the possible synergistic or multiplicative effects.

METHODS: Heterogeneity of studies was evaluated using the Cochran Q-test and the I-square index. To compensate for the heterogeneity of the variables in the study we used a random effects model. Meta-analysis was performed using STATA. To estimate the additive or supra-additive effects, we calculated relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), synergy index (S), and multiplicative index (V).

RESULTS: We could include four studies with 1982 AMD patients and 1797 control subjects. Considering the GG-no smoking as a reference line the meta-analysis result of AMD odds ratios for stratified combined factors was 3.05 (95% CI 2.32-4.02) for nonGG-no smoking, 2.24 (95% CI 1.39-3.63) for GG-smoking and 4.59 (95% CI 3.51-6.01) for nonGG-smoking. The meta-analysis of synergy analysis revealed RERI = 2.01 (95% CI 1.01-3.25), AP = 0.40 (95% CI 0.22-0.54), S = 2.02 (95% CI 1.35-3.01), and V = 1.31 (95% CI 0.94 -1.83).

CONCLUSION: This analysis revealed the synergistic effect of these two factors indicating that there is a common pathway of ARMS2/LOC387715 and smoking in AMD pathogenesis which may be the complement system pathway.

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Joint association of complement component 3 and CC-cytokine ligand2 (CCL2) or complement component 3 and CFH polymorphisms in age-related macular degeneration.

Bonyadi M, Jabbarpoor Bonyadi MH, Yaseri M, Mohammadian T, Fotouhi N, Javadzadeh A, Soheilian M.

BACKGROUND: To determine the joint effect of complement component 3(C3 R102G) with CC-cytokine ligand2 (CCL2-2518) or complement factor H (CFH) Y402H polymorphisms on advanced age-related macular degeneration (AMD).

METHODS: In this case-control study, 233 patients with advanced AMD and 159 unrelated healthy controls enrolled for evaluation. Selected polymorphisms were determined by polymerase chain reaction and

restriction fragment length polymorphism.

RESULTS: A combination of AA CCL2 (rs1024611) and GG C3 (R102G) genotypes resulted in a super-additivity of the risks: OR = 10.13, 95% CI 1.04-98.49, p = 0.04, adjusted OR = 7.74, 95% CI 0.71-84.75, p < 0.1, adjusted synergy indices: relative excess risk due to interaction (RERI) = 1.38, the attributable proportion due to interaction (AP) = 24.7% and the synergy index (S) = 1.43. Combination of at-risk genotypes of CFH Y402H and C3 R102G resulted in a strong super-additive risk: adjusted OR = 22.65, 95% CI 2.32-220.91, p = 0.007, adjusted AP = 90.4% and the S = 12.86. Attributable proportion of risk owing to C3-CCL2 and C3-CFH interaction calculated at 25% and 90% for advanced AMD.

CONCLUSION: We have previously shown a strong association of C3 (R102G) and CFH Y402H with AMD whereas no association was found for CCL2-2518. This study enclosed strong synergistic association of risk genotypes of C3 and CFH Y402H with AMD. We also revealed synergistic influence of CCL2-2518 and the at-risk genotype of the C3 in AMD with an estimated AP = 50.9% (adjusted AP = 24.7%). Present findings show that CCL2-2518 polymorphism is not an innocent bystander in AMD susceptibility when combined with the at-risk genotype of C3 (R102G).

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Associations between Rs4244285 and Rs762551 gene polymorphisms and age-related macular degeneration.

Stasiukonyte N, Liutkeviciene R, Vilkeviciute A, Banevicius M, Kriauciuniene L.

BACKGROUND: Age-related macular degeneration is the leading cause of blindness in elderly individuals in developed countries. The etiology and pathophysiology of age-related macular degeneration have not been elucidated yet. Knowing that the main pathological change of age-related macular degeneration is formation of drusen containing about 40% of lipids, there have been attempts to find associations between age-related macular degeneration and genes controlling lipid metabolism.

PURPOSE: To determine the frequency of CYP2C19 (G681A) Rs4244285 and CYP1A2 (-163C>A) Rs762551 genotypes in patients with age-related macular degeneration.

METHODS: The study enrolled 150 patients with early age-related macular degeneration and 296 age- and gender-matched healthy controls. The genotyping of Rs4244285 and Rs762551 was carried out by using the real-time polymerase chain reaction method.

RESULTS: The CYP1A2 (-163C>A) Rs762551 C/C genotype was more frequently detected in patients with age-related macular degeneration than in the control group (32.7% vs. 21.6%, p = 0.011) and was associated with an increased risk of developing early age-related macular degeneration (OR = 1.759, 95% CI: 1.133-2.729; p = 0.012). The CYP1A2 (-163C>A) Rs762551 C/A genotype was more frequently documented in the control group compared with patients with age-related macular degeneration (46.3% vs. 30.7%, p = 0.002) and was associated with a decreased risk of having age-related macular degeneration (OR = 0.580. 95% CI: 0.362-0.929, p = 0.023) in the co-dominant model.

CONCLUSION: The study showed that the CYP1A2 (-163C>A) Rs762551 C/C genotype was associated with an increased risk of age-related macular degeneration.

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Stem cells

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Characterization of tubular liquid crystal structure in embryonic stem cell derived embryoid bodies.

Xu M, Jones OD, Wang L, Zhou X, Davis HG, Bryant JL, Ma J, Isaacs WB, Xu X.

BACKGROUND: Massive liquid crystal droplets have been found during embryonic development in more than twenty different tissues and organs, including the liver, brain and kidney. Liquid crystal deposits have also been identified in multiple human pathologies, including vascular disease, liver dysfunction, age-related macular degeneration, and other chronic illnesses. Despite the involvement of liquid crystals in such a large number of human processes, this phenomenon is poorly understood and there are no in vitro systems to further examine the function of liquid crystals in biology.

RESULTS: We report the presence of tubular birefringent structures in embryoid bodies (EBs) differentiated in culture. These birefringent tubular structures initiate at the EB surface and penetrated the cortex at a variety of depths. Under crossed polarized light, these tubules are seen as a collection of birefringent Maltese crosses and tubules with birefringent walls and a non-birefringent lumen. The fluidity of these birefringent structures under pressure application led to elongation and widening, which was partially recoverable with pressure release. These birefringent structures also displayed heat triggered phase transition from liquid crystal to isotropic status that is partially recoverable with return to ambient temperature. These pressure and temperature triggered changes confirm the birefringent structures as liquid crystals. The first report of liquid crystal so early in development.

CONCLUSION: The structure of the liquid crystal tubule network we observed distributed throughout the differentiated embryoid bodies may function as a transportation network for nutrients and metabolic waste during EB growth, and act as a precursor to the vascular system. This observation not only reveals the involvement of liquid crystals earlier than previously known, but also provides a method for studying liquid crystals in vitro.

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Diet, lifestyle & low vision

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Experiences of patients undergoing repeated intravitreal anti-vascular endothelial growth factor injections for neovascular age-related macular degeneration.

Boyle J, Vukicevic M, Koklanis K, Itsiopoulos C, Rees G.

Abstract: Current therapy to slow disease progression in patients with neovascular age-related macular degeneration (AMD) entails regular intravitreal anti-vascular endothelial growth factor (VEGF) injections, often indefinitely. Little is known about the burden imposed on patients by this repetitive treatment schedule and how this can be best managed. The aim of this study was to explore the psychosocial impact of repeated intravitreal injections on patients with neovascular AMD. Forty patients (16 males, 24 females) with neovascular AMD undergoing anti-VEGF treatment were recruited using purposive sampling from a private ophthalmology practice and public hospital in Melbourne. Patients were surveyed using the Macular Disease Treatment Satisfaction Questionnaire (MacTSQ; Bradley, Health Psychology Research Unit, Surrey, England) and underwent semi-structured, one-on-one interviews. Interview topics were: treatment burden and satisfaction; tolerability; barriers to adherence; treatment motivation; and patient education. Interviews were audio recorded and thematic analysis performed using NVivo 10 (QSR International, Doncaster, Australia). Patients recognised the importance of treatment to preserve eyesight, yet experienced significant psychosocial and practical burden from the treatment schedule. Important issues included treatment-related anxiety, financial considerations and transport burden placed on relatives or carers. Many patients were restricted to sedentary activities post-injection owing to treatment side effects. Patients prioritised treatment, often sacrificing family, travel and social commitments owing to a fear of losing eyesight if treatment was not received. Whilst anti-VEGF injections represent the current mainstay of treatment for neovascular AMD, the ongoing treatment protocol imposes significant burden on patients. An

understanding of the factors that contribute to the burden of treatment may help inform strategies to lessen its impact and assist patients to better manage the challenges of treatment.

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Association of the Intestinal Microbiome with the Development of Neovascular Age-Related Macular Degeneration.

Zinkernagel MS, Zysset-Burri DC, Keller I, Berger LE, Leichtle AB, Largiadèr CR, Fiedler GM, Wolf S.

Abstract: Age-related macular degeneration (AMD) is the most frequent cause of blindness in the elderly. There is evidence that nutrition, inflammation and genetic risk factors play an important role in the development of AMD. Recent studies suggest that the composition of the intestinal microbiome is associated with metabolic diseases through modulation of inflammation and host metabolism. To investigate whether compositional and functional alterations of the intestinal microbiome are associated with AMD, we sequenced the gut metagenomes of patients with AMD and controls. The genera Anaerotruncus and Oscillibacter as well as Ruminococcus torques and Eubacterium ventriosum were relatively enriched in patients with AMD, whereas Bacteroides eggerthii was enriched in controls. Patient's intestinal microbiomes were enriched in genes of the L-alanine fermentation, glutamate degradation and arginine biosynthesis pathways and decreased in genes of the fatty acid elongation pathway. These findings suggest that modifications in the intestinal microbiome are associated with AMD, inferring that this common sight threatening disease may be targeted by microbiome-altering interventions.

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Smoking and Eye Pathologies. A systemic review. Part II. Retina diseases, uveitis, optic neuropathies, thyroid-associated orbitopathy.

Nita M, Grzybowski A.

BACKGROUND: Tobacco smoking has detrimental influence on human health.

AIM: The analysis of influence of tobacco smoking on retina diseases, uveitis, optic neuropathies, and thyroid-associated orbitopathy in adults and children.

METHODS: A comprehensive review of the literature performed through MEDLINE and PubMed searches, covering the years 2000-2016.

RESULTS: In adults, tobacco smoking is a strong risk factor for age-related macular degeneration, polypoidal choroidal vasculopathy, uveitis and inflamed cystoid macular edema as well as Grave`s ophthalmopathy. Tobacco smoking reduces thickness of the retina and choroid, plays a role in episcleritis, sclerits, tobacco optic neuropathy, and Leberamp#039;s hereditary optic neuropathy. In children, maternal smoking is a significant risk factor for stages 3 and 4 retinopathy of prematurity, optic nerve hypoplasia among babies with a birth weight over 2500 g and thinner retinal nerve fiber layer.

CONCLUSION: Tobacco smoking plays an important role in the pathogenesis of many posterior eye segment diseases leading to blindness in adults and children.

PMID: 28078992

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The Age-Related Eye Disease 2 Study: Micronutrients in the Treatment of Macular Degeneration.

Gorusupudi A, Nelson K, Bernstein PS.

Abstract: Age-related macular degeneration (AMD) is one of the leading causes of vision loss in the elderly. With an increasingly aged population worldwide, the need for the prevention of AMD is rising. Multiple studies investigating AMD with the use of animal models and cell culture have identified oxidative stress-related retinal damage as an important contributing factor. In general, diet is an excellent source of the antioxidants, vitamins, and minerals necessary for healthy living; moreover, the general public is often receptive to recommendations made by physicians and health care workers regarding diet and supplements as a means of empowering themselves to avoid common and worrisome ailments such as AMD, which has made epidemiologists and clinicians enthusiastic about dietary intervention studies. A wide variety of nutrients, such as minerals, vitamins, ω-3 (n-3) fatty acids, and various carotenoids, have been associated with reducing the risk of AMD. Initial results from the Age-Related Eye Disease Study (AREDS) indicated that supplementation with antioxidants (β-carotene and vitamins C and E) and zinc was associated with a reduced risk of AMD progression. The AREDS2 follow-up study, designed to improve upon the earlier formulation, tested the addition of lutein, zeaxanthin, and ω-3 fatty acids. In this review, we examine the science behind the nutritional factors included in these interventional studies and the reasons for considering their inclusion to lower the rate of AMD progression.

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Rehabilitation Approaches in Macular Degeneration Patients.

Maniglia M, Cottereau BR, Soler V, Trotter Y.

Abstract: Age related macular degeneration (AMD) is a visual disease that affects elderly population. It entails a progressive loss of central vision whose consequences are dramatic for the patient's quality of life. Current rehabilitation programs are restricted to technical aids based on visual devices. They only temporarily improve specific visual functions such as reading skills. Considering the rapid increase of the aging population worldwide, it is crucial to intensify clinical research on AMD in order to develop simple and efficient methods that improve the patient's visual performances in many different contexts. One very promising approach to face this challenge is based on perceptual learning (PL). Through intensive practice, PL can induce neural plasticity in sensory cortices and result in long-lasting enhancements for various perceptual tasks in both normal and visually impaired populations. A growing number of studies showed how appropriate PL protocols improve visual functions in visual disorders, namely amblyopia, presbyopia or myopia. In order to successfully apply these approaches to more severe conditions such as AMD, numerous challenges have to be overcome. Indeed, the overall elderly age of patients and the reduced cortical surface that is devoted to peripheral vision potentially limit neural plasticity in this population. In addition, ocular fixation becomes much less stable because patients have to rely on peripheral fixation spots outside the scotoma whose size keeps on evolving. The aim of this review article is to discuss the recent literature on this topic and to offer a unified approach for developing new rehabilitation programs of AMD using PL. We argue that with an appropriate experimental and training protocol that is adapted to each patient needs, PL can offer fascinating opportunities for the development of simple, non-expensive rehabilitation approaches a large spectrum of visual functions in AMD patients.

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