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**Drug treatment**


**Long-term treatment with anti-VEGF does not induce cell aging in primary retinal pigment epithelium.**

Schottler J, Randoll N, Lucius R, Caliebe A, Roider J, Klettner A.

Abstract: Anti-Vascular Endothelial Growth Factor (VEGF) therapy is given repeatedly for an extended period of time to patients when treated for age-related macular degeneration. While short-term effects of anti-VEGF agents on retinal pigment epithelial (RPE) cells have been investigated, the effects of long-term and repeated treatment on these cells are scarce. In this study, we have investigated the effects of anti-VEGF treatment after long-term, repeated treatment on cell aging and morphology.

The experiments were conducted in primary porcine RPE cells passage one and two. Cells were treated with 125 μg/ml bevacizumab, ranibizumab, aflibercept or rituximab once a week for 1 day, 4 days, 7 days, 4 weeks and 12 weeks. Cell survival was evaluated with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide tetrazolium (MTT) and trypan blue exclusion assay. Activity of β-galactosidase was assessed in a commercially available assay. Influence of these compounds was investigated on the expression of cathepsin D and amyloid β, and the expression and phosphorylation of mechanistic target of rapamycin (mTOR), all proteins involved in senescence and aging, in Western blot. The secretion of Pigment Epithelium Derived Factor (PEDF) and Transforming Growth Factor (TGF)-β was investigated in Enzyme-linked Immunosorbent Assay (ELISA). The cellular morphology was investigated with electron microscopy, investigating the number and area of mitochondria and autophagosomes. Statistical analysis was conducted using a mixed linear model.

Weekly treatment up to 12 weeks displayed no toxic effects on RPE cells in any of the substances tested. Ranibizumab showed a significant increase in β-galactosidase signal on day 4 (p < 0.05) and 7 (p < 0.05) after treatment. In long-term, however, ranibizumab displayed no significant difference to untreated cells. Bevacizumab displayed a significant reduction of the β-galactosidase signal after 12 weeks (p < 0.05). Aflibercept significantly decreased β-galactosidase after 1 day (p < 0.01) and 12 weeks (p < 0.05). Rituximab and bevacizumab also decreased β-galactosidase signal after 12 weeks (p < 0.05). The expression of mTOR, phospho-mTOR, amyloid β and cathepsin D was not significantly altered by any of the compounds tested. RPE cells secreted considerate amounts of TGF-β. Bevacizumab treated cells showed significantly lower TGF-β secretion than ranibizumab and rituximab (p < 0.05). In contrast, only small amounts of PEDF were secreted which were not altered by any substance tested. Ultrastructural analysis showed no alterations in mitochondria after long-term treatment with either substance. Autophagosomes were not reduced by long-term anti-VEGF treatment compared to control. However, the area of autophagosomes in bevacizumab and aflibercept treated cells was significantly less compared to both ranibizumab and rituximab treated cells (all p < 0.05).
Taken together, weekly treatment with VEGF-antagonists up to 3 months does not induce premature aging in primary RPE cells in any tested compound. A significant difference can be found between bevacizumab and aflibercept on the one hand, and ranibizumab (and rituximab) on the other hand, with more autophagosomal area in ranibizumab and (rituximab). Taken together, our data provide indications for long-term safety of anti-VEGF compounds. Further research is warranted.

PMID: 29522724

Retina. 2018 Mar 5. [Epub ahead of print]

EFFECT OF INTRAOCULAR PRESSURE-LOWERING MEDICATIONS ON NEOVASCULAR AGE-RELATED MACULAR DEGENERATION TREATMENT OUTCOMES IN THE COMPARISON OF AGE-RELATED MACULAR DEGENERATION TREATMENT TRIALS.

Rahimy E, Ying GS, Pan W, Hsu J.

PURPOSE: To evaluate the effect of intraocular pressure-lowering medications on treatment outcomes in the Comparison of AMD Treatments Trials.

METHODS: Secondary analysis of Comparison of AMD Treatments Trials data. Medication logs were reviewed for continuous 2-year use of agents that increased aqueous outflow (Group A: topical prostaglandins) or suppressed aqueous production (Group B: topical beta blockers and carbonic anhydrase inhibitors). Eyes were excluded if mixed-mechanism intraocular pressure-lowering agents or medications from more than one group were taken. Anatomical and vision responses to treatment at years 1, 2, and over the entire 2-year period in each group were compared with controls (no intraocular pressure-lowering medications).

RESULTS: Inclusion criteria were met by 28 Group A patients, 19 Group B patients, and 857 controls. After 2 years, the control group had a mean visual acuity improvement of +6.3 letters from baseline, compared with +3.5 letters in Group A (P = 0.38), and +13.8 letters in Group B (P = 0.052). Mean retinal thickness change from baseline was -54.9 μm in controls, -80.6 μm in Group A (P = 0.26), and -96.8 μm in Group B (P = 0.13). Mean total thickness change from baseline was -163 μm in controls, -180 μm in Group A (P = 0.63), and -238 μm in Group B (P = 0.08). In longitudinal analysis with adjustment by their baseline values, anti-vascular endothelial growth factor treatment drug and regimen, Group B had more visual acuity improvement (difference of 2.6 letters, 95% confidence interval: -3.4-8.5 letters), more reduction in the retinal thickness (-17.9 μm, 95% confidence interval: -36.5 to 0.7 μm), and total thickness from baseline (mean difference of -54.7 μm, 95% confidence interval: -103 to 6.2 μm) compared with the control group.

CONCLUSION: Concurrent aqueous suppressant use during anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration was associated with a trend toward greater reductions in retinal and total thickness as well as improved visual outcomes over 2 years. A similar effect was not observed to the same extent with agents that increase aqueous outflow. Because of the small sample size and secondary analysis, these findings must be cautiously interpreted and perhaps serve as a basis for future prospective studies.

PMID: 29517580


Aqueous Humor Cytokine Levels and Anatomic Response to Intravitreal Ranibizumab in Diabetic Macular Edema.

IMPORTANCE: Variability in response to anti-vascular endothelial growth factor (VEGF) treatment in diabetic macular edema (DME) remains a significant clinical challenge. Biomarkers could help anticipate responses to anti-VEGF therapy.

OBJECTIVES: To investigate aqueous humor cytokine level changes in response to intravitreal ranibizumab therapy for the management of DME, and to determine the association between baseline aqueous levels and anatomic response.

DESIGN, SETTING, AND PARTICIPANTS: In this prospective multicenter cohort study, 49 participants with diabetes mellitus complicated by center-involved DME, with a central subfield thickness of 310 μm or greater on spectral-domain optical coherence tomography (SD-OCT), were recruited from December 22, 2011, to June 13, 2013 and statistical analysis were performed from March 1, 2017, to June 1, 2017. A total of 48 participants proceeded to follow-up.

INTERVENTIONS: Participants received monthly injections of ranibizumab, 0.5 mg, for 3 months. Aqueous fluid for cytokine analysis was obtained at baseline and repeated at the 2-month visit. Multiplex immunoassay was carried out in duplicate for VEGF, placental growth factor, transforming growth factor beta 2, intercellular adhesion molecule 1 (ICAM-1), interleukin 6 (IL-6), IL-8, IL-10, vascular intercellular adhesion molecule, and monocyte chemoattractant protein 1.

MAIN OUTCOMES AND MEASURES: Baseline and 2-month change in aqueous cytokine levels, 3-month change in SD-OCT central subfield thickness and macular volume (MV), and the statistical association between baseline aqueous cytokine levels and these measures of anatomic response to ranibizumab in center-involved DME.

RESULTS: Among the 48 participants, the mean (SD) age was 61.9 (7.1) years and 36 participants (75.0%) were men. The following cytokines were lower at month 2 vs baseline: ICAM-1 (median change, -190.88; interquartile range [IQR], -634.20 to -26.54; P < .001), VEGF (median change, -639.45; IQR, -1040.61 to -502.61; P < .001), placental growth factor (median change, -1.31; IQR, -5.99 to -0.01; P < .001), IL-6 (median change, -38.61; IQR, -166.72 to -2.80; P < .001), and monocyte chemoattractant protein 1 (median change, -90.13; IQR, -382.74 to 109.47; P = .01). When controlling for age, foveal avascular zone size, and severity of retinopathy, multiple linear regression determined that increasing baseline aqueous ICAM-1 was associated with a favorable anatomic response, in terms of reduced SD-OCT MV at 3 months (every additional 100 pg/mL of baseline ICAM-1 was associated with a reduction of 0.0379 mm3; P = .01). Conversely, increasing baseline aqueous VEGF was associated with a less favorable SD-OCT MV response at 3 months (every additional 100 pg/mL of baseline VEGF was associated with an increase of 0.0731 mm3; P = .02) and was associated with lower odds of being a central subfield thickness responder (odds ratio, 0.868; 95% CI, 0.755-0.998).

CONCLUSIONS AND RELEVANCE: Elevated aqueous ICAM-1 and reduced VEGF levels at baseline are associated with a favorable anatomic response to ranibizumab in DME, although there is not always direct correlation between anatomic and visual acuity response.

PMID: 29522144


An analysis of ranibizumab treatment and visual outcomes in real-world settings: the UNCOVER study.

Eldem B, Lai TYY, Ngah NF, Vote B, Yu HG, Fabre A, Backer A, Clunas NJ.

PURPOSE: To describe intravitreal ranibizumab treatment frequency, clinical monitoring, and visual outcomes (including mean central retinal thickness [CRT] and visual acuity [VA] changes from baseline) in neovascular age-related macular degeneration (nAMD) in real-world settings across three ranibizumab
METHODS: Non-interventional multicenter historical cohort study of intravitreal ranibizumab use for nAMD in routine clinical practice between April 2010 and April 2013. Eligible patients were diagnosed with nAMD, received at least one intravitreal ranibizumab injection during the study period, and had been observed for a minimum of 1 year (up to 3 years). Reimbursement scenarios were defined as self-paid, partially-reimbursed, and fully-reimbursed.

RESULTS: More than three-fourths (n = 2521) of the analysis population was partially-reimbursed for ranibizumab, while 16.4% (n = 532) was fully-reimbursed, and 5.8% was self-paid (n = 188). The average annual ranibizumab injection frequency was 4.1 injections in the partially-reimbursed, 4.7 in the fully-reimbursed and 2.6 in the self-paid populations. The average clinical monitoring frequency was estimated to be 6.7 visits/year, with similar frequencies observed across reimbursement categories. On average, patients experienced VA reduction of -0.7 letters and a decrease in CRT of -44.4 μm. The greatest mean CRT change was observed in the self-paid group, with -92.6 μm.

CONCLUSIONS: UNCOVER included a large, heterogeneous ranibizumab-treated nAMD population in real-world settings. Patients in all reimbursement scenarios attained vision stability on average, indicating control of disease activity.

PMID: 29502232

Ophthalmol Ther. 2018 Mar 5. [Epub ahead of print]

Aflibercept in Diabetic Macular Oedema Previously Refractory to Standard Intravitreal Therapy: An Irish Retrospective Study.

McCloskey CF, Mongan AM, Chetty S, McAteer DMJ, Quinn SM.

INTRODUCTION: To determine visual and anatomical outcomes of diabetic macular oedema (DMO) patients in a tertiary centre following conversion to aflibercept having been refractory to previous treatment with bevacizumab/ranibizumab.

METHODS: A retrospective case series of patients with a diagnosis of DMO undergoing aflibercept intravitreal therapy for at least 6 months who had previous treatment with three consecutive bevacizumab/ranibizumab injections pre-switch. Exclusion criteria included other procedures affecting visual outcome performed within the treatment period. Outcomes measured included visual acuity (VA), central macular thickness (CMT) and injection frequency.

RESULTS: Eighteen eyes of 13 patients were included. Mean VA pre-switch was 61.5 ± 13.8 letters and CMT was 433.2 ± 101.4. Mean number of prior bevacizumab/ranibizumab treatments was 11.3 ± 7.2. Mean follow-up post-switch was 22.5 months (SD 7.9). Mean VA improved from baseline by 4.8 letters at 6 months (p = 0.005), by 6.1 letters at 12 months (p = 0.006), by 7.9 letters (p = 0.004) at 18 months and by 6.4 letters (p = 0.1) at 24 months. Mean CMT decreased from baseline by 108.6 μm at 6 months (p = 0.01), 117.7 μm at 12 months (p = 0.0003), 158.0 μm at 18 months (p = 0.005) and by 123.3 μm at 24 months (p = 0.02).

CONCLUSION: Switching to aflibercept in treatment-resistant DMO produces significant improvements in visual and anatomical outcomes, with eventual maintenance of VA levels.

PMID: 29508370


Optical Coherence Tomography Angiography to Distinguish Changes of Choroidal
Neovascularization after Anti-VEGF Therapy: Monthly Loading Dose versus Pro Re Nata Regimen.


PURPOSE: To compare the qualitative and quantitative choroidal neovascularization (CNV) changes after antivascular endothelial growth factor (anti-VEGF) therapy in treatment-naïve and treated eyes with age-related macular degeneration (AMD) using optical coherence tomography angiography (OCTA).

METHODS: Consecutive patients with neovascular AMD underwent multimodal imaging, including OCTA (AngioPlex, CIRRUS HD-OCT model 5000; Carl Zeiss Meditec, Inc., Dublin, OH) at baseline and at three monthly follow-up visits. Treatment-naïve AMD patients undergoing anti-VEGF loading phase were included in group A, while treated patients were included in group B. Qualitative and quantitative OCTA analyses were performed on outer retina to choriocapillaris (ORCC) slab. CNV size was measured using a free image analysis software (ImageJ, open-source imaging processing software, 2.0.0).

RESULTS: Twenty-five eyes of 25 patients were enrolled in our study (mean age 78.32 ± 6.8 years): 13 treatment-naïve eyes in group A and 12 treated eyes in group B. While qualitative analysis revealed no significant differences from baseline to follow-up in the two groups, quantitative analysis showed in group A a significant decrease in lesion area (P = 0.023); in group B, no significant change in the lesion area was observed during anti-VEGF therapy (P = 0.93).

CONCLUSION: Treatment-naïve and treated eyes with CNV secondary to neovascular AMD respond differently to anti-VEGF therapy. This should be taken into account when using OCTA for CNV follow-up or planning therapeutic strategies.

PMID: 29507810 PMCID: PMC5817334


Visual acuity loss associated with excessive "dry macula" in exudative age-related macular degeneration.


PURPOSE: To investigate the correlation between visual acuity and central macular thickness (CMT) and choroidal thickness (CCT) in patients with wet age-related macular degeneration (AMD).

METHODS: In this retrospective analysis, 14 eyes that received >10 ranibizumab injections (based on pro re nata [PRN] regimen) and maintained initial visual acuity gain were analyzed. The following 5 parameters were measured at the foveal center: CMT (distance from the inner limiting membrane [ILM] to Bruch's membrane); central retinal thickness (CRT; distance from the ILM to the inner limit of the retinal pigment epithelium or subretinal fluid [SRF]); SRF thickness (SRFT); pigment epithelium detachment thickness (PEDT); and CCT. The correlation between the logarithm of the minimum angle of resolution (logMAR) best-corrected visual acuity (BCVA) and the 5 parameters was examined with generalized estimating equations.

RESULTS: CMT, CRT, and CCT were negatively correlated with logMAR BCVA (P=0.031, 0.023, and 0.036, respectively) when only CMT values less than the thickness that maximized visual acuity for each eye were used for the analysis. Each 100-μm reduction in CMT, CRT, or CCT improved logMAR BCVA by -0.1, -0.08, or -0.07, respectively. SRFT and PEDT were not correlated with BCVA. The median CMT that maximized the visual acuity was 230 μm.

CONCLUSION: Dry macula with CMT <230 μm was associated with temporary decrease in visual acuity in AMD patients whose visual acuity was maintained with PRN regimen.

PMID: 29503524 PMCID: PMC5824750
Neuroretinal atrophy following resolution of macular oedema in retinal vein occlusion.


BACKGROUND/AIMS: To characterise neuroretinal atrophy in retinal vein occlusion (RVO).

METHODS: We included patients with central/branch RVO (CRVO=196, BRVO=107) who received ranibizumab according to a standardised protocol for 6 months. Retinal atrophy was defined as the presence of an area of retinal thickness (RT) <260 µm outside the foveal centre. Moreover, the thickness of three distinct retinal layer compartments was computed as follows: (1) retinal nerve fibre layer to ganglion cell layer, (2) inner plexiform layer (IPL) to outer nuclear layer (ONL) and (3) inner segment/outer segment junction to retinal pigment epithelium. To characterise atrophy further, we assessed perfusion status on fluorescein angiography and best-corrected visual acuity (BCVA), and compared these between eyes with/without atrophy.

RESULTS: 23 patients with CRVO and 11 patients with BRVO demonstrated retinal atrophy, presenting as sharply demarcated retinal thinning confined to a macular quadrant. The mean RT in the atrophic quadrant at month 6 was 249±26 µm (CRVO) and 244±29 µm (BRVO). Individual layer analysis revealed pronounced thinning in the IPL to ONL compartment. Change in BCVA at 6 months was similar between the groups (BRVO, +15 vs +18 letters; CRVO, +14 vs +18 letters).

CONCLUSIONS: In this exploratory analysis, we describe the characteristics of neuroretinal atrophy in RVO eyes with resolved macular oedema after ranibizumab therapy. Our analysis shows significant, predominantly retinal thinning in the IPL to ONL compartment in focal macular areas in 11% of patients with RVO. Eyes with retinal atrophy did not show poorer BCVA outcomes.

PMID: 29511062

Anterior infectious necrotizing scleritis secondary to Pseudomonas aeruginosa infection following intravitreal ranibizumab injection.

Coussa RG, Wakil SM, Saheb H, Lederer DE, Oliver KM, Cheema DP.

PURPOSE: To report the occurrence and management of severe infectious scleritis in a 75 year-old woman following intravitreal ranibizumab injection.

OBSERVATIONS: A 75 year-old monocular woman receiving monthly intravitreal ranibizumab injection for wet age related macular degeneration in the left eye presented with severe dull pain, decreased vision, and scleral melt with discharge 2 weeks after her last injection. The dilated fundus exam was devoid of vitritis. The patient was admitted to our hospital for both diagnostic and therapeutic purposes. She was initially started on aggressive oral and topical antibiotics, but showed no significant improvement. The scleral cultures were positive for Pseudomonas aeruginosa. In view of the aggressive nature of her infection, intravenous antibiotics were added to the treatment regimen. The patient recovered her baseline visual function after two weeks of intravenous, oral and, topical antibiotics.

CONCLUSIONS AND IMPORTANCE: To our knowledge, this is the first case of anterior infectious necrotizing scleritis secondary to Pseudomonas aeruginosa infection following intravitreal ranibizumab injection. Clinicians performing intravitreal injections should have a high index of suspicion for iatrogenic infections including scleritis and endophthalmitis, as these infections require aggressive topical and systemic antibiotics as well as possible hospitalization.

PMID: 29503939 PMCID: PMC5758012
Ophthalmologe. 2018 Mar 8. [Epub ahead of print]

[Statement from the BVA, the DOG, and the RG on treatment of choroidal neovascularization in diseases other than neovascular age-related macular degeneration: October 2017]. [Article in German]

Berufsverband der Augenärzte Deutschlands e. V. (BVA); Deutsche Ophthalmologische Gesellschaft (DOG); Retinologische Gesellschaft e. V. (RG).

PMID: 29520492


Aflibercept in diabetic macular edema refractory to previous bevacizumab: outcomes and predictors of success.

Călugăru D, Călugăru M.

PMID: 29523991

Other treatment & diagnosis

Eye (Lond). 2018 Mar 9. [Epub ahead of print]

Prophylactic laser in age-related macular degeneration: the past, the present and the future.

Findlay Q, Jobling AI, Vessey KA, Greferath U, Phipps JA, Guymer RH, Fletcher EL.

Abstract: The presence of drusen in the posterior eye is a hallmark feature of the early stages of age-related macular degeneration and their size is an indicator of risk of progression to vision-threatening forms of the disease. Since the initial observations that laser treatment can resolve drusen, there has been great interest in whether laser treatment can be used to reduce the progression of age-related macular degeneration. In this article, we review the development of lasers for the treatment of those with age-related macular degeneration. We provide an overview of the clinical trial results that demonstrated drusen resolution but that had mixed effects on progression of disease. In addition, we provide a summary of the recent developments in pulsed lasers that are designed to reduce the energy applied to the posterior eye to provide the therapeutic effects of conventional continuous wave lasers while reducing the secondary tissue effects.

PMID: 29520049


A Tablet-Based Retinal Function Test in Neovascular Age-Related Macular Degeneration Eyes and At-Risk Fellow Eye.

Ho CYD, Wu Z, Turpin A, Lawson DJ, Luu CD, McKendrick AM, Guymer RH.

PURPOSE: To determine the feasibility of a tablet-based application to detect changes in retinal sensitivity and correlations with underlying pathology in neovascular age-related macular degeneration (nAMD) eyes undergoing treatment and in at-risk fellow eyes.

METHOD: Participants with nAMD in at least one eye were recruited, examined, and imaged using spectral-domain optical coherence tomography (SD-OCT). Retinal sensitivity was measured within the central 5° at
12 locations using a customized test delivered on an iPad. Test points were superimposed on SD-OCT locations to investigate structure/function relationships.

RESULTS: Included in the study were 53 nAMD eyes and 21 at-risk fellow eyes. In nAMD eyes, the mean retinal sensitivity was 24.1 ± 1.8 dB with reduced retinal sensitivity associated with the presence of atrophy (P < 0.01), retinal pigment epithelium (RPE) disruption (P < 0.01), and absent ellipsoid zone (EZ) (P < 0.01), but not with the presence of subretinal fluid (P = 0.94) nor intraretinal fluid (P = 0.52). In at-risk eyes, the average retinal sensitivity was 28.8 ± 0.6 dB, with reduced sensitivity significantly associated with the presence of drusen, atrophy, RPE disruption, and absent EZ (P < 0.01).

CONCLUSION: The tablet-based test of retinal sensitivity was able to be performed by an elderly cohort with nAMD. The ability to correlate differences in sensitivity with pathology is encouraging when considering using the tablet devices as a home monitoring tool with remote surveillance. Dual pathology often present with retinal fluid confounded our ability to correlate fluid with sensitivity.

TRANSLATIONAL RELEVANCE: These findings highlight the potential of tablet-based devices in performing visual function measures as a home monitoring tool with remote surveillance for the earlier detection of nAMD.

Retina. 2018 Mar 5. [Epub ahead of print]

PHOTODYNAMIC THERAPY FOR SYMPTOMATIC SUBFOVEAL RETINAL PIGMENT EPITHELIAL DETACHMENT IN CENTRAL SEROUS CHORIORETINOPATHY: Outcomes and Prognostic Factors.

Hwang S, Kang SW, Kim SJ, Jang JW, Kim KT.

PURPOSE: To report the clinical outcomes of reduced-fluence photodynamic therapy (PDT) for symptomatic subfoveal retinal pigment epithelial detachment (RPED) in central serous chorioretinopathy and identify prognostic factors affecting treatment outcome.

METHODS: This retrospective interventional study included 35 eyes of 35 patients with serous subfoveal RPED with choroidal hyperpermeability. Cases with evidence of age-related macular degeneration were excluded from the study. Reduced-fluence PDT was applied to each patient. Best-corrected visual acuity, anatomical resolution of RPED, subjective symptom improvement, and complications were analyzed.

RESULTS: One month after reduced-fluence PDT, 28 eyes (80.0%) manifested complete resolution of subfoveal RPED. Among the patients whose eyes manifested complete resolution, 19 (67.9%) reported subjective vision improvement. This subjective improvement was significantly associated with the presence of dysmorphopsia at baseline. Logarithm of the minimal angle of resolution visual acuity improved from 0.15 (Snellen equivalent of 20/28) to 0.09 (20/25) between baseline and 3 months after PDT (P = 0.008). Older age and increased RPED height were independent risk factors of poor resolution of RPED after PDT. The mean follow-up period after treatment was 10.4 ± 13.6 months; recurrence of RPED did not occur in any case.

CONCLUSION: Subfoveal RPED in central serous chorioretinopathy responded well to reduced-fluence PDT, especially in younger patients with less RPED. Dysmorphopsia, rather than decreased visual acuity, is a main symptomatic presentation in subfoveal RPED.

PMID: 29517581


Retinal pigment epithelium changes in Kartagener syndrome.
Garcia MD, Ventura CV, Dias JR, Chang TCP, Berrocal AM.

PURPOSE: We present the first case in the literature of a patient with Kartagener syndrome and ocular findings of nonexudative age-related macular degeneration.

OBSERVATIONS: A 55-year-old woman with Kartagener syndrome and chronic angle closure glaucoma presented for evaluation of the retina. Optos ultra-widefield imaging of the fundus showed glaucomatous cupping, drusen, and retinal pigment epithelium changes within the macular region. Humphrey visual field testing confirmed glaucomatous changes. Drusenoid pigment epithelial detachments were observed bilaterally with optical coherence tomography.

CONCLUSIONS AND IMPORTANCE: We hypothesize that in addition to the lungs, spermatozoa and the Fallopian tubes, the retinal pigment epithelium may also be affected by ciliary dysfunction in individuals with Kartagener syndrome. Given recent advances in our knowledge of retinal ciliopathies, further studies are needed to understand how ciliary dysfunction affects the retina in Kartagener syndrome.

PMID: 29511746 PMCID: PMC5834646


In vivo photoacoustic imaging of chorioretinal oxygen gradients.


Abstract: Chorioretinal imaging has a crucial role for the patients with chorioretinal vascular diseases, such as neovascular age-related macular degeneration. Imaging oxygen gradients in the eye could better diagnose and treat ocular diseases. Here, we describe the use of photoacoustic ocular imaging (PAOI) in measuring chorioretinal oxygen saturation (CR - sO2) gradients in New Zealand white rabbits (n = 5) with ocular ischemia. We observed good correlation (R2 = 0.98) between pulse oximetry and PAOI as a function of different oxygen percentages in inhaled air. We then used an established ocular ischemia model in which intraocular pressure is elevated to constrict ocular blood flow, and notice a positive correlation (R2 = 0.92) between the injected volume of phosphate buffered saline (PBS) and intraocular pressure (IOP) as well as a negative correlation (R2 = 0.98) between CR - sO2 and injected volume of PBS. The CR - sO2 was measured before (baseline), during (ischemia), and after the infusion (600-μL PBS). The ischemia-reperfusion model did not affect the measurement of the sO2 using a pulse oximeter on the animal's paw, but the chorioretinal PAOI signal showed a nearly sixfold decrease in CR - sO2 (n = 5, p = 0.00001). We also observe a sixfold decrease in CR - sO2 after significant elevation of IOP during ischemia, with an increase close to baseline during reperfusion. These data suggest that PAOI can detect changes in chorioretinal oxygenation and may be useful for application to imaging oxygen gradients in ocular disease.

PMID: 29524321

Pathogenesis


A Type III Complement Factor D Deficiency: Structural insights for inhibition of the alternative pathway.

Sng CCT, O'Byrne S, Prigozhin DM, et al

PMID: 29522842

[The relationship between necroptosis and blinding eye diseases]. [Article in Chinese]

Xie LL, Jiang B.

Abstract: As a programmed cell death manner which is distinguished from apoptosis and autophagy, necroptosis is a newly discovered pathway of regulated necrosis that requires the protein receptor interacting protein kinases 1 and 3 and mixed lineage kinase domain-like protein. Necroptosis is mediated by death receptors, toll-like receptors and probably other mediators. Emerging evidences have delineated that necroptosis plays an important role in the occurrence and development of various blinding eye diseases. In this review, the related mechanism of necroptosis, the relationship between necroptosis and multiple blinding eye diseases, such as age-related macular degeneration, retinitis pigmentosa and glaucoma, and the potential therapeutic targets of necroptosis are discussed. (Chin J Ophthalmol, 2018, 54: 234-240).

PMID: 29518884


A bilayer photoreceptor-retinal tissue model with gradient cell density design: a study of microvalve -based bioprinting.

Shi P, Edgar TYS, Yeong WY, Yeung LH, Laude A.

Abstract: ARPE-19 and Y79 cells were precisely and effectively delivered to form an in vitro retinal tissue model via 3D cell bioprinting technology. The samples were characterized by cell viability assay, hematoxylin and eosin (HE) and immunofluorescent staining, scanning electrical microscopy (SEM) and confocal microscopy etc. The bioprinted ARPE-19 cells formed a high-quality cell monolayer in 14 days. Manually seeded ARPE-19 cells were poorly controlled during and after cell seeding, and they aggregated to form uneven cell layer. The Y79 cells were subsequently bioprinted on the ARPE-19 cell monolayer to form two distinctive patterns. The microvalve-based bioprinting is efficient and accurate to build the in vitro tissue models with the potential to provide similar pathological responses and mechanism to human diseases, to mimic the phenotypic endpoints that are comparable to clinical studies, and to provide a realistic prediction of clinical efficacy.

PMID: 29510003


Targeting Hif1a rescues cone degeneration and prevents subretinal neovascularization in a model of chronic hypoxia.

Barben M, Schori C, Samardzija M, Grimm C.

BACKGROUND: Degeneration of cone photoreceptors leads to loss of vision in patients suffering from age-related macular degeneration (AMD) and other cone dystrophies. Evidence, such as choroidal ischemia and decreased choroidal blood flow, implicates reduced tissue oxygenation in AMD pathology and suggests a role of the cellular response to hypoxia in disease onset and progression. Such a chronic hypoxic situation may promote several cellular responses including stabilization of hypoxia-inducible factors (HIFs).

METHODS: To investigate the consequence of a chronic activation of the molecular response to hypoxia in cones, von Hippel Lindau protein (VHL) was specifically ablated in cones of the all-cone R91W;Nrl-- mouse. Retinal function and morphology was evaluated by ERG and light microscopy, while differential gene expression was tested by real-time PCR. Retinal vasculature was analyzed by immunostainings and
fluorescein angiography. Two-way ANOVA with Šidák's multiple comparison test was performed for statistical analysis.

RESULTS: Cone-specific ablation of Vhl resulted in stabilization and activation of hypoxia-inducible factor 1A (HIF1A) which led to increased expression of genes associated with hypoxia and retinal stress. Our data demonstrate severe cone degeneration and pathologic vessel growth, features that are central to AMD pathology. Subretinal neovascularization was accompanied by vascular leakage and infiltration of microglia cells. Interestingly, we observed increased expression of tissue inhibitor of metalloproteinase 3 (Timp3) during the aging process, a gene associated with AMD and Bruch's membrane integrity. Additional deletion of Hif1a protected cone cells, prevented pathological vessel growth and preserved vision.

CONCLUSIONS: Our data provide evidence for a HIF1A-mediated mechanism leading to pathological vessel growth and cone degeneration in response to a chronic hypoxia-like situation. Consequently, our results identify HIF1A as a potential therapeutic target to rescue hypoxia-related vision loss in patients.

Epidemiology


Choroidal neovascularization secondary to tuberculosis: Presentation and management.

Lee Kim E, Rodger DC, Rao NA.

PURPOSE: While there are many known etiologies of choroidal neovascularization (CNV), tuberculosis is not a well-known causative agent. In this case series, we highlight CNV occurring secondary to tuberculous chorioretinitis, its presentation, and its management.

OBSERVATIONS: We retrospectively reviewed the charts and imaging of four patients who presented with presumed tuberculous chorioretinitis and CNV. Three of these patients had signs of intraocular inflammation and were also found to have active macular CNV. The one remaining patient had chorioretinal scars from prior posterior uveitis and previously treated macular CNV membranes. The three patients with active disease were started on anti-tuberculosis medications and oral corticosteroids, and they also received intravitreal anti-vascular endothelial growth factor (VEGF) injections as needed for the CNV. There was a significant improvement in the clinical course of all three patients with active disease-the intraocular inflammation subsided, and CNV recurrences were mitigated. Upon completion of systemic treatment, all patients have remained quiescent.

CONCLUSIONS AND IMPORTANCE: Our findings demonstrate that CNV may occur in the course of tuberculous chorioretinitis with marked loss of vision, and management with anti-tuberculosis medications, oral corticosteroids, and intravitreal anti-VEGF injections results in notable improvement in their clinical course.

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Orthostatic hypertension as a risk factor for age-related macular degeneration: Evidence from the Irish longitudinal study on ageing.

Bhuachalla BN, McGarrigle CA, O'Leary N, Akuffo KO, Peto T, Beatty S, Kenny RA.

PURPOSE: Age related macular degeneration (AMD) is a leading cause of irreversible visual loss in developed countries. It is associated with vascular risk factors including hypertension. Dysregulated blood
pressure (BP) behaviour including orthostatic hypertension (OHTN), hypotension (OH) and BP variability (BPV) are associated with end-organ damage, particularly in the brain. We investigated if abnormal orthostatic BP (OBP) was a risk factor for AMD, for which a vascular aetiology is implicated.

METHODS: A nationally representative, cross-sectional study was carried out 2009/2010 in The Irish Longitudinal Study on Ageing (TILDA). Beat-to-beat BP data, measured by digital photoplethysmography during active stand, was used to characterise OBP behaviour in the 30-110 s after standing. OH, OHTN, BPV and normal stabilisation recovery phenotypes were defined. AMD was identified following masked grading of 45° monoscopic colour retinal photographs, which were centred on the macula and taken with a NIDEK AFC-210 non-mydriatic auto-fundus camera. The relationship between OBP recovery phenotypes and AMD in 3750 adults aged ≥50 years was investigated using multivariate logistic regression models, adjusted for traditional AMD risk factors.

RESULTS: From 30 to 110 s post active stand, systolic and diastolic OHTN was associated with increased odds of AMD after adjustment for demographics, health behaviours including smoking, family history of AMD, self-report (SR) diabetes, SR cataracts, objective hypertension and prescribed antihypertensives. No evidence of heterogeneity of OHTN effect was found between those who were hypertensive to those who were normotensive.

CONCLUSIONS: This study provides evidence that OHTN may be an independent cardiovascular risk factor for AMD.

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Genetics & gene therapy


Retinitis pigmentosa associated with a mutation in BEST1.

Dalvin LA, Abou Chehade JE, Chiang J, Fuchs J, Iezzi R, Marmorstein AD.

PURPOSE: There is only one prior report associating mutations in BEST1 with a diagnosis of retinitis pigmentosa (RP). The imaging studies presented in that report were more atypical of RP and shared features of autosomal recessive bestrophinopathy and autosomal dominant vitreoretinochoroidopathy. Here, we present a patient with a clinical phenotype consistent with classic features of RP.

OBSERVATIONS: The patient in this report was diagnosed with simplex RP based on clinically-evident bone spicules with characteristic ERG and EOG findings. The patient had associated massive cystoid macular edema which resolved following a short course of oral acetazolamide. Genetic testing revealed that the patient carries a novel heterozygous deletion mutation in BEST1 which is not carried by either parent. While this suggests BEST1 is causative, the patient also inherited heterozygous copies of several mutations in other genes known to cause recessive retinal degenerative disease.

CONCLUSIONS AND IMPORTANCE: How some mutations in BEST1 associate with peripheral retinal degeneration phenotypes, while others manifest as macular degeneration phenotypes is currently unknown. We speculate that RP due to BEST1 mutation requires mutations in other modifier genes.

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Stem cells

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Cellular regeneration strategies for macular degeneration: past, present and future.
Chichagova V, Hallam D, Collin J, Zerti D, Dorgau B, Felemban M, Lako M, Steel DH.

Abstract: Despite considerable effort and significant therapeutic advances, age-related macular degeneration (AMD) remains the commonest cause of blindness in the developed world. Progressive late-stage AMD with outer retinal degeneration currently has no proven treatment. There has been significant interest in the possibility that cellular treatments may slow or reverse visual loss in AMD. A number of modes of action have been suggested, including cell replacement and rescue, as well as immune modulation to delay the neurodegenerative process. Their appeal in this enigmatic disease relate to their generic, non-pathway-specific effects. The outer retina in particular has been at the forefront of developments in cellular regenerative therapies being surgically accessible, easily observable, as well as having a relatively simple architecture. Both the retinal pigment epithelium (RPE) and photoreceptors have been considered for replacement therapies as both sheets and cell suspensions. Studies using autologous RPE, and to a lesser extent, foetal retina, have shown proof of principle. A wide variety of cell sources have been proposed with pluripotent stem cell-derived cells currently holding the centre stage. Recent early-phase trials using these cells for RPE replacement have met safety endpoints and hinted at possible efficacy. Animal studies have confirmed the promise that photoreceptor replacement, even in a completely degenerated outer retina may restore some vision. Many challenges, however, remain, not least of which include avoiding immune rejection, ensuring long-term cellular survival and maximising effect. This review provides an overview of progress made, ongoing studies and challenges ahead.

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Diet, lifestyle & low vision


The effects of zinc supplementation on primary human retinal pigment epithelium.


Abstract: Population-based and interventional studies have shown that elevated zinc levels can reduce the progression to advanced age-related macular degeneration. The objective of this study was to assess whether elevated extracellular zinc has a direct effect on retinal pigment epithelial cells (RPE), by examining the phenotype and molecular characteristics of increased extracellular zinc on human primary RPE cells. Monolayers of human foetal primary RPE cells were grown on culture inserts and maintained in medium supplemented with increasing total concentrations of zinc (0, 75, 100, 125 and 150 μM) for up to 4 weeks. Changes in cell viability and differentiation as well as expression and secretion of proteins were investigated. RPE cells developed a confluent monolayer with cobblestone morphology and transepithelial resistance (TER) >200 Ω*cm² within 4 weeks. There was a zinc concentration-dependent increase in TER and pigmentation, with the largest effects being achieved by the addition of 125 μM zinc to the culture medium, corresponding to 3.4 nM available (free) zinc levels. The cells responded to addition of zinc by significantly increasing the expression of Retinoid Isomerohydrolase (RPE65) gene; cell pigmentation; Premelanosome Protein (PMEL17) immunoreactivity; and secretion of proteins including Apolipoprotein E (APOE), Complement Factor H (CFH), and High-Temperature Requirement A Serine Peptidase 1 (HTRA1) without an effect on cell viability. This study shows that elevated extracellular zinc levels have a significant and direct effect on differentiation and function of the RPE cells in culture, which may explain, at least in part, the positive effects seen in clinical settings. The results also highlight that determining and controlling of available, as opposed to total added, zinc will be essential to be able to compare results obtained in different laboratories.

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Modified images reflecting effects of age-related macular degeneration on perception of everyday scenes.

Denniss J, Astle AT.

BACKGROUND: Depictions of vision with age-related macular degeneration (AMD) in public information material typically show a central region of absolute vision loss. Patients with early and moderate disease frequently do not report this. We aimed to measure how a group of people with AMD perceive everyday scenes in order to produce accurate depictions.

METHODS: We report on six people aged 65-82 years with monocular AMD (visual acuity +0.04 to +1.64 logMAR) and normal vision in the fellow eye. Participants viewed four images monocularly, alternating between eyes. The image was digitally altered to approximate participants' descriptions of their perception with the affected eye. The altered image was viewed with the unaffected eye, and compared with the original image viewed with the affected eye. This was repeated iteratively until a perceptual match was achieved between the modified image/unaffected eye and the original image/affected eye.

RESULTS: For five AMD participants with visual acuity +0.04 to +0.50 logMAR the modified images did not resemble those in current public information material. Image modifications required to achieve perceptual similarity with the affected eyes included localised distortion, contrast reduction and blur. Widespread colour desaturation was also required in some cases. One participant with advanced geographic atrophy reported an absolute positive scotoma, similar to existing depictions.

CONCLUSIONS: Vision in people with AMD may not conform to the common depiction of a central region of absolute vision loss. The accurate representations of AMD patients' vision produced in this study will enable better understanding of the visual consequences of AMD.

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