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MD Research News

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Drug Treatment

Int J Ophthalmol. 2016 Aug 18;9(8):1156-62. eCollection 2016.

Fixed bimonthly aflibercept in naïve and switched neovascular age-related macular degeneration patients: one year outcomes.

Warwick AN, Leaver HH, Lotery AJ, Goverdhan SV.

AIM: To determine real life clinical outcomes in poorly responsive and treatment-naïve neovascular age related macular degeneration (nvAMD) patients using bimonthly fixed dosing aflibercept regimen.

METHODS: This was a retrospective study of 165 eyes with nvAMD started on aflibercept at Southampton Eye Unit between June 2013 and June 2014. Patients were either switched from pro re nata (PRN) ranibizumab/bevacizumab due to poor response (107 eyes), or treatment-naïve (58 eyes). Patients initially received 3-monthly intravitreal aflibercept injections followed by 2-monthly fixed doses. Clinic visits were scheduled at month 0, 4, 10 and 12. Mean change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) from baseline were assessed using the Wilcoxon signed-rank test. The proportion of patients maintaining BCVA (<15 letters loss) at 12mo was also evaluated.

RESULTS: Mean BCVA change at month 12 was +3.29 and +4.67 letters in the switched and naïve aflibercept groups respectively (P<0.01). BCVA was maintained in 95.3% of switched and 96.6% of naïve patients. CRT at month 12 showed a decrease of -6.16 μm in the switched group and -35.36 μm in the naïve group (P<0.01). Patients previously treated with ranibizumab/bevacizumab had on average received 7.4 ranibizumab/bevacizumab injections over 12.6mo, attending 10 clinic visits. The fixed dosing aflibercept regimen required an average of 7.1 injections (naïve group), 7.5 injections (switched group) and 4 clinic visits per year.

CONCLUSION: Fixed bimonthly aflibercept is effective in both treatment-naïve and poorly responsive nvAMD patients. Adopting a fixed dosing regimen can reduce patient burden without compromising on outcomes.

PMID: 27588271

Digit J Ophthalmol. 2016 Jun 30;22(2):46-53. eCollection 2016.

Combined therapy (intravitreal bevacizumab plus verteporfin photodynamic therapy) versus intravitreal bevacizumab monotherapy for choroidal neovascularization due to age-related macular degeneration: a 1-year follow-up study.

Saviano S, Leon PE, Mangogna A, Tognetto D.

PURPOSE: To assess the efficacy and safety of combined intravitreal bevacizumab and low-fluency-rate photodynamic therapy (PDT) in the treatment of choroidal neovascularization (CNV) associated with age-related macular degeneration (AMD) and to compare it with intravitreal bevacizumab monotherapy.

METHODS: A total of 62 eyes of 62 patients with angiographic evidence of CNV were divided into 2 groups: the eyes of one group were treated with a combined therapy of 1 intravitreal bevacizumab injection (1.25 mg) and PDT within 7 days; the eyes of the other group received intravitreal bevacizumab monotherapy. Clinical evidence of complications, best-corrected visual acuity (BVCA) and fluorescein leakage were evaluated. Best-corrected visual acuity and optical coherence tomography (OCT) were tested monthly and followed for 12 months.

RESULTS: In the combined group the mean BCVA increased from 0.61 logMAR before the treatment to 0.54 logMAR at 12 months' follow-up. In the monotherapy group the mean BCVA increased from 0.65 logMAR to 0.60 logMAR at 12 months' follow-up. There was no significant difference in visual acuity outcomes between groups ($P > 0.05$). In the combined group the mean number of treatments was 1.19 per patient; in the monotherapy group, 5.31 per patient ($P < 0.01$).

CONCLUSIONS: Combined therapy appears to be an effective option for CNV associated with AMD treatment allowing a significant reduction of intravitreal injections.

PMID: 27582675

Retina. 2016 Aug 29. [Epub ahead of print]

ROLE OF ADDITIONAL DEXAMETHASONE FOR THE MANAGEMENT OF PERSISTENT OR RECURRENT NEOVASCULAR AGE-RELATED MACULAR DEGENERATION UNDER RANIBIZUMAB TREATMENT.

Rezar-Dreindl S, Eibenberger K, Buehl W, Georgopoulos M, Weigert G, Krall C, Dunavoelgyi R, Schmidt-Erfurth U, Sacu S.

PURPOSE: To assess the efficacy of a combination therapy of intravitreal ranibizumab together with a dexamethasone implant in comparison with ranibizumab monotherapy in neovascular age-related macular degeneration.

METHODS: Forty eyes of recurrent or persistent neovascular age-related macular degeneration were included in this prospective study. Patients were randomly assigned to two groups. Based on a pro re nata treatment regimen, the first group received intravitreal ranibizumab monotherapy (IVM). The second group received a combination of intravitreal dexamethasone implant and ranibizumab (intravitreal combination [IVC]) at baseline and was retreated with ranibizumab as needed. A second dexamethasone implant was allowed for retreatment after at least 6 months. Retreatment criteria included evidence of subretinal fluid, cystoid macular edema or new hemorrhage, and/or a visual acuity decrease of 5 Early Treatment Diabetic Retinopathy Study letters.

RESULTS: During 12 months, a mean of 7.95/5.5 (IVM/IVC; $P = 0.042$) retreatments were given. The median time until first retreatment differed significantly between the groups ($P = 0.004$). Functional variables could be maintained in both groups with no differences between them. Visual acuity changed from 62 letters at baseline to 67 at Month 12 in the IVM and remained stable at 68 letters in the IVC group ($P = 0.68$); macular sensitivity changed from 6.95 dB to 7.01 dB in IVM and from 7.24 dB to 7.12 dB in IVC ($P = 0.4$). Central retinal thickness decreased, however, with no difference between the groups ($P = 0.38$). In the IVM/IVC group, 11/12 (55/60%) patients were phakic at the time of study entry. One (9%) patient from the IVM and 4 (33%) from the IVC group were referred to cataract surgery after study completion ($P = 0.4$).

CONCLUSION: This pilot study indicates combined therapy to delay retreatment in patients with persistent/recurrent neovascular age-related macular degeneration and an overall reduction in required ranibizumab retreatments compared with ranibizumab monotherapy with consistent functional outcomes.

PMID: 27575409

Graefes Arch Clin Exp Ophthalmol. 2016 Aug 30. [Epub ahead of print]

Vision-related quality of life: 12-month aflibercept treatment in patients with treatment-resistant neovascular age-related macular degeneration.

Zhu M, Wijeyakumar W, Syed AR, Joachim N, Hong T, Broadhead GK, Li H, Luo K, Chang A.

PURPOSE: To assess changes in vision-related quality of life (VR-QoL) among patients with treatment-resistant neovascular age-related macular degeneration (nAMD) following intravitreal aflibercept treatment over 48 weeks.

METHODS: We conducted a prospective study in which 49 patients with nAMD resistant to anti-vascular endothelial growth factor therapy were switched to intravitreal aflibercept. Patients were treated with three loading doses every 4 weeks followed by injections every 8 weeks, for a total of 48 weeks. Ophthalmic examinations performed at each visit included best-corrected visual acuity (BCVA) and central macular thickness (CMT) measurement. The National Eye Institute Visual Functioning Questionnaire 25 (NEI VFQ-25) was used to assess VR-QoL at baseline and weeks 24 and 48. Changes in NEI VFQ-25 composite and subscale scores were analyzed using paired t tests. The relationship between the change in VR-QoL and changes in BCVA and CMT, and the impact of the better-seeing eye (BSE, defined as the eye reading the greater number of letters at baseline) vs. the worse-seeing eye (WSE, the fellow eye to the BSE) were assessed.

RESULTS: Mean NEI VFQ-25 composite scores improved significantly at weeks 24 and 48 compared to baseline (4.5 ± 9.2 and 4.4 ± 11.8, respectively, all $p < 0.01$). Among subscales, general vision and near and distance activities showed significant improvements at weeks 24 and 48 (all $p < 0.05$). Improvement in the NEI VFQ-25 composite score was significantly associated with increased BCVA at week 48 (β coefficient = 0.43, $p = 0.029$), but not with change in CMT (β coefficient = -0.007, $p = 0.631$). There was no association between VR-QoL changes and BSE or WSE.

CONCLUSION: Despite previous anti-VEGF treatment in this cohort, overall VR-QoL improved following aflibercept therapy over 48 weeks. This improvement was related to improved vision in treatment eyes regardless of whether they were the BSE or WSE.

PMID: 27572301

Am J Ophthalmol. 2016 Aug 24. [Epub ahead of print]

Baseline Choroidal Thickness as a Predictor for Treatment Outcomes in Central Retinal Vein Occlusion.

Rayess N, Rahimy E, Ying GS, Pefkianaki M, Franklin J, Regillo CD, Ho AC, Hsu J.

PURPOSE: To evaluate the association between initial subfoveal choroidal thickness and response to anti-vascular endothelial growth factor (anti-VEGF) therapy in central retinal vein occlusion (CRVO) eyes.

DESIGN: Retrospective cohort study.

METHODS: 43 eyes from 42 patients with treatment-naïve CRVO. All patients included were treated with a standard algorithm of 3 monthly anti-VEGF injections. Serial enhanced depth imaging optical coherence tomography scans were used to measure subfoveal choroidal thickness and central macular thickness (CMT). Baseline predictors (particularly choroidal thickness) for functional response (best-corrected visual acuity gain ≥2 lines) were assessed at 3 months follow-up using univariate and multivariate analyses.

RESULTS: 43 eyes from 42 patients were included. Initial choroidal thickness in CRVO eyes (246 ± 102 μm) was greater than their fellow eye (197 ± 86 μm; P=0.023). In addition, mean choroidal thickness at baseline for functional responders (272.2 ± 107.3 μm) was greater than non-responders (209.6 ± 85.8 μm; P=0.039). A higher baseline choroidal thickness (for every 100 μm increase in choroidal thickness) was found to be a positive predictor for functional response (regression coefficient: 0.7; P=0.04) on univariate

analysis, whereas age (< 70 years old) was the only positive predictor for functional response with an odds ratio of 6.49 (95% CI: 1.11-38.1; P=0.03) on multivariate regression analysis.

CONCLUSION: Baseline choroidal thickness and age may help predict which patients with CRVO have favorable visual outcomes following short-term anti-VEGF therapy.

PMID: 27567889

Other Treatment and Diagnosis

Br J Ophthalmol. 2016 Sep 1. [Epub ahead of print]

Choroidal thickness in non-neovascular versus neovascular age-related macular degeneration: a fellow eye comparative study.

Govetto A, Sarraf D, Figueroa MS, Pierro L, Ippolito M, Risser G, Bandello F, Hubschman JP.

PURPOSE: To investigate the possible differences in choroidal thickness (CT) between non-neovascular (NNV) and neovascular (NV) age-related macular degeneration (AMD).

METHODS: A retrospective, observational chart review of consecutive patients diagnosed with NNV AMD in one eye and with NV AMD in the fellow eye was carried out. NNV AMD was classified into four subgroups according to the Beckman Initiative for Macular Research AMD Classification Committee Meeting. CT was manually assessed using enhanced depth imaging optical coherence tomography from 1500 µm nasal to 1500 µm temporal to the fovea. Parametric and non-parametric tests were used to compare quantitative variables, a $\chi 2$ test was used to compare categorical variables and logistic regression was used to evaluate associations of CT with other variables of interest.

RESULTS: In this study, 322 eyes from 161 patients were included and 102 (63.35%) were female and 59 (36.65%) were male, with a mean age of 80.80±8.45 years (range 58-99 years). Mean follow-up was 11.2±10.8 months (range 1-38 months). In NNV AMD eyes, the choroid was significantly thicker in the subfoveal and temporal regions of the macula, if compared with NV AMD fellow eyes. Differences in CT between NNV AMD and NV AMD fellow eyes were higher at earlier stages of NNV AMD.

CONCLUSIONS: Subfoveal and temporal choroid was significantly thicker in NNV AMD compared with NV AMD fellow eyes. There was a significant choroidal thinning at advanced stages of NNV AMD.

PMID: 27587716

Retina. 2016 Aug 31. [Epub ahead of print]

EXPLORING PHOTORECEPTOR REFLECTIVITY THROUGH MULTIMODAL IMAGING OF OUTER RETINAL TUBULATION IN ADVANCED AGE-RELATED MACULAR DEGENERATION.

Litts KM, Wang X, Clark ME, Owsley C, Freund KB, Curcio CA, Zhang Y.

PURPOSE: To investigate the microscopic structure of outer retinal tubulation (ORT) and optical properties of cone photoreceptors in vivo, we studied ORT appearance by multimodal imaging, including spectral domain optical coherence tomography (SD-OCT) and adaptive optics scanning laser ophthalmoscopy.

METHODS: Four eyes of four subjects with advanced age-related macular degeneration underwent color fundus photography, infrared reflectance imaging, SD-OCT, and adaptive optics scanning laser ophthalmoscopy with a high-resolution research instrument. Outer retinal tubulation was identified in closely spaced (11 µm) SD-OCT volume scans.

RESULTS: Outer retinal tubulation in cross-sectional and en face SD-OCT was a hyporeflective area representing a lumen surrounded by a hyperreflective border consisting of cone photoreceptor mitochondria and external limiting membrane, per previous histology. In contrast, ORT by adaptive optics scanning laser ophthalmoscopy was a hyporeflective structure of the same shape as in en face SD-OCT but lacking visualizable cone photoreceptors.

CONCLUSION: Lack of ORT cone reflectivity by adaptive optics scanning laser ophthalmoscopy indicates that cones have lost their normal directionality and waveguiding property due to loss of outer segments and subsequent retinal remodeling. Reflective ORT cones by SD-OCT, in contrast, may depend partly on mitochondria as light scatterers within inner segments of these degenerating cells, a phenomenon enhanced by coherent imaging. Multimodal imaging of ORT provides insight into cone degeneration and reflectivity sources in optical coherence tomography.

PMID: 27584549

Graefes Arch Clin Exp Ophthalmol. 2016 Aug 31. [Epub ahead of print]

Long-term longitudinal modifications in mesopic microperimetry in early and intermediate age-related macular degeneration.

Vujosevic S, Pucci P, Casciano M, Longhin E, Convento E, Bini S, Midena E.

PURPOSE: To evaluate functional changes (retinal sensitivity and fixation characteristics) determined by microperimetry in patients with early and intermediate AMD over 6 years.

METHODS: Prospective, longitudinal follow-up (FU) study of 16 patients (29 eyes) with early and intermediate AMD (AREDS 2 and AREDS 3 classification). All eyes underwent: complete ophthalmic examination with best corrected visual acuity (BCVA) determination, color fundus photo (CFP), optical coherence tomography and microperimetry. All CFP were evaluated by two retinal specialists masked to functional data for changes in severity of clinical features over the course of FU.

RESULTS: Of 17 eyes graded as AREDS 2 at baseline, 14 (82.35 %) remained stable, and 3 (18.75 %) progressed to AREDS 3. Of 12 eyes graded as AREDS 3 at baseline, 10 remained stable (83.33 %), and 2 (16.67 %) progressed to AREDS 4. Mean BCVA significantly deteriorated in both AREDS 2 ($p = 0.006$) and AREDS 3 ($p = 0.016$), with greater decrease in AREDS 3 ($p = 0.01$)6. Mean retinal sensitivity (RS) significantly decreased over time in both AREDS 2 ($p < 0.0001$) and AREDS 3 group ($p = 0.002$), with greater decrease in AREDS 3 ($p = 0.006$). The mean number of dense scotomas did not change in AREDS 2 ($p = 0.3$), but significantly increased in the AREDS 3 group ($p = 0.035$). Points with decreased RS were located in all but the central point ($p < 0.0001$ for all), without significant differences in number among rings. In the AREDS 2 group, fixation stability remained unchanged. In the AREDS 3 group, four eyes deteriorated from stable to unstable fixation at FU ($p = 0.045$).

CONCLUSION: A significant deterioration in RS is reported in early and intermediate AMD eyes, whereas fixation stability changed only in intermediate AMD (AREDS 3) over long-term follow-up. Microperimetry examination can become a new functional biomarker in early and intermediate AMD patients.

PMID: 27582087

Pathogenesis

Mol Vis. 2016 Aug 12;22:1015-23. eCollection 2016.

Substance P promotes the recovery of oxidative stress-damaged retinal pigmented epithelial cells by modulating Akt/GSK-3β signaling.

Baek SM, Yu SY, Son Y, Hong HS.

PURPOSE: Senescence of the retina causes an accumulation of reactive oxygen species (ROS). Oxidative stress associated with ROS can damage RPE cells, leading to neovascularization and severe ocular disorders, including age-related macular degeneration (AMD). Thus, the early treatment of the damage caused by oxidative stress is critical for preventing the development of ocular diseases such as AMD. In this study, we examined the role of substance P (SP) in the recovery of RPE cells damaged by oxidative stress.

METHODS: To induce oxidative stress, RPE cells were treated with H2O2 at various doses. Recovery from oxidative stress was studied following treatment with SP by analyzing cell viability, cell proliferation, cell apoptosis, and Akt/glycogen synthase kinase (GSK)-3β activation in RPE cells in vitro.

RESULTS: H2O2 treatment reduced cellular viability in a dose-dependent manner. SP inhibited the reduction of cell viability due to H2O2 and caused increased cell proliferation and decreased cell apoptosis. Cell survival under oxidative stress requires the activation of Akt signaling that enables cells to resist oxidative stress-induced damage. SP treatment activated Akt/GSK-3β signaling in RPE cells, which were damaged due to oxidative stress, and the inhibition of Akt signaling in SP-treated RPE cells prevented SP-induced recovery. Pretreatment with the neurokinin 1 receptor (NK1R) antagonist reduced the recovery effect of SP on damaged RPE cells.

CONCLUSIONS: SP can protect RPE cells from oxidant-induced cell death by activating Akt/GSK-3β signaling via NK1R. This study suggests the possibility of SP as a treatment for oxidative stress-related diseases.

PMID: 27582624

Mitochondrion. 2016 Aug 28. [Epub ahead of print]

Immunolocalisation pattern of complex I-V in ageing human retina: Correlation with mitochondrial ultrastructure.

Chandra Nag T, Wadhwa S.

ABSTRACT: Earlier studies reported accumulation of mitochondrial DNA mutations in ageing and age-related macular degeneration. To know about the mitochondrial status with age, we examined immunoreactivity (IR) to markers of mitochondria (anti-mitochondrial antibody and voltage-dependent anion channel-1) and complex I-V (that mediate oxidative phosphorylation, OXPHOS) in donor human retinas (age: 19-94years; N=26; right eyes). In all samples, at all ages, IR to anti-mitochondrial antibody and voltage-dependent anion channel-1 was prominent in photoreceptor cells. Between second and seventh decade of life, strong IR to complex I-V was present in photoreceptors over macular to peripheral retina. With progressive ageing, the photoreceptors showed a decrease in complex I-IR (subunit NDUFB4) at eighth decade, and a weak or absence of IR in 10 retinas between ninth and tenth decade. Patchy IR to complex III and complex IV was detected at different ages. IR to ND1 (complex I) and complex II and V remained unaltered with ageing. Nitrosative stress (evaluated by IR to a nitro-tyrosine antibody) was found in photoreceptors. Superoxide dismutase-2 was found upregulated in photoreceptors with ageing. Mitochondrial ultrastructure was examined in two young retinas with intact complex IR and six aged retinas whose counterparts showed weak to absence of IR. Observations revealed irregular, photoreceptor inner segment mitochondria in aged maculae and mid-peripheral retina between eighth and ninth decade; many cones possessed autophagosomes with damaged mitochondria, indicating age-related alterations. A trend in age-dependent reduction of complex I-IR was evident in aged photoreceptors, whereas patchy complex IV-IR (subunits I and II) was age-independent, suggesting that the former is prone to damage with ageing perhaps due to oxidative stress. These changes in OXPHOS system may influence the energy budget of human photoreceptors, affecting their viability.

PMID: 27581213

Int J Biol Sci. 2016 Jul 18;12(9):1041-51. eCollection 2016.

Multiple Growth Factors, But Not VEGF, Stimulate Glycosaminoglycan Hyperelongation in Retinal Choroidal Endothelial Cells.

Al Gwairi O, Osman N, Getachew R, Zheng W, Liang XL, Kamato D, Thach L, Little PJ.

ABSTRACT: A major feature of early age-related macular degeneration (AMD) is the thickening of Bruch's membrane in the retina and an alteration in its composition with increased lipid deposition. In certain pathological conditions proteoglycans are responsible for lipid retention in tissues. Growth factors are known to increase the length of glycosaminoglycan chains and this can lead to a large increase in the interaction between proteoglycans and lipids. Using choroidal endothelial cells, we investigated the effects of a number of AMD relevant growth factors TGFβ, thrombin, PDGF, IGF and VEGF on proteoglycan synthesis. Cells were characterized as of endothelial origin using the specific cell markers endothelial nitric oxide synthesis and von Willebrand factor and imaged using confocal microscopy. Cells were treated with growth factors in the presence and absence of the appropriate inhibitors and were radiolabeled with [35S]-SO4. Proteoglycans were isolated by ion exchange chromatography and sized using SDS-PAGE. Radiosulfate incorporation was determined by the cetylpyridinium chloride (CPC) precipitation technique. To measure cellular glycosaminoglycan synthesizing capacity we added xyloside and assessed the xyloside-GAGs by SDS-PAGE. TGFβ, thrombin, PDGF & IGF dose-dependently stimulated radiosulfate incorporation and GAG elongation as well as xyloside-GAG synthesis, however VEGF treatment did not stimulate any changes in proteoglycan synthesis. VEGF did not increase pAKT but caused a large increase in pERK relative to the response to PDGF. Thus, AMD relevant agonists cause glycosaminoglycan hyperelongation of proteoglycans synthesised and secreted by retinal choroidal endothelial cells. The absence of a response to VEGF is intriguing and identifies proteoglycans as a novel potential target in AMD. Future studies will examine the relevance of these changes to enhanced lipid binding and the development of AMD.

PMID: 27570478

Cell Mol Life Sci. 2016 Aug 29. [Epub ahead of print]

Age-related macular degeneration, glaucoma and Alzheimer's disease: amyloidogenic diseases with the same glymphatic background?

Wostyn P, De Groot V, Van Dam D, Audenaert K, Killer HE, De Deyn PP.

PMID: 27572287

Genetics

Sci Rep. 2016 Aug 30;6:31531.

Mapping rare, deleterious mutations in Factor H: Association with early onset, drusen burden, and lower antigenic levels in familial AMD.

Wagner EK, Raychaudhuri S, Villalonga MB, Java A, Triebwasser MP, Daly MJ, Atkinson JP, Seddon JM.

ABSTRACT: The genetic architecture of age-related macular degeneration (AMD) involves numerous genetic variants, both common and rare, in the coding region of complement factor H (CFH). While these variants explain high disease burden in some families, they fail to explain the pathology in all. We selected families whose AMD was unexplained by known variants and performed whole exome sequencing to probe for other rare, highly penetrant variants. We identified four rare loss-of-function variants in CFH associated with AMD. Missense variant CFH 1:196646753 (C192F) segregated perfectly within a family characterized

by advanced AMD and drusen temporal to the macula. Two families, each comprising a pair of affected siblings with extensive extramacular drusen, carried essential splice site variant CFH 1:196648924 (IVS6+1G>A) or missense variant rs139360826 (R175P). In a fourth family, missense variant rs121913058 (R127H) was associated with AMD. Most carriers had early onset bilateral advanced AMD and extramacular drusen. Carriers tended to have low serum Factor H levels, especially carriers of the splice variant. One missense variant (R127H) has been previously shown not to be secreted. The two other missense variants were produced recombinantly: compared to wild type, one (R175P) had no functional activity and the other (C192F) had decreased secretion.

PMID: 27572114

BMC Genomics. 2016 Aug 30;17:695.

Genotype distribution-based inference of collective effects in genome-wide association studies: insights to age-related macular degeneration disease mechanism.

Woo HJ, Yu C, Kumar K, Gold B, Reifman J.

BACKGROUND: Genome-wide association studies provide important insights to the genetic component of disease risks. However, an existing challenge is how to incorporate collective effects of interactions beyond the level of independent single nucleotide polymorphism (SNP) tests. While methods considering each SNP pair separately have provided insights, a large portion of expected heritability may reside in higher-order interaction effects.

RESULTS: We describe an inference approach (discrete discriminant analysis; DDA) designed to probe collective interactions while treating both genotypes and phenotypes as random variables. The genotype distributions in case and control groups are modeled separately based on empirical allele frequency and covariance data, whose differences yield disease risk parameters. We compared pairwise tests and collective inference methods, the latter based both on DDA and logistic regression. Analyses using simulated data demonstrated that significantly higher sensitivity and specificity can be achieved with collective inference in comparison to pairwise tests, and with DDA in comparison to logistic regression. Using age-related macular degeneration (AMD) data, we demonstrated two possible applications of DDA. In the first application, a genome-wide SNP set is reduced into a small number (□100) of variants via filtering and SNP pairs with significant interactions are identified. We found that interactions between SNPs with highest AMD association were epigenetically active in the liver, adipocytes, and mesenchymal stem cells. In the other application, multiple groups of SNPs were formed from the genome-wide data and their relative strengths of association were compared using cross-validation. This analysis allowed us to discover novel collections of loci for which interactions between SNPs play significant roles in their disease association. In particular, we considered pathway-based groups of SNPs containing up to □10, 000 variants in each group. In addition to pathways related to complement activation, our collective inference pointed to pathway groups involved in phospholipid synthesis, oxidative stress, and apoptosis, consistent with the AMD pathogenesis mechanism where the dysfunction of retinal pigment epithelium cells plays central roles.

CONCLUSIONS: The simultaneous inference of collective interaction effects within a set of SNPs has the potential to reveal novel aspects of disease association.

PMID: 27576376

Stem Cells

Stem Cell Res Ther. 2016 Sep 2;7(1):127.

A strategy to ensure safety of stem cell-derived retinal pigment epithelium cells.

Choudhary P, Whiting PJ.

ABSTRACT: Cell replacement and regenerative therapy using embryonic stem cell-derived material holds promise for the treatment of several pathologies. However, the safety of this approach is of prime importance given the teratogenic potential of residual stem cells, if present in the differentiated cell product. Using the example of embryonic stem cell-derived retinal pigment epithelium (RPE) for the treatment of age -related macular degeneration, we present a novel strategy for ensuring the absence of stem cells in the RPE population. Based on an unbiased screening approach, we identify and validate the expression of CD59, a cell surface marker expressed on RPE but absent on stem cells. We further demonstrate that flow sorting on the basis of CD59 expression can effectively purify RPE and deplete stem cells, resulting in a population free from stem cell impurity. This purification helps to ensure removal of stem cells and hence increases the safety of cells that may be used for clinical transplantation. This strategy can potentially be applied to other pluripotent stem cell-derived material and help mitigate concerns of using such cells for therapy.

PMID: 27590276

Diet, Lifestyle and Low Vision

Br J Ophthalmol. 2016 Sep 1. [Epub ahead of print]

Pilot evaluation of short-term changes in macular pigment and retinal sensitivity in different phenotypes of early age-related macular degeneration after carotenoid supplementation.

Corvi F, Souied EH, Falfoul Y, Georges A, Jung C, Querques L, Querques G.

PURPOSE: To investigate the response of carotenoid supplementation in different phenotypes of early age -related macular degeneration (AMD) by measuring macular pigment optical density (MPOD) and retinal sensitivity.

METHODS: Consecutive patients with only medium/large drusen and only reticular pseudodrusen (RPD) and age-matched and sex-matched controls were enrolled. At baseline, participants underwent a complete ophthalmological examination including measurement of best-corrected visual acuity (BCVA), MPOD and retinal sensitivity. Patients were put on vitamin supplementation (lutein 10 mg/day, zeaxanthin 2 mg/day) and 3 months later underwent a repeated ophthalmological examination.

RESULTS: Twenty patients with medium/large drusen, 19 with RPD and 15 control subjects were included. At baseline, in controls, mean MPOD and BCVA were significantly higher compared with RPD (p=0.001 and p=0.01) but similar to medium/large drusen (p=0.9 and p=0.4). Mean retinal sensitivity was significantly higher in controls compared with RPD and medium/large drusen (for all p<0.0001). After 3 months of carotenoid supplementation the mean MPOD significantly increased in RPD (p=0.002), thus showing no more difference compared with controls (p=0.3); no significant changes were found in mean retinal sensitivity and BCVA (p=0.3 and p=0.7). Medium/large drusen did not show significant changes on MPOD, retinal sensitivity and BCVA (p=0.5, p=0.7 and p=0.7, respectively).

CONCLUSIONS: Patients with early AMD, especially RPD phenotype, show lower macular sensitivity and MPOD than controls. After supplementation, MPOD significantly increased in RPD. These results suggest different pathophysiology for RPD as compared with medium/large drusen and may open new ways to identifying further therapeutic targets in this phenotype of early AMD.

PMID: 27587715

Ophthalmology. 2016 Aug 25. [Epub ahead of print]

Distinguishing between Better and Worse Visual Acuity by Studying the Correlation with Quality of Life in Neovascular Age-Related Macular Degeneration.

Elshout M, van der Reis MI, de Jong-Hesse Y, Webers CA, Schouten JS.

PURPOSE: To determine whether there is a level of visual acuity (VA) in neovascular age-related macular degeneration (nAMD) above which the correlation of VA with disease-related quality of life (QoL) is significantly greater than below this level.

DESIGN: An observational, cross-sectional study.

PARTICIPANTS: A total of 184 patients with nAMD aged at least 50 years were included in the study.

METHODS: In face-to-face interviews, we assessed QoL with the Macular Disease-Dependent Quality of Life (MacDQoL) questionnaire. We measured VA with standardized Radner reading charts. We used regression splines analysis with a single hinge point, with the MacDQoL score as the dependent variable and VA as the independent variable. The x-coordinate (VA) of the hinge point was varied and tested with each iteration. A second method of regression splines analysis was also performed, without a preset hinge point.

MAIN OUTCOME MEASURES: The primary outcome measure is the cutoff point at or below which VA is associated with significantly less change in QoL than above this cutoff. The linear coefficients below and above the cutoff are defined as change in MacDQoL score per logarithm of the minimum angle of resolution (logMAR) unit of change in VA.

RESULTS: With Snellen equivalent VA 0.05 (1.3 logMAR) or worse, the linear coefficient was 0.15. With VA better than 0.05, the linear coefficient was 2.40 (P value of the difference: 0.009).

CONCLUSIONS: When VA is above 0.05, there is a stronger and significant relation between VA and QoL. At or below this level, the relation between VA and QoL approaches zero. With better VA, a difference in VA implies a significant difference in QoL. With poorer VA, a difference in VA is unlikely to imply a difference in QoL. Therefore, in treating nAMD, the aim should be to keep Snellen VA above 0.05 to have an impact on QoL. If it is certain that the best-corrected VA below 0.05 is permanent, these findings imply there may be less, if any, benefit to continue further treatment. This is to be evaluated on a case-by-case basis.

PMID: 27568997

Restor Neurol Neurosci. 2016 Aug 11. [Epub ahead of print]

Perceptual learning leads to long lasting visual improvement in patients with central vision loss.

Maniglia M, Pavan A, Sato G, Contemori G, Montemurro S, Battaglini L, Casco C.

BACKGROUND: Macular Degeneration (MD), a visual disease that produces central vision loss, is one of the main causes of visual disability in western countries. Patients with MD are forced to use a peripheral retinal locus (PRL) as a substitute of the fovea. However, the poor sensitivity of this region renders basic everyday tasks very hard for MD patients.

OBJECTIVE: We investigated whether perceptual learning (PL) with lateral masking in the PRL of MD patients, improved their residual visual functions.

METHOD: Observers were trained with two distinct contrast detection tasks: (i) a Yes/No task with no feedback (MD: N=3; controls: N=3), and (ii) a temporal two-alternative forced choice task with feedback on incorrect trials (i.e., temporal-2AFC; MD: N=4; controls: N=3). Observers had to detect a Gabor patch (target) flanked above and below by two high contrast patches (i.e., lateral masking). Stimulus presentation

was monocular with durations varying between 133 and 250 ms. Participants underwent 24- 27 training sessions in total.

RESULTS: Both PL procedures produced significant improvements in the trained task and learning transferred to visual acuity. Besides, the amount of transfer was greater for the temporal-2AFC task that induced a significant improvement of the contrast sensitivity for untrained spatial frequencies. Most importantly, follow-up tests on MD patients trained with the temporal-2AFC task showed that PL effects were retained between four and six months, suggesting long-term neural plasticity changes in the visual cortex.

CONCLUSION: The results show for the first time that PL with a lateral masking configuration has strong, non-invasive and long lasting rehabilitative potential to improve residual vision in the PRL of patients with central vision loss.

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