

Issue 313

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This free weekly bulletin lists the latest published research articles on macular degeneration (MD) and some other macular diseases as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases.

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Drug treatment

Klin Monbl Augenheilkd. 2017 Jan 23. [Epub ahead of print]

[Strategies of Intravitreal Injections with Anti-VEGF: "Pro re Nata versus Treat and Extend"]. [Article in German]

Hufendiek K, Pielen A, Framme C.

Abstract: The goal of this report is to provide a review on different strategies for the use of pro re nata (PRN) and treat and extend (T&E) regimens with intravitreal anti-VEGF agents (bevacizumab, ranibizumab or aflibercept) in patients with retinal diseases such as neovascular AMD, diabetic macular oedema and macular oedema due to retinal vein occlusion. The main focus is to present the effectiveness and visual outcomes of both PRN and T&E regimens in the main pivotal trials and studies based on currently available evidence. We also discuss the advantages and disadvantages of both regimens, as well as monitoring and treatment of the disease, including treatment intervals and injection frequency. Currently there is increasing interest in establishing a regimen which offers the best visual outcome with lower injection frequency, and with reduced treatment burden by individualising treatment intervals and minimising the number of clinic visits and costs. Studies have shown that the PRN regimens in a clinical setting are insufficient in assuring the best visual outcome. The PRN regime requires frequent clinic visits to monitor disease status and intravitreal treatment if needed in a reactive approach. Individualised T&E regimens can improve visual outcome and require fewer injections than those administered in a monthly regimen and fewer monitoring visits than those in a PRN regimen.

PMID: 28114697

Retina. 2017 Jan 26. [Epub ahead of print]

MACULAR CHOROIDAL VOLUME CHANGES AFTER INTRAVITREAL BEVACIZUMAB FOR EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

Palkovits S, Seidel G, Pertl L, Malle EM, Hausberger S, Makk J, Singer C, Osterholt J, Herzog SA, Haas A, Weger M.

PURPOSE: To evaluate the effect of intravitreal bevacizumab on the macular choroidal volume and the subfoveal choroidal thickness in treatment naïve eyes with exudative age-related macular degeneration.

METHODS: The macular choroidal volume and the subfoveal choroidal thickness were measured using enhanced depth imaging optical coherence tomography. After a screening examination, each patient received 3 monthly intravitreal injections of 1.25 mg bevacizumab. One month after the third injection was a final assessment.

RESULTS: Forty-seven patients with a mean age of 80 ± 6.4 years were included. The macular choroidal volume decreased significantly from median 4.1 mm (interquartile range 3.4-5.9) to median 3.9 mm

(interquartile range 3.1-5.6) between the baseline and final examination (difference -0.46 mm, 95% confidence interval: -0.57 to 0.35, $P < 0.001$). Similarly, subfoveal choroidal thickness had decreased from 157.0 μm (interquartile range 116.0-244.5) at baseline to 139.0 μm (interquartile range 102.5-212.0) at the final examination ($P < 0.001$). Both parameters macular choroidal volume at baseline and subfoveal choroidal thickness at baseline were not associated with the response to treatment.

CONCLUSION: The macular choroidal volume and the subfoveal choroidal thickness decreased significantly after 3 monthly bevacizumab injections for exudative age-related macular degeneration.

PMID: 28129216

Curr Eye Res. 2017 Jan 27;1-5. [Epub ahead of print]

Comparison of Intravitreal Bevacizumab, Intravitreal Ranibizumab and Laser Photocoagulation for Treatment of Type 1 Retinopathy of Prematurity in Turkish Preterm Children.

Kabataş EU, Kurtul BE, Altıaylık Özer P, Kabataş N.

PURPOSE: To evaluate effectiveness of treatment modalities, major complications and refractive errors in children who were treated with intravitreal bevacizumab (IVB), intravitreal ranibizumab (IVR) or laser photocoagulation (LP) for type 1 retinopathy of prematurity (ROP).

METHODS: Premature infants who underwent IVB monotherapy (Group 1), IVR monotherapy (Group 2) or LP (Group 3) for type 1 ROP and infants with spontaneously regressed ROP (Group 4) were included for the study. Major complications, recurrence rate, recurrence time, total retinal vascularization time and refractive errors at 18 months of corrected age (CA) were determined.

RESULTS: Groups 1, 2, 3 and 4 included 24 eyes of 12 patients, 12 eyes of six patients, 72 eyes of 36 patients and 148 eyes of 74 patients, respectively. Recurrence of the disease occurred in two eyes of one patient in Group 1 at 52 weeks of postmenstrual age (PMA) and two eyes of one patient at 48 weeks of PMA in Group 2. In Group 3, disease did not regress after the first treatment in 10 eyes of five patients. The mean vascularization time in Group 1 was 73 ± 10.1 weeks of PMA and 61.8 ± 6.6 weeks of PMA in Group 2 ($p = 0.027$). Macular ectopia was seen in two eyes of one patient and exudative retinal detachment (ERD) occurred in two eyes of one patient in Group 3. Mean spherical equivalent was 1.49 ± 3.04 diopters (D) in Group 1, -1.79 ± 2.87 D in Group 2, -1.27 ± 2.8 D in Group 3 and 1.52 ± 1.07 D in Group 4 at 18 months of CA. There was no significant difference in astigmatism values in all groups.

CONCLUSION: IVB, IVR and LP are options that can successfully treat ROP. Myopia was observed to be the main refractive error in all treatment groups. Vascularization of the retina was completed later in the IVB group than in the IVR group.

PMID: 28128986

Eye (Lond). 2017 Jan 27. [Epub ahead of print]

Surveillance of sight loss due to delay in ophthalmic treatment or review: frequency, cause and outcome.

Foot B, MacEwen C.

Purpose: To determine the frequency of patients suffering harm due to delay in ophthalmic care in the UK over a 12-month period.

Methods: Patients with deterioration in vision in at least one eye of 3 lines of Snellen acuity or 15 letters on ETDRS chart or deterioration in visual field deviation of 3 decibels due to health service initiated delay in review or care were ascertained through the BOSU using prospective active surveillance involving all UK

consultant ophthalmologists. Demographic details, diagnosis, cause and length of delay, and vision loss were then sought by questionnaire.

Results: 238 cases reported between March 2015 and February 2016. 197/238 questionnaires were returned (83%). Twenty-eight reports were out of the study period or did not meet the case definition. Median age was 76 years (range: 1 to 98 years). Median delay was 22 weeks (range: 2 days to 5½ years). Seventy two per cent experienced permanent reduction in visual acuity, 23% permanent deterioration in visual field. Main diagnoses were Glaucoma 42%, Age-related Macular Degeneration (AMD) 23%, and Diabetic Retinopathy (DR) 16%. Eighteen patients were eligible for Severely Sight Impaired (SSI) or Sight Impaired (SI) registration. Main causes were delayed follow-up (76%), lost referral (7%), and delayed treatment (8%).

Conclusion: Patients are suffering preventable harm due to health service initiated delay leading to permanently reduced vision. This is occurring in patients of all ages, but most consistently in those with chronic conditions. Delayed follow-up or review is the cause in the majority of cases indicating a lack of capacity within the hospital eye service.

PMID: 28128796

Br J Ophthalmol. 2017 Jan 24. [Epub ahead of print]

Intravitreal ziv-aflibercept for the treatment of choroidal neovascularisation associated with conditions other than age-related macular degeneration.

Braimah IZ, Stewart M, Videkar C, Dedhia CJ, Chhablani J; 'Ziv-aflibercept study group'.

AIM: To report the short-term outcomes of eyes with choroidal neovascularisation (CNV) associated with causes other than age-related macular degeneration (AMD) after treatment with intravitreal ziv-aflibercept (IVZ) injections.

METHODS: This retrospective study included eyes with non-AMD-related CNV that were treated with IVZ (1.25 mg/0.05 mL) on a pro re nata basis. The primary outcome measure is the mean change in best-corrected visual acuity (BCVA) and secondary outcome measures include the mean change in central macular thickness (CMT) and adverse events.

RESULTS: 23 eyes of 19 patients with CNV due to high myopia (9), macular telangiectasia (4), central serous chorioretinopathy (3), choroidal osteoma (2), choroiditis (2), Best's disease (2) and idiopathic (1) were treated. The mean follow-up period was 4±1.9 months. The median number of IVZ injections was 1 (range, 1-3) and the median treatment-free interval at the time of the final visit was 3 months (range, 1-8). The mean BCVA improved from 0.67 LogMAR to 0.58 LogMAR (p=0.0507). Nine of 23 (39%) eyes had BCVA gains of at least 0.1 LogMAR, 11 (48%) eyes had stable BCVA (within 0.1 LogMAR of baseline) and 3 (13%) eyes had a BCVA decline of at least 0.1 LogMAR at the final visit. The mean CMT improved significantly from baseline until the final visit (22 vs 174.5 µm; p=0.037). No ocular or systemic adverse events were noted.

CONCLUSIONS: IVZ improves CMT in patients with CNV associated with causes other than AMD, but improvements in BCVA are modest.

PMID: 28119292

Arch Soc Esp Oftalmol. 2017 Jan 19. [Epub ahead of print]

Cardiovascular involvement in patients with diabetic macular oedema treated with intravitreal ranibizumab in routine clinical practice. [Article in English, Spanish]

Díaz-Rodríguez R, Abreu-González R, Dolz-Marco R, Gallego-Pinazo R.

OBJECTIVE: To determine the cardiovascular events in naïve patients with diabetic macular oedema, before and after being treated with intravitreal ranibizumab.

MATERIAL AND METHODS: A retrospective and descriptive study was conducted on patients with diabetic macular oedema and foveal involvement, who started treatment with intravitreal ranibizumab in 2014 in the Hospital Universitario Nuestra Señora de Candelaria and the Hospital Universitario y Politécnico La Fe. During the follow-up until August 2015, a record was made of parameters, including the prevalence and incidence of stroke and myocardial infarction.

RESULTS: Among the 1,324 intravitreal ranibizumab injections administered in 2014, only 159 of them corresponded to treatment initiation in 99 patients, with more than half requiring treatment of both eyes. The study patients included 58.4% males, in the 6th decade of life (Mean=65.93±11.24 years), non-smokers (86.7%), type 2 diabetes (91.9%), hypertension (70.7%), and with dyslipidaemia (65.7%). Prior to treatment initiation, it was found that 6 patients (6.1%) suffered from an acute myocardial infarction, and 8 (8.1%) from stroke, and only one (1%) with post-stroke (P=.039).

CONCLUSION: In our experience it seems that the intravitreal ranibizumab in diabetic macular oedema could be a safe alternative in patients with a history of stroke and myocardial infarction.

PMID: 28110972

Clin Ophthalmol. 2017 Jan 6;11:161-177. eCollection 2017.

Switching to aflibercept among patients with treatment-resistant neovascular age-related macular degeneration: a systematic review with meta-analysis.

Spooner K, Hong T, Wijeyakumar W, Chang AA.

PURPOSE: To systematically review anatomical and functional outcomes subsequent to switching from bevacizumab/ranibizumab to aflibercept monotherapy in patients with treatment-resistant neovascular age-related macular degeneration (nAMD).

DESIGN: Systematic review and meta-analysis.

METHODS: Medline, PubMed, Embase, and Cochrane databases were searched up to July 2016 for available scientific literature which met inclusion criteria. Eligible studies reported visual and anatomical outcomes with at least 6 months of follow-up among patients with nAMD and persistent or resistant exudative fluid despite previous anti-vascular endothelial growth factor (VEGF) therapy (bevacizumab and/or ranibizumab) and were switched to aflibercept monotherapy. Mean changes in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were pooled using random-effects models with 95% confidence intervals (CIs).

RESULTS: Of 82 papers reviewed, 28 studies met inclusion criteria of this review. Pooled results showed a small mean improvement in BCVA at 6 and 12 months following switching (1.11 letters, 95% CI -0.25 to 2.46, P=0.17 and 0.63 letters, 95% CI -0.26 to 1.52, P=0.17, respectively). There was a significant improvement in mean CRT following switching (-61.90 µm, 95% CI -77.10 to -46.80, P<0.001 and -50.00 µm, 95% CI -63.20 to -36.80, P<0.001 at 6 and 12 months, respectively).

CONCLUSION: Pooled analysis demonstrated significantly improved anatomical outcomes; however, visual function remained stable, having a comparable effect to other anti-VEGF agents in preservation of vision. These patients had poorly responsive chronic disease with limited potential for visual recovery. Switching to aflibercept with frequent monitoring may be a suitable option for patients who have developed treatment resistance.

PMID: 28123287 PMCID: PMC5229260

Ophthalmology. 2017 Feb;124(2):e18-e19.

Re: Sharma et al.: Macular morphology and visual acuity in the second year of the comparison of age-related macular degeneration treatments trials (Ophthalmology 2016;123:865-875).

Uzun S, Pehlivan E.

PMID: 28126085

Other treatment & diagnosis

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

Imaging Protocols in Clinical Studies in Advanced Age-Related Macular Degeneration: Recommendations from Classification of Atrophy Consensus Meetings.

Holz FG, Sadda SR, Staurengi G, Lindner M, Bird AC, Blodi BA, Bottoni F, Chakravarthy U, Chew EY, Csaky K, Curcio CA, Danis R, Fleckenstein M, Freund KB, Grunwald J, Guymer R, Hoyng CB, Jaffe GJ, Liakopoulos S, Monés JM, Oishi A, Pauleikhoff D, Rosenfeld PJ, Sarraf D, Spaide RF, Tadayoni R, Tufail A, Wolf S, Schmitz-Valckenberg S; CAM group.

PURPOSE: To summarize the results of 2 consensus meetings (Classification of Atrophy Meeting [CAM]) on conventional and advanced imaging modalities used to detect and quantify atrophy due to late-stage non-neovascular and neovascular age-related macular degeneration (AMD) and to provide recommendations on the use of these modalities in natural history studies and interventional clinical trials.

DESIGN: Systematic debate on the relevance of distinct imaging modalities held in 2 consensus meetings.

PARTICIPANTS: A panel of retina specialists.

METHODS: During the CAM, a consortium of international experts evaluated the advantages and disadvantages of various imaging modalities on the basis of the collective analysis of a large series of clinical cases. A systematic discussion on the role of each modality in future studies in non-neovascular and neovascular AMD was held.

MAIN OUTCOME MEASURES: Advantages and disadvantages of current retinal imaging technologies and recommendations for their use in advanced AMD trials.

RESULTS: Imaging protocols to detect, quantify, and monitor progression of atrophy should include color fundus photography (CFP), confocal fundus autofluorescence (FAF), confocal near-infrared reflectance (NIR), and high-resolution optical coherence tomography volume scans. These images should be acquired at regular intervals throughout the study. In studies of non-neovascular AMD (without evident signs of active or regressed neovascularization [NV] at baseline), CFP may be sufficient at baseline and end-of-study visit. Fluorescein angiography (FA) may become necessary to evaluate for NV at any visit during the study. Indocyanine-green angiography (ICG-A) may be considered at baseline under certain conditions. For studies in patients with neovascular AMD, increased need for visualization of the vasculature must be taken into account. Accordingly, these studies should include FA (recommended at baseline and selected follow-up visits) and ICG-A under certain conditions.

CONCLUSIONS: A multimodal imaging approach is recommended in clinical studies for the optimal detection and measurement of atrophy and its associated features. Specific validation studies will be necessary to determine the best combination of imaging modalities, and these recommendations will need to be updated as new imaging technologies become available in the future.

PMID: 28109563

JAMA Ophthalmol. 2017 Jan 19. [Epub ahead of print]

The Potential Importance of Detection of Neovascular Age-Related Macular Degeneration When Visual Acuity Is Relatively Good.

Ho AC, Albin TA, Brown DM, Boyer DS, Regillo CD, Heier JS.

Abstract: The advent of anti-vascular endothelial growth factor treatment has changed the prognosis for patients with neovascular age-related macular degeneration (nvAMD). The ability to stabilize or improve vision with these treatments is a major step in enabling patients to continue to function at the highest possible level. Many studies have demonstrated that the better the visual acuity (VA) is at the time of treatment initiation, the higher the likelihood that VA will be better during at least the following 2 years; as such, detection of nvAMD when VA is relatively good is important. Data on the VA of patients with intermediate AMD and VA at the time of nvAMD diagnosis suggest that patients are typically losing an average of 3 to 5 lines of vision and possibly more between the time that intermediate AMD progresses to nvAMD and the diagnosis of nvAMD is made. The average patient may have nvAMD for 6 to 12 months before diagnosis and treatment initiation. Current efforts in management of nvAMD are primarily aimed at optimizing anti-vascular endothelial growth factor treatments that have the potential to improve VA outcomes by a magnitude of letters. Additional tools or other efforts to identify patients with nvAMD before substantial vision loss has occurred may reduce the amount of visual loss sustained with anti-vascular endothelial growth factor therapy, and have the potential to improve VA outcomes substantially.

PMID: 28114653

Acta Ophthalmol. 2017 Jan 30. [Epub ahead of print]

Identification and clinical role of choroidal neovascularization characteristics based on optical coherence tomography angiography.

Sulzbacher F, Pollreisz A, Kaider A, Kicking S, Sacu S, Schmidt-Erfurth U; Vienna Eye Study Center.

PURPOSE: To suggest a novel classification of neovascular age-related macular degeneration (AMD) based on optical coherence tomography angiography (OCTA) and to correlate morphological characteristics based on optical coherence tomography (OCT)/OCTA with clinical criteria of disease activity.

METHODS: A total of 88 eyes with neovascular AMD (14 treatment-naïve, 74 eyes following anti-vascular endothelial growth factor treatment (VEGF)) were examined using the AngioVue OCTA system (Optovue, Inc., Fremont, CA, USA) and evaluated based on vascular morphology. Choroidal neovascularization (CNV)-vessel morphology based on OCTA and associations with retinal layers were described and correlated with clinical markers of disease activity.

RESULTS: In treatment-naïve CNV, CNV-vessel morphology based on OCTA showed a dense-net configuration (DN) in 12 of 14 eyes, a loose-net configuration (LN) in one of 14 eyes and an unidentifiable CNV pattern in one of 14 eyes, whereas in treated CNV, DN was registered in 43.2% (32/74), LN in 27% (20/74), DN with additional LN (mixed type) in 14.9% (11/74) and an unidentifiable CNV pattern in 14.9% (11/74). Clinical correlations revealed a significantly longer disease duration for LN with a median value of 4.3 years compared to DN with 2.0 years ($p = 0.009$) and for CNV involving the outer retina with 3.1 years compared to CNV not involving the outer retina with 1.9 years ($p = 0.051$).

CONCLUSION:

Optical coherence tomography angiography (OCTA) allows identification of distinct CNV-specific vascular patterns at the level of the outer retinal layer and choriocapillaris. Correlation with clinical and functional parameters may be useful to better understand pathophysiological mechanisms and guide efficient therapeutic strategies.

PMID: 28133946

Sci Rep. 2017 Jan 27;7:41595.

An Ocular Protein Triad Can Classify Four Complex Retinal Diseases.

Kuiper JJ, Beretta L, Nierkens S, van Leeuwen R, Ten Dam-van Loon NH, Ossewaarde-van Norel J, Bartels MC, de Groot-Mijnen JD, Schellekens P, de Boer JH, Radstake TR.

Abstract: Retinal diseases generally are vision-threatening conditions that warrant appropriate clinical decision-making which currently solely depends upon extensive clinical screening by specialized ophthalmologists. In the era where molecular assessment has improved dramatically, we aimed at the identification of biomarkers in 175 ocular fluids to classify four archetypical ocular conditions affecting the retina (age-related macular degeneration, idiopathic non-infectious uveitis, primary vitreoretinal lymphoma, and rhegmatogenous retinal detachment) with one single test. Unsupervised clustering of ocular proteins revealed a classification strikingly similar to the clinical phenotypes of each disease group studied. We developed and independently validated a parsimonious model based merely on three proteins; interleukin (IL)-10, IL-21, and angiotensin converting enzyme (ACE) that could correctly classify patients with an overall accuracy, sensitivity and specificity of respectively, 86.7%, 79.4% and 92.5%. Here, we provide proof-of-concept for molecular profiling as a diagnostic aid for ophthalmologists in the care for patients with retinal conditions.

PMID: 28128370

PLoS One. 2017 Jan 23;12(1):e0170526. eCollection 2017.

Peripheral Reticular Pigmentary Degeneration and Choroidal Vascular Insufficiency, Studied by Ultra Wide-Field Fluorescein Angiography.

Bae K, Cho K, Kang SW, Kim SJ, Kim JM.

PURPOSE: To explore the pathogenesis of peripheral reticular pigmentary degeneration (PRPD) and its clinical significance.

METHODS: This cross-sectional, observational study (conducted between January 2010 and May 2015) enrolled 441 eyes of 229 subjects, including 35 eyes with PRPD and 406 eyes without PRPD, which was identified by ultra-wide-field fluorescein angiography (UWFA). The distribution and angiographic circulation time of PRPD were assessed by UWFA. The frequencies of systemic and ophthalmologic comorbidities were compared between groups. Univariate and multivariate generalized estimation equation methods were used to determine the risk factors for PRPD.

RESULTS: The patients with PRPD had a mean age of 75.7 ± 8.5 years (range, 59-93 years), whereas the patients without PRPD had a mean age of 60.1 ± 14.9 years (range, 9-92 years). All eyes with PRPD manifested the lesion in the superior nasal periphery with or without circumferential extension. Among those, only 16 eyes (45.7%) in the PRPD group showed distinctive features in the same location on fundus photographs. There was significant choroidal filling delay in the PRPD group when compared with the control group (1.42 ± 1.22 vs. -0.02 ± 1.05 seconds, $P < 0.001$). Multivariate regression analysis revealed that older age ($P < 0.001$), stroke ($P = 0.018$), ischemic optic neuropathy ($P < 0.001$), and age-related macular degeneration ($P = 0.022$) were significantly associated with PRPD.

CONCLUSIONS: UWFA may enhance the diagnostic sensitivity of PRPD. Choroidal vascular insufficiency with compromised systemic circulation in the elderly was related to the manifestation of PRPD. These results help to better understand the pathophysiology of PRPD. Co-existence of systemic and ophthalmic circulatory disorders should be considered in patients with PRPD.

PMID: 28114409

Vestn Oftalmol. 2016;132(6):78-86.

[Macular drusen variability: multimodal imaging potential]. [Article in Russian;]

Semenova NS, Akopyan VS, Rodin AS.

Abstract: Insufficient knowledge of macular drusen (MD), the absence of a pathogenetically reasoned treatment, and strong correlation with age-related macular degeneration (AMD) progression make MD an important area of research.

AIM: To define clinical features of MD provided by modern imaging techniques.

MATERIAL AND METHODS: The study included patients with hard or soft drusen observed at ophthalmoscopy. All patients underwent fluorescein angiography, swept-source optical coherence tomography (OCT), OCT angiography, autofluorescence examination (both short-wave and near infrared), and scanning laser ophthalmoscopy in Multicolor mode. The retina, choroid and vitreoretinal interface were assessed in 50 patients with AMD and drusen. Another group consisted of 5 patients with geographic atrophy (GA) that resulted from soft drusen regression. In this second group we performed retrospective analysis of OCT scans paying special attention to signs of soft drusen transition to retinal pigment epithelium atrophy.

RESULTS: Two types of hard drusen were defined: cuticular drusen and reticular pseudodrusen. Their appearances (as well as soft drusen appearance) in different imaging modalities were comparatively analyzed. Evaluation of vitreoretinal interfaces revealed the high prevalence of vitreomacular adhesion in patients with mixed reticular and cuticular drusen. Choroidal thickness measurements in 9 macular sectors showed no significant difference between the study and control groups. All medical records of patients with regressed drusen appeared to contain OCT signs of "nascent" GA.

CONCLUSION: The study has demonstrated the potential of modern diagnostic techniques for distinguishing between different types of macular drusen. Prognostic value of the features revealed is to be further investigated.

PMID: 28121303

Graefes Arch Clin Exp Ophthalmol. 2017 Jan 27. [Epub ahead of print]

Inner retinal layer change in glaucoma patients receiving anti-VEGF for neovascular age related macular degeneration.

Saleh R, Karpe A, Zinkernagel MS, Munk MR.

PURPOSE: The purpose was to evaluate the effects of long-term anti-VEGF treatment on the retinal nerve fiber layer (RNFL) and retinal ganglion cell layer (RGCL) thickness for patients with neovascular AMD and glaucoma.

METHODS: Medical records of respective patients who had received more than 15 anti-VEGF injections were reviewed. Initial and latest SD-OCT macular scans were segmented and changes of the RNFL and RGCL thickness at the four outer ETDRS quadrants were evaluated. Secondary outcome measures included changes of visual field parameters seen in automated perimetry.

RESULTS: Sixteen patients were included (mean age 78 ± 6 years). The mean total number of anti-VEGF injections was 39 ± 16 . The mean treatment duration was 6.1 ± 2.1 years. The mean IOP decreased from 18 ± 5 mmHg at baseline to 15 ± 5 mmHg at the last visit ($p = 0.026$). The mean RNFL thickness volume of the outer ETDRS quadrants (0.98 ± 0.18 mm³ to 0.97 ± 0.18 mm³ $p = 0.61$) and its average thickness (37.9 ± 7.3 μ m to 37.2 ± 7.4 μ m, $p = 0.6$) did not significantly change. However, the average RGCL thickness decreased significantly from 0.86 ± 0.12 mm³ to 0.79 ± 0.11 mm³ ($p = 0.01$), and from 27.7 ± 4.2 to 25.9 ± 3.7 μ m ($p = 0.01$). Number of injections correlated with the RGCL change ($r^2 = 0.36$, $p = 0.01$). The mean sensitivity, mean defect and absolute scotomata did not significantly change with p-values of 0.28, 0.21 and

0.07, respectively.

CONCLUSION: Patients under long term treatment with anti-VEGF and concurrent glaucoma show significant decrease in macular RGLC volume. However, this decrease is comparable to reported RGCL decrease in patients under anti-VEGF treatment without underlying glaucoma and suggests that glaucoma patients may not be at a higher risk for losing macular RNFL and RGCL, at least if adequate control of intraocular pressure is maintained.

PMID: 28127658

Invest Ophthalmol Vis Sci. 2017 Jan 1;58(1):292-298.

Intraocular Vascular Endothelial Growth Factor Levels in Pachychoroid Neovascularopathy and Neovascular Age-Related Macular Degeneration.

Hata M, Yamashiro K, Ooto S, Oishi A, Tamura H, Miyata M, Ueda-Arakawa N, Takahashi A, Tsujikawa A, Yoshimura N.

PURPOSE: To investigate the difference in intraocular vascular endothelial growth factor (VEGF) concentration between pachychoroid neovascularopathy and neovascular age-related macular degeneration (nAMD) and its associations with responses to three monthly anti-VEGF injections as an initial treatment for the two conditions.

METHODS: This study included nine eyes with treatment-naïve pachychoroid neovascularopathy and 21 eyes with treatment-naïve nAMD. Before the initial intravitreal anti-VEGF injection, aqueous humor samples were collected and the concentration of VEGF was measured using enzyme-linked immunosorbent assay. The concentration was compared between the two conditions, and its associations with responses to anti-VEGF therapy were investigated.

RESULTS: The mean VEGF concentration in pachychoroid neovascularopathy was significantly lower than that in nAMD (63.4 ± 17.8 pg/ml and 89.8 ± 45.0 pg/ml, respectively; $P = 0.035$). The VEGF concentration was associated with the presence or absence of drusen ($\beta = 0.503$, $P = 0.004$). After anti-VEGF therapy, 6 (66.7%) of 9 eyes with pachychoroid neovascularopathy and 17 (81.0%) of 21 eyes with nAMD achieved dry macula ($P = 0.640$). Dry macula at 3 months and 12 months was significantly associated with a low VEGF concentration in pachychoroid neovascularopathy ($P = 0.013$ and $P = 0.042$, respectively), but not in nAMD ($P = 0.108$ and $P = 0.219$).

CONCLUSIONS: The mean VEGF concentration in pachychoroid neovascularopathy was lower than that in nAMD, suggesting that the way in which VEGF is involved in angiogenesis may differ between pachychoroid neovascularopathy and nAMD.

PMID: 28114590

Prog Retin Eye Res. 2017 Jan 18. [Epub ahead of print]

Retinal oxygen: From animals to humans.

Linsenmeier RA, Zhang HF.

Abstract: This article discusses retinal oxygenation and retinal metabolism by focusing on measurements made with two of the principal methods used to study O₂ in the retina: measurements of PO₂ with oxygen-sensitive microelectrodes in vivo in animals with a retinal circulation similar to that of humans, and oximetry, which can be used non-invasively in both animals and humans to measure O₂ concentration in retinal vessels. Microelectrodes uniquely have high spatial resolution, allowing the mapping of PO₂ in detail, and when combined with mathematical models of diffusion and consumption, they provide information about retinal metabolism. Mathematical models, grounded in experiments, can also be used to simulate situations

that are not amenable to experimental study. New methods of oximetry, particularly photoacoustic ophthalmoscopy and visible light optical coherence tomography, provide depth-resolved methods that can separate signals from blood vessels and surrounding tissues, and can be combined with blood flow measures to determine metabolic rate. We discuss the effects on retinal oxygenation of illumination, hypoxia and hyperoxia, and describe retinal oxygenation in diabetes, retinal detachment, arterial occlusion, and macular degeneration. We explain how the metabolic measurements obtained from microelectrodes and imaging are different, and how they need to be brought together in the future. Finally, we argue for revisiting the clinical use of hyperoxia in ophthalmology, particularly in retinal arterial occlusions and retinal detachment, based on animal research and diffusion theory.

PMID: 28109737

Ophthalmology. 2017 Feb;124(2):e19-e20.

Re: Zarubina et al.: Prevalence of subretinal drusenoid deposits in older persons with and without age-related macular degeneration, by multimodal imaging (Ophthalmology 2016;123:1090-1100).

Mathis T, De Bats F, Mauget-Faÿsse M, Denis P, Kodjikian L.

PMID: 28126086

Pathogenesis

Sci Rep. 2017 Jan 30;7:41533.

Contributions of age-related alterations of the retinal pigment epithelium and of glia to the AMD-like pathology in OXYS rats.

Telegina DV, Kozhevnikova OS, Bayborodin SI, Kolosova NG.

Abstract: Age-related macular degeneration (AMD) is a major cause of blindness in developed countries, and the molecular pathogenesis of early events of AMD is poorly understood. It is known that age-related alterations of retinal pigment epithelium (RPE) cells and of glial reactivity are early hallmarks of AMD. Here we evaluated contributions of the age-related alterations of the RPE and of glia to the development of AMD-like retinopathy in OXYS rats. We showed that destructive alterations in RPE cells are a primary change during the development of retinopathy in OXYS rats. Furthermore, a defect of retinal maturation and decreased immune function at the preclinical stage of retinopathy were observed in OXYS rats in addition to the impairment of RPE cell proliferation and of their capacity for division. At the active stage of the disease, the atrophic alterations increased, and reactive gliosis was observed when disease progressed, but immune function stayed weakened. Unexpectedly, we did not observe migration of microglia and macrophages into the photoreceptor layer. These results and the wide spectrum of age-related retinal alterations in humans as well as individual differences in the risk of AMD may be attributed to genetic factors and to differences in the underlying molecular events.

PMID: 28134357

J Mol Med (Berl). 2017 Jan 28. [Epub ahead of print]

Targeting the tight junction protein, zonula occludens-1, with the connexin43 mimetic peptide, α CT1, reduces VEGF-dependent RPE pathophysiology.

Obert E, Strauss R, Brandon C, Grek C, Ghatnekar G, Gourdie R, Rohrer B.

Abstract: A critical target tissue in age-related macular degeneration (AMD) is the retinal pigment epithelium

(RPE), which forms the outer blood-retina barrier (BRB). RPE-barrier dysfunction might result from attenuation/disruption of intercellular tight junctions. Zonula occludens-1 (ZO-1) is a major structural protein of intercellular junctions. A connexin43-based peptide mimetic, α CT1, was developed to competitively block interactions at the PDZ2 domain of ZO-1, thereby inhibiting ligands that selectively bind to this domain. We hypothesized that targeting ZO-1 signaling using α CT1 would maintain BRB integrity and reduce RPE pathophysiology by stabilizing gap- and/or tight-junctions. RPE-cell barrier dysfunction was generated in mice using laser photocoagulation triggering choroidal neovascularization (CNV) or bright light exposure leading to morphological damage. α CT1 was delivered via eye drops. α CT1 treatment reduced CNV development and fluid leakage as determined by optical coherence tomography, and damage was correlated with disruption in cellular integrity of surrounding RPE cells. Light damage significantly disrupted RPE cell morphology as determined by ZO-1 and occludin staining and tiling pattern analysis, which was prevented by α CT1 pre-treatment. In vitro experiments using RPE and MDCK monolayers indicated that α CT1 stabilizes tight junctions, independent of its effects on Cx43. Taken together, stabilization of intercellular junctions by α CT1 was effective in ameliorating RPE dysfunction in models of AMD-like pathology.

KEY MESSAGE:

The connexin43 mimetic α CT1 accumulates in the mouse retinal pigment epithelium following topical delivery via eye drops. α CT1 eye drops prevented RPE-cell barrier dysfunction in two mouse models. α CT1 stabilizes intercellular tight junctions. Stabilization of cellular junctions via α CT1 may serve as a novel therapeutic approach for both wet and dry age-related macular degeneration.

PMID: 28132078

Neurobiol Aging. 2017 Jan 10;52:66-70. [Epub ahead of print]

Aging retinal function is improved by near infrared light (670 nm) that is associated with corrected mitochondrial decline.

Sivapathasuntharam C, Sivaprasad S, Hogg C, Jeffery G.

Abstract: Aging is associated with cellular decline and reduced function, partly mediated by mitochondrial compromise. However, aged mitochondrial function is corrected with near infrared light (670 nm) that improves their membrane potentials and adenosine triphosphate production and also reduces age-related inflammation. We ask if 670 nm light can also improve declining retinal function. Electroretinograms were measured in 2-, 7-, and 12-month old C57BL/6 mice. Significant age-related declines were measured in the photoreceptor generated a-wave and the postreceptor b-wave. Seven- and 12-month-old mice were exposed to 670 nm for 15 minutes daily over 1 month. These showed significant improved retinal function in both waves of approximately 25% but did not reach levels found in 2-month-old animals. Our data suggest, 670 nm light can significantly improve aged retinal function, perhaps by providing additional adenosine triphosphate production for photoreceptor ion pumps or reduced aged inflammation. This may have implications for the treatment of retinal aging and age-related retinal disease, such as macular degeneration.

PMID: 28129566

J Biomed Res. 2017 Jan 19. [Epub ahead of print]

Insensitivity of PI3K/Akt/GSK3 signaling in peripheral blood mononuclear cells of age-related macular degeneration patients.

Xunxian L, Zemin Y.

Abstract: Our recent studies with cultured retinal pigment epithelium cells suggested that overexpression of interleukin 17 receptor C (IL-17RC), a phenomenon observed in peripheral blood and chorioretinal tissues

with age-related macular degeneration (AMD), was associated with altered activation of phosphatidylinositol 3-kinase (PI3K), Akt, and glycogen synthase kinase 3 (GSK3). We wondered whether or not altered PI3K, Akt, and GSK3 activities could be detected in peripheral blood mononuclear cells (PBMC) obtained from AMD patients. In the patients' PBMC, absent or reduced serine-phosphorylation of GSK3 α or GSK3 β was observed, which was accompanied with increased phosphorylation of GSK3 substrates (e.g. CCAAT enhancer binding protein α , insulin receptor substrate 1, and TAU), indicative of enhanced GSK3 activation. In addition, decreased protein mass of PI3K85 α and tyrosine-phosphorylation of PI3K50 α was present in PBMC of the AMD patients, suggesting impaired PI3K activation. Moreover, abnormally lowered molecular weight forms of Akt and GSK3 were detected in PBMC of the AMD patients. These data demonstrate that despite the presence of high levels of IL-17RC, Wnt-3a and vascular endothelial growth factor, the PI3K/Akt/GSK3 signaling pathway is insensitive to these stimuli in PBMC of the AMD patients. Thus, measurement of PI3K/Akt/GSK3 expression and activity in PBMC may serve as a surrogate biomarker for AMD.

PMID: 28110316

Invest Ophthalmol Vis Sci. 2017 Jan 1;58(1):162-167.

HTRA1 and TGF- β 1 Concentrations in the Aqueous Humor of Patients With Neovascular Age-Related Macular Degeneration.

Tosi GM, Caldi E, Neri G, Nuti E, Marigliani D, Baiocchi S, Traversi C, Cevenini G, Tarantello A, Fusco F, Nardi F, Orlandini M, Galvagni F.

PURPOSE: The purpose of this study was to evaluate the expression of high-temperature requirement A serine peptidase 1 (HTRA1), TGF- β 1, bone morphogenetic protein 4 (BMP4), growth differentiation factor 6 (GDF6), and VEGFA proteins in the aqueous humor of patients with naïve choroidal neovascularization (nCNV) secondary to AMD.

METHODS: We measured by ELISA the concentrations of HTRA1, TGF- β 1, BMP4, GDF6, and VEGFA in the aqueous humor of 23 patients affected by nCNV who received three consecutive monthly intravitreal injections of 0.5 mg ranibizumab. Samples were collected at baseline (before the first injection), month 1 (before the second injection), and month 2 (before the third injection). Twenty-three age-matched cataract patients served as controls.

RESULTS: Bone morphogenetic protein 4 and GDF6 were not detectable in any samples. Baseline HTRA1 was higher than controls ($P < 0.0001$) and higher than both the month 1 ($P < 0.0001$) and the month 2 ($P < 0.0001$) values. Baseline VEGFA was higher than controls ($P < 0.0001$), not different from month 1 value ($P = 0.0821$), but higher than month 2 value ($P < 0.0001$). Baseline TGF- β 1 was higher than controls ($P = 0.0015$) and not different from month 1 ($P = 0.129$) and month 2 values ($P = 0.5529$). No correlation was found in naïve patients between concentrations of HTRA1 and TGF- β 1, HTRA 1 and VEGFA, or TGF- β 1 and VEGFA.

CONCLUSIONS: In nCNV patients, HTRA1 and TGF- β 1 were significantly higher compared to controls. After treatment, TGF- β 1 was persistently elevated, while HTRA1 returned to control levels, suggesting the involvement of TGF- β 1 and HTRA1 in neovascular AMD and a VEGFA-independent role for TGF- β 1.

PMID: 28114575

Eye (Lond). 2017 Jan 27. [Epub ahead of print]

Local complement activation in aqueous humor in patients with age-related macular degeneration.

Schick T, Steinhauer M, Aslanidis A, Altay L, Karlstetter M, Langmann T, Kirschfink M, Fauser S.

Purpose: To investigate complement activation in aqueous humor and in plasma of patients with

neovascular age-related macular degeneration (nAMD).

Patients and methods: Aqueous humor and EDTA-plasma of 31 nAMD patients and 30 age-matched controls was collected. The levels of the complement factor 3 (C3), the regulators factor H (FH), and factor I (FI), and of the complement activation products Ba, C3a, and the terminal complement complex (sC5b-9) were measured. Associations between complement levels and phenotype were determined using Mann-Whitney U-test.

Results: In plasma, no significant differences were found between the nAMD group and the control group. In aqueous humor, significantly increased levels of Ba ($P=0.002$), and C3a ($P=0.002$) indicate local complement activation in nAMD patients and a trend for a concomitant upregulation of the complement regulators FH ($P=0.02$) and FI ($P=0.04$).

Conclusions: Our findings provide strong evidence for a local complement dysregulation in nAMD patients.

PMID: 28128795

J Biol Chem. 2017 Jan 23. [Epub ahead of print]

Cellular uptake and delivery of Myeloperoxidase to lysosomes promotes lipofuscin degradation and lysosomal stress in retinal cells.

Yogalingam G, Lee AR, Mackenzie DS, Maures TJ, Rafalko A, Prill H, Berguig G, Hague C, Christianson T, Bell SM, LeBowitz JH.

Abstract: Neutrophil myeloperoxidase (MPO) catalyzes the H_2O_2 -dependent oxidation of chloride anion to generate hypochlorous acid, a potent antimicrobial agent. Besides its well defined role in innate immunity, aberrant degranulation of neutrophils in several inflammatory diseases leads to redistribution of MPO to the extracellular space, where it can mediate tissue damage by promoting the oxidation of several additional substrates. Here, we demonstrate that mannose-6-phosphate (M6P) receptor-mediated cellular uptake and delivery of MPO to lysosomes of retinal pigmented epithelial (RPE) cells acts to clear this harmful enzyme from the extracellular space, with lysosomal-delivered MPO exhibiting a half-life of 10 hours. Lysosomal-targeted MPO exerts both cell-protective and cytotoxic functions. From a therapeutic standpoint, MPO catalyzes the in vitro degradation of N-retinylidene-N-retinylethanolamine (A2E), a toxic form of retinal lipofuscin that accumulates in RPE lysosomes and drives the pathogenesis of Stargardt macular degeneration (SD). Furthermore, chronic cellular uptake and accumulation of MPO in lysosomes coincides with A2E elimination in a cell-based model of macular degeneration. However, lysosomal-delivered MPO also disrupts lysosomal acidification in RPE cells, which coincides with nuclear translocation of the lysosomal stress-sensing transcription factor EB (TFEB) and eventually, cell death. Based on these findings we predict that under periods of acute exposure, cellular uptake and lysosomal degradation of MPO mediates elimination of this harmful enzyme, whereas chronic exposure results in progressive accumulation of MPO in lysosomes. Lysosomal-accumulated MPO can be both cell-protective, by promoting the degradation of toxic retinal lipofuscin deposits and cytotoxic, by triggering lysosomal stress and cell death.

PMID: 28115520

Epidemiology

Sci Rep. 2017 Jan 25;7:41386.

Systemic, Ocular and Genetic Risk Factors for Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy in Singaporeans.

Cheung CM, Laude A, Yeo I, Tan SP, Fan Q, Mathur R, Lee SY, Chan CM, Tan G, Lim TH, Cheng CY, Wong TY.

Abstract: To examine the association of systemic, ocular and genetic risk factors in neovascular age-related macular degeneration (nAMD) in a large cohort of Asian patients, and to further compare risk factors between those with typical AMD and polypoidal choroidal vasculopathy (PCV) subtypes. We recruited 456 cases and 1,824 controls matched for age, gender and ethnicity. Data on systemic and ocular risk factors were collected on questionnaires. In a subgroup of subjects, we included genetic data on four AMD-associated single nucleotide polymorphisms (SNPs). Risk factors for nAMD and subtypes were analyzed. Systemic risk factors for nAMD included older age, male gender, higher BMI and higher HDL-cholesterol. Ocular risk factors included pseudophakic and shorter axial length. Risk factors common to both typical AMD and PCV subtypes included age, BMI and HDL-cholesterol. Shorter axial length was only associated with PCV, while male gender and pseudophakia were only associated with typical AMD. In the subgroup with genotype data, ARMS2 rs10490924 and CFH rs800292 were associated with nAMD. None of the risk factors were significantly different between PCV and typical AMD. Systemic, ocular and genetic risk factors were largely similar for typical AMD and PCV subtypes in this Asian population based in Singapore.

PMID: 28120909 PMCID: PMC5264642

Retina. 2017 Jan 19. [Epub ahead of print]

RISK FACTORS AND CLINICAL SIGNIFICANCE OF PRECHOROIDAL CLEFT IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Kim JM, Kang SW, Son DY, Bae K.

PURPOSE: To investigate the risk factors associated with prechioroidal cleft occurrence after treatment for neovascular age-related macular degeneration (nAMD) and to elucidate its clinical significance.

METHODS: Two hundred thirty-four subjects who were treated for neovascular age-related macular degeneration were assessed to identify prechioroidal cleft on optical coherence tomography. Clinical variables were compared between patients manifesting a cleft (cleft group) and patients who did not (control group).

RESULTS: Prechioroidal cleft was detected in 29 of 234 patients (8.1%). Although the baseline visual acuity was not different between the 2 groups, logMAR visual acuity at final visit was 0.89 ± 0.74 (with approximate Snellen equivalent of 20/160) in the cleft group and 0.65 ± 0.69 (with approximate Snellen equivalent of 20/100) in controls ($P < 0.05$). Within cleft group, the early-onset (<6 months) subgroup had even worse visual outcomes than the late-onset subgroup ($P < 0.05$). Multiple logistic regression analyses revealed that the incidence of prechioroidal cleft was positively correlated with having received intravitreal gas injection to displace a submacular hemorrhage and a diagnosis of retinal angiomatous proliferation and typical neovascular age-related macular degeneration ($P < 0.05$).

CONCLUSION: Diagnosis of retinal angiomatous proliferation and typical neovascular age-related macular degeneration, and a submacular hemorrhage treated by pneumatic displacement were the independent risk factors for development of prechioroidal cleft. Eyes with a cleft, especially clefts that develop early, generally had worse prognoses than eyes without clefts.

PMID: 28114175

Genetics

Genet Mol Res. 2017 Jan 23;16(1).

Next-generation sequencing analysis of the ARMS2 gene in Turkish exudative age-related macular degeneration patients.

Bardak H, Gunay M, Ercalik Y, Bardak Y, Ozbas H, Bagci O.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries. It is a complex disease with both genetic and environmental risk factors. To improve clinical management of this condition, it is important to develop risk assessment and prevention strategies for environmental influences, and establish a more effective treatment approach. The aim of the present study was to investigate age-related maculopathy susceptibility protein 2 (ARMS2) gene sequences among Turkish patients with exudative AMD. In addition to 39 advanced exudative AMD patients, 250 healthy individuals for whom exome sequencing data were available were included as a control group. Patients with a history of known environmental and systemic AMD risk factors were excluded. Genomic DNA was isolated from peripheral blood and analyzed using next-generation sequencing. All coding exons of the ARMS2 gene were assessed. Three different ARMS2 sequence variations (rs10490923, rs2736911, and rs10490924) were identified in both the patient and control group. Within the control group, two further ARMS2 gene variants (rs7088128 and rs36213074) were also detected. Logistic regression analysis revealed a relationship between the rs10490924 polymorphism and AMD in the Turkish population.

PMID: 28128407

Stem cells

Cell Stem Cell. 2017 Jan 21. [Epub ahead of print]

Nicotinamide Ameliorates Disease Phenotypes in a Human iPSC Model of Age-Related Macular Degeneration.

Saini JS, Corneo B, Miller JD, Kiehl TR, Wang Q, Boles NC, Blenkinsop TA, Stern JH, Temple S.

Abstract: Age-related macular degeneration (AMD) affects the retinal pigment epithelium (RPE), a cell monolayer essential for photoreceptor survival, and is the leading cause of vision loss in the elderly. There are no disease-altering therapies for dry AMD, which is characterized by accumulation of subretinal drusen deposits and complement-driven inflammation. We report the derivation of human-induced pluripotent stem cells (hiPSCs) from patients with diagnosed AMD, including two donors with the rare ARMS2/HTRA1 homozygous genotype. The hiPSC-derived RPE cells produce several AMD/drusen-related proteins, and those from the AMD donors show significantly increased complement and inflammatory factors, which are most exaggerated in the ARMS2/HTRA1 lines. Using a panel of AMD biomarkers and candidate drug screening, combined with transcriptome analysis, we discover that nicotinamide (NAM) ameliorated disease-related phenotypes by inhibiting drusen proteins and inflammatory and complement factors while upregulating nucleosome, ribosome, and chromatin-modifying genes. Thus, targeting NAM-regulated pathways is a promising avenue for developing therapeutics to combat AMD.

PMID: 28132833

Prog Retin Eye Res. 2017 Jan 19. [Epub ahead of print]

Cell-based therapeutic strategies for replacement and preservation in retinal degenerative diseases.

Jones MK, Lu B, Girman S, Wang S.

Abstract: Cell-based therapeutics offer diverse options for treating retinal degenerative diseases, such as age-related macular degeneration (AMD) and retinitis pigmentosa (RP). AMD is characterized by both genetic and environmental risks factors, whereas RP is mainly a monogenic disorder. Though treatments exist for some patients with neovascular AMD, a majority of retinal degenerative patients have no effective therapeutics, thus indicating a need for universal therapies to target diverse patient populations. Two main cell-based mechanistic approaches are being tested in clinical trials. Replacement therapies utilize cell-derived retinal pigment epithelial (RPE) cells to supplant lost or defective host RPE cells. These cells are similar in morphology and function to native RPE cells and can potentially supplant the responsibilities of RPE in vivo. Preservation therapies utilize supportive cells to aid in visual function and photoreceptor

preservation partially by neurotrophic mechanisms. The goal of preservation strategies is to halt or slow the progression of disease and maintain remaining visual function. A number of clinical trials are testing the safety of replacement and preservation cell therapies in patients; however, measures of efficacy will need to be further evaluated. In addition, a number of prevailing concerns with regards to the immune-related response, longevity, and functionality of the grafted cells will need to be addressed in future trials. This review will summarize the current status of cell-based preclinical and clinical studies with a focus on replacement and preservation strategies and the obstacles that remain regarding these types of treatments.

PMID: 28111323

Neuroscience. 2017 Jan 25. [Epub ahead of print]

Talkin' about my (Re)generation: The Who of Intrinsic Retinal Stem Cells.

Otteson DC.

Abstract: World-wide, two degenerative retinal diseases, glaucoma and age-related macular degeneration, are estimated to affect more than 12% of individuals over the age of 40 (Tham et al., 2014; Wong et al., 2014). Current therapies can slow progression, but cannot restore lost neurons or vision. Thus, there is increasing interest in developing strategies for therapeutic retinal regeneration. Nearly 50 years of research on retinal neurogenesis and regeneration has identified Müller glia as intrinsic retinal stem cells in teleost fish. In the mammalian retina, there is no de novo neurogenesis in adults and only very limited injury-induced regeneration has been induced using exogenous growth factors. The study by Webster, et al (Evidence of BrdU Positive Retinal Neurons after Application of an Alpha7 Nicotinic Acetylcholine Receptor Agonist, this issue) is the first to show robust, retinal neurogenesis in an adult, mammalian retina in the absence of overt injury and provides evidence that the source of the new neurons is likely to be the Müller glia. This exciting finding has the potential to be a game-changer in the field of retinal regeneration.

PMID: 28131621

Diet, lifestyle & low vision

Br J Nutr. 2017 Jan;117(1):108-123. Epub 2017 Jan 26.

Serum and macular response to carotenoid-enriched egg supplementation in human subjects: the Egg Xanthophyll Intervention clinical Trial (EXIT).

Kelly D, Nolan JM, Howard AN, Stack J, Akuffo KO, Moran R, Thurnham DI, Dennison J, Meagher KA, Beatty S.

Abstract: The macular carotenoids lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ) accumulate at the macula, where they are collectively referred to as macular pigment (MP). Augmentation of this pigment, typically achieved through diet and supplementation, enhances visual function and protects against progression of age-related macular degeneration. However, it is known that eggs are a rich dietary source of L and Z, in a highly bioavailable matrix. In this single-blind placebo-controlled study, L- and MZ-enriched eggs and control non-enriched eggs were fed to human subjects (mean age 41 and 35 years, respectively) over an 8-week period, and outcome measures included MP, visual function and serum concentrations of carotenoids and cholesterol. Serum carotenoid concentrations increased significantly in control and enriched egg groups, but to a significantly greater extent in the enriched egg group ($P < 0.001$ for L, Z and MZ). There was no significant increase in MP in either study group post intervention, and we saw no significant improvement in visual performance in either group. Total cholesterol increased significantly in each group, but it did not exceed the upper limit of the normative range (6.5 mmol/l). Therefore, carotenoid-enriched eggs may represent an effective dietary source of L, Z and MZ, reflected in significantly raised serum concentrations of these carotenoids, and consequentially improved bioavailability for capture by target tissues. However, benefits in terms of MP augmentation and/or improved visual performance were

not realised over the 8-week study period, and a study of greater duration will be required to address these questions.

PMID: 28122649

Front Aging Neurosci. 2017 Jan 10;8:333. doi: 10.3389/fnagi.2016.00333. eCollection 2016.

The Walnuts and Healthy Aging Study (WAHA): Protocol for a Nutritional Intervention Trial with Walnuts on Brain Aging.

Rajaram S, Valls-Pedret C, Cofán M, Sabaté J, Serra-Mir M, Pérez-Heras AM, Arechiga A, Casaroli-Marano RP, Alforja S, Sala-Vila A, Doménech M, Roth I, Freitas-Simoes TM, Calvo C, López-Illamola A, Haddad E, Bitok E, Kazzi N, Huey L, Fan J, Ros E.

Abstract: Introduction: An unwanted consequence of population aging is the growing number of elderly at risk of neurodegenerative disorders, including dementia and macular degeneration. As nutritional and behavioral changes can delay disease progression, we designed the Walnuts and Healthy Aging (WAHA) study, a two-center, randomized, 2-year clinical trial conducted in free-living, cognitively healthy elderly men and women. Our interest in exploring the role of walnuts in maintaining cognitive and retinal health is based on extensive evidence supporting their cardio-protective and vascular health effects, which are linked to bioactive components, such as n-3 fatty acids and polyphenols. Methods: The primary aim of WAHA is to examine the effects of ingesting walnuts daily for 2 years on cognitive function and retinal health, assessed with a battery of neuropsychological tests and optical coherence tomography, respectively. All participants followed their habitual diet, adding walnuts at 15% of energy (≈ 30 -60 g/day) (walnut group) or abstaining from walnuts (control group). Secondary outcomes include changes in adiposity, blood pressure, and serum and urinary biomarkers in all participants and brain magnetic resonance imaging in a subset. Results: From May 2012 to May 2014, 708 participants (mean age 69 years, 68% women) were randomized. The study ended in May 2016 with a 90% retention rate. Discussion: The results of WAHA might provide high-level evidence of the benefit of regular walnut consumption in delaying the onset of age-related cognitive impairment and retinal pathology. The findings should translate into public health policy and sound recommendations to the general population (ClinicalTrials.gov identifier NCT01634841).

PMID: 28119602 PMCID: PMC5222811

J Nutr Biochem. 2017 Jan 9;42:37-42. [Epub ahead of print]

Two dietary polyphenols, fisetin and luteolin, reduce inflammation but augment DNA damage-induced toxicity in human RPE cells.

Hytti M, Szabó D, Piippo N, Korhonen E, Honkakoski P, Kaarniranta K, Petrovski G, Kauppinen A.

Abstract: Plant-derived polyphenols are known to possess anti-inflammatory and antioxidant effects. In recent years, several studies have investigated their potential benefits for treating chronic diseases associated with prolonged inflammation and excessive oxidative stress, such as age-related macular degeneration (AMD). Previously, two polyphenols, fisetin and luteolin, have been reported to increase the survival of retinal pigment epithelial (RPE) cells suffering from oxidative stress as well as decreasing inflammation but the benefits of polyphenol therapy seem to depend on the model system used. Our aim was to analyze the effects of fisetin and luteolin on inflammation and cellular viability in a model of nonoxidative DNA damage-induced cell death in human RPE (hRPE) cells. Pretreatment of ARPE-19 or primary hRPE cells with the polyphenols augmented etoposide-induced cell death as measured by the lactate dehydrogenase and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays. However, the treatment was able to reduce the release of two proinflammatory cytokines, IL-6 and IL-8, which were determined by enzyme-linked Immunosorbent assay. Analyses of caspase 3 activity, p53 acetylation and SIRT1 protein levels revealed the apoptotic nature of etoposide-evoked cell death and that fisetin and luteolin augmented the etoposide-induced acetylation of p53 and decreased SIRT1 levels. Taken together,

our findings suggest that the cytoprotective effects of fisetin and luteolin depend on the stressor they need to combat, whereas their anti-inflammatory potential is sustained over a variety of model systems. Careful consideration of disease pathways will be necessary before fisetin or luteolin can be recommended as therapeutic agents for inflammatory diseases in general and specifically AMD.

PMID: 28113103

PLoS One. 2017 Jan 23;12(1):e0170743. eCollection 2017.

Does Vertical Reading Help People with Macular Degeneration: An Exploratory Study.

Calabrèse A, Liu T, Legge GE.

Abstract: Individuals with macular degeneration often develop a Preferred Retinal Locus (PRL) used in place of the impaired fovea. It is known that many people adopt a PRL left of the scotoma, which is likely to affect reading by occluding text to the right of fixation. For such individuals, we examined the possibility that reading vertical text, in which words are rotated 90° with respect to the normal horizontal orientation, would be beneficial for reading. Vertically oriented words would be tangential to the scotoma instead of being partially occluded by it. Here we report the results of an exploratory study that aimed at investigating this hypothesis. We trained individuals with macular degeneration who had PRLs left of their scotoma to read text rotated 90° clockwise and presented using rapid serial visual presentation (RSVP). Although training resulted in improved reading of vertical text, the training did not result in reading speeds that appreciably exceeded reading speeds following training with horizontal text. These results do not support the hypothesis that people with left PRLs read faster with vertical text.

PMID: 28114373

J Vis. 2017 Jan 1;17(1):33.

Object crowding in age-related macular degeneration.

Wallace JM, Chung ST, Tjan BS.

Abstract: Crowding, the phenomenon of impeded object identification due to clutter, is believed to be a key limiting factor of form vision in the peripheral visual field. The present study provides a characterization of object crowding in age-related macular degeneration (AMD) measured at the participants' respective preferred retinal loci with binocular viewing. Crowding was also measured in young and age-matched controls at the same retinal locations, using a fixation-contingent display paradigm to allow unlimited stimulus duration. With objects, the critical spacing of crowding for AMD participants was not substantially different from controls. However, baseline contrast energy thresholds in the noncrowded condition were four times that of the controls. Crowding further exacerbated deficits in contrast sensitivity to three times the normal crowding-induced contrast energy threshold elevation. These findings indicate that contrast-sensitivity deficit is a major limiting factor of object recognition for individuals with AMD, in addition to crowding. Focusing on this more tractable deficit of AMD may lead to more effective remediation and technological assistance.

PMID: 28129416

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