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Drug treatment

Retina. 2014 Jul 28. [Epub ahead of print]

INTRAOCULAR PRESSURE IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION SWITCHED TO AFLIBERCEPT INJECTION AFTER PREVIOUS ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENTS.

Rusu IM, Deobhakta A, Yoon D, Lee M, Slakter JS, Klancnik JM, Thompson D, Freund KB.

PURPOSE: To assess for change in intraocular pressure (IOP) in neovascular age-related macular degeneration patients switched to aflibercept after receiving previous treatments of intravitreal bevacizumab or ranibizumab.

METHODS: This is a retrospective chart review of the first 53 patients (53 eyes) treated with at least 2 injections of 2 mg in 0.05 mL of aflibercept by March 6, 2013, after at least 2 previous injections of 0.5 mg in 0.05 mL of ranibizumab with or without previous injections of 1.25 mg in 0.05 mL of bevacizumab. The analysis was restricted to the first such sequence within each patient. The last previous anti-vascular endothelial growth factor injection before the switch to aflibercept was ranibizumab in all cases included in the study. Each person served as his or her own control. The pre-aflibercept IOP in the before state (treatment with bevacizumab or ranibizumab) was the preinjection IOP measure before dilation at the visit of the first aflibercept injection. Statistical analysis was performed using Microsoft Excel.

RESULTS: There were 41 patients who were first treated with ranibizumab followed by aflibercept and 12 patients treated with ranibizumab and bevacizumab followed by aflibercept. For each of these sequences, IOP in the treated eye during treatment with aflibercept (the after state) was computed in 3 different ways: the first IOP, the last IOP, and the mean IOP for the period when treated with aflibercept. The pooled data showed a mean pre-aflibercept (the before state) IOP of 14.87 that decreased to a mean first IOP of 14.57, mean last IOP of 13.79, and a mean IOP of 14.14 during aflibercept treatment. The inference is based on the pooled analysis. The 95% confidence interval for the differences (after minus before) were -0.30 (-1.12 to 0.52), -1.08 (-1.83 to -0.32), and -0.73 (-1.30 to -0.17) for the first, last, and mean IOPs, respectively. The corresponding P values were 0.46 for the first, 0.006 for the last, 0.01 for the mean IOP during the aflibercept treatment period.

CONCLUSION: Intraocular pressure was found to be significantly lower in patients switched to aflibercept after previous treatments with ranibizumab and/or bevacizumab. Aflibercept may have a more favorable IOP safety profile in patients previously on other anti-vascular endothelial growth factor treatments.

PMID: 25072648 [PubMed - as supplied by publisher]

Eye (Lond). 2014 Aug 1. doi: 10.1038/eye.2014.180. [Epub ahead of print]

Short-term intraocular pressure trends following intravitreal ranibizumab injections for neovascular age-related macular degeneration-the role of oral acetazolamide in protecting glaucoma patients.

Murray CD, Wood D, Allgar V, Walters G, Gale RP.

Purpose: To determine the effect of oral acetazolamide on lowering the peak and duration of intraocular pressure (IOP) rise in glaucoma and glaucoma suspect patients, following intravitreal injection of ranibizumab for neovascular age-related macular degeneration.

Methods: The study was an open-label, parallel, randomised, controlled trial (EudraCT Number: 2010-023037-35). Twenty-four glaucoma or glaucoma suspect patients received either 500 mg acetazolamide or no treatment 60-90 min before 0.5 mg ranibizumab. The primary outcome measure was the difference in IOP immediately after injection (T0) and 5, 10, and 30 min following injection. ANCOVA was used to compare groups, adjusting for baseline IOP. The study was powered to detect a 9-mm Hg difference at T0.

Results: The IOP at T0 was 2.3 mm Hg higher in the non-treated group (mean 44.5 mm Hg, range (19-86 mm Hg)) compared with the treated group (mean 42.2 mm Hg, range (25-58 mm Hg)), but was not statistically significant after adjusting for baseline IOP (P=0.440). At 30 min, IOP was 4.9 mm Hg higher in the non-treated group (mean 20.6 mm Hg, range (11-46 mm Hg)) compared with the treated group (mean 15.7 mm Hg, range (8-21 mm Hg)). This was statistically significant after adjusting for baseline IOP (P=0.013).

Conclusions: Although the primary end points were not reached, 500 mg oral acetazolamide, 60-90 min before intravitreal injection, results in a statistically significant reduction in IOP at 3O min post injection. Prophylactic treatment may be considered as an option to minimise neuro-retinal rim damage in high-risk glaucoma patients who are most vulnerable to IOP spikes and undergoing repeated intravitreal injections of ranibizumab.Eye advance online publication, 1 August 2014; doi:10.1038/eye.2014.180.

PMID: 25081290 [PubMed - as supplied by publisher]

BMJ Open. 2014 Jul 29;4(7):e005094. doi: 10.1136/bmjopen-2014-005094.

Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial.

Dakin HA, Wordsworth S, Rogers CA, Abangma G, Raftery J, Harding SP, Lotery AJ, Downes SM, Chakravarthy U, Reeves BC; IVAN Study Investigators.

OBJECTIVE: To assess the incremental cost and cost-effectiveness of continuous and discontinuous regimens of bevacizumab (Avastin) and ranibizumab (Lucentis) for neovascular age-related macular degeneration (nAMD) from a UK National Health Service (NHS) perspective.

DESIGN: A within-trial cost-utility analysis with a 2-year time horizon, based on a multicentre factorial, non-inferiority randomised controlled trial.

SETTING: 23 hospital ophthalmology clinics.

PARTICIPANTS: 610 patients aged ≥50 years with untreated nAMD in the study eye.

INTERVENTIONS: 0.5 mg ranibizumab or 1.25 mg bevacizumab given continuously (monthly) or discontinuously (as-needed) for 2 years.

MAIN OUTCOME MEASURES: Quality-adjusted life-years (QALYs).

RESULTS: Total 2-year costs ranged from £3002/patient ($4700; 95% CI £2601 to £3403) for

discontinuous bevacizumab to £18 590/patient ($29 106; 95% CI £18 258 to £18 922) for continuous ranibizumab. Ranibizumab was significantly more costly than bevacizumab for both continuous (+£14 989/patient ($23 468); 95% CI £14 522 to £15 456; p<0.001) and discontinuous treatment (+£8498 ($13 305); 95% CI £7700 to £9295; p<0.001), with negligible difference in QALYs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Patients receiving continuous bevacizumab accrued higher total costs (+£599 ($938); 95% CI £91 to £1107; p=0.021) than those receiving discontinuous bevacizumab, but also accrued non-significantly more QALYs (+0.020; 95% CI -0.032 to 0.071; p=0.452). Continuous bevacizumab therefore cost £30 220 ($47 316) per QALY gained versus discontinuous bevacizumab. However, bootstrapping demonstrated that if the NHS is willing to pay £20 000/QALY gained, there is a 37% chance that continuous bevacizumab is cost-effective versus discontinuous bevacizumab.

CONCLUSIONS: Ranibizumab is not cost-effective compared with bevacizumab, being substantially more costly and producing little or no QALY gain. Discontinuous bevacizumab is likely to be the most cost-effective of the four treatment strategies evaluated in this UK trial, although there is a 37% chance that continuous bevacizumab is cost-effective.

PMID: 25079928 [PubMed - in process]

Retina. 2014 Jul 30. [Epub ahead of print]

EFFECT OF RANIBIZUMAB ON HIGH-SPEED INDOCYANINE GREEN ANGIOGRAPHY AND MINIMUM INTENSITY PROJECTION OPTICAL COHERENCE TOMOGRAPHY FINDINGS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Nicholson BP, Nigam D, Toy B, Stetson PF, Agrón E, Jacobs-El N, Cunningham D, Cukras C, Wong W, Wiley H, Chew E, Ferris F, Meyerle CB.

PURPOSE: The purpose of this 1-year prospective study was to investigate how induction/pro re nata ranibizumab intravitreal treatment of eyes with neovascular age-related macular degeneration affects the anatomy of choroidal neovascularization (CNV) and the overlying outer retinal tissue.

METHODS: High-speed indocyanine green (HS-ICG) angiography measurements provided quantification of the CNV size in 60 patients followed for 1 year. Minimum intensity projection optical coherence tomography (MinIP OCT), a novel algorithm assessing minimum optical intensity between the internal limiting membrane and retinal pigment epithelium, measured the area of outer retinal disruption overlying the CNV. Fluorescein angiography was also assessed to evaluate late retinal leakage.

RESULTS: After 1 year, the mean area of CNV measured with indocyanine green angiography decreased by 5.8%. The mean area of MinIP OCT of outer retinal disruption overlying the CNV decreased by 4.2%. Mean area of fluorescein angiography leakage decreased by 6.3%. Both the area of outer retinal disruption measured with MinIP OCT and the area of leakage on fluorescein angiography typically exceeded the area of CNV on indocyanine green angiography at baseline and 1 year.

CONCLUSION: Choroidal neovascularization treated with induction/pro re nata intravitreal ranibizumab for 1 year essentially remained static. Minimum intensity projection optical coherence tomography suggests that the area of outer retinal disruption overlying the CNV may be greater than the CNV itself and often correlates with the leakage area on fluorescein angiography. Additionally, there was minimal change in the area of outer retinal disruption on MinIP OCT even when fluid resolved. Measurements of the extent of CNV lesions based on indocyanine green angiography and MinIP OCT may provide useful outcome variables to help assess the CNV complex longitudinally and warrant further validation.

PMID: 25077529 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Jul 25. pii: S0002-9394(14)00448-6. doi: 10.1016/j.ajo.2014.07.027. [Epub ahead of print]

Intravitreal Aflibercept for Macular Edema Secondary to Central Retinal Vein Occlusion: 18-Month Results of the Phase 3 GALILEO Study.

Ogura Y, Roider J, Korobelnik JF, Holz FG, Simader C, Schmidt-Erfurth U, Vitti R, Berliner AJ, Hiemeyer F, Stemper B, Zeitz O, Sandbrink R; GALILEO Study Group.

PURPOSE: To evaluate intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion (CRVO).

DESIGN: Randomized, double-masked, phase 3 study.

METHODS: 177 patients with macular edema secondary to CRVO were randomized to receive 2 mg intravitreal aflibercept (n=106) or sham (n=71) every 4 weeks for 20 weeks. From weeks 24 to 48, patients were monitored every 4 weeks; the former group received intravitreal aflibercept as needed (PRN), and the sham group received sham. From weeks 52 to 76, patients were monitored every 8 weeks, and both groups received intravitreal aflibercept PRN. The primary endpoint (proportion of patients who gained ≥15 letters) was at week 24. This study reports exploratory outcomes at week 76.

RESULTS: The proportion of patients who gained ≥15 letters in the intravitreal aflibercept and sham groups was 60.2% versus 22.1% at week 24 (patients discontinued before week 24 were considered non-responders; P<.0001), 60.2% versus 32.4% at week 52 (last-observation-carried-forward, P<.001), and 57.3% versus 29.4% at week 76 (last-observation-carried-forward; P<.001). Mean μm change from baseline central retinal thickness was -448.6 versus -169.3 at week 24 (P<.0001), -423.5 versus -219.3 at week 52 (P<.0001), and -389.4 versus -306.4 at week 76 (P=.1122). Over 76 weeks, the most common ocular serious adverse event in the intravitreal aflibercept group was macular edema (3.8%).

CONCLUSIONS: The visual and anatomic improvements seen after fixed, monthly dosing at week 24 were largely maintained when treatment intervals were extended. Patients with macular edema following CRVO benefitted from early treatment with intravitreal aflibercept.

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Br J Ophthalmol. 2014 Jul 29. pii: bjophthalmol-2014-305041. doi: 10.1136/bjophthalmol-2014-305041. [Epub ahead of print]

Ranibizumab in retinal vein occlusion: treatment recommendations by an expert panel.

Gerding H, Monés J, Tadayoni R, Boscia F, Pearce I, Priglinger S.

Abstract: Retinal vein occlusion (RVO) is a common cause of retinal vascular disease, resulting in potentially irreversible loss of vision despite the existence of several therapeutic options. The humanised monoclonal antibody fragment ranibizumab binds to and inhibits vascular endothelial growth factor, a key driver of macular oedema in RVO. In 2010, ranibizumab was approved in the USA for the treatment of macular oedema in RVO and, in 2011, ranibizumab was approved in the European Union for the treatment of visual impairment caused by macular oedema secondary to RVO in branch and central RVO. Ranibizumab provides an additional therapeutic option for this complex disease: an option that was not fully considered during the preparation of current international guidelines. An expert panel was convened to critically evaluate the evidence for treatment with ranibizumab in patients with visual impairment caused by macular oedema secondary to RVO and to develop treatment recommendations, with the aim of assisting physicians to optimise patient treatment.

PMID: 25075121 [PubMed - as supplied by publisher]

Ophthalmology. 2014 Jul 23. pii: S0161-6420(14)00526-0. doi: 10.1016/j.ophtha.2014.06.013. [Epub ahead of print]

Outer Retinal Tubulation in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Lee JY, Folgar FA, Maguire MG, Ying GS, Toth CA, Martin DF, Jaffe GJ; CATT Research Group.

PURPOSE: To determine the prevalence of, risk factors for, and visual acuity (VA) correlations with outer retinal tubulation (ORT) seen on spectral-domain optical coherence tomography (SD OCT) in eyes with neovascular age-related macular degeneration (AMD) after anti-vascular endothelial growth factor (VEGF) therapy.

DESIGN: Prospective cohort study within a randomized clinical trial.

PARTICIPANTS: Patients with SD OCT images at weeks 56 and 104 in the Comparison of AMD Treatments Trials (CATT).

METHODS: Participants in the CATT were assigned randomly to ranibizumab (0.5 mg) or bevacizumab (1.25 mg) treatment and to a monthly or pro re nata (PRN) injection-dosing regimen. A subset of eyes was imaged with SD OCT beginning at week 56. Cirrus 512×128 or Spectralis 20°×20° volume cube scan protocols were used to acquire SD OCT images. Two independent readers at the CATT OCT reading center graded scans, and a senior reader arbitrated discrepant grades. The prevalence of ORT, identified as tubular structures seen on at least 3 consecutive Cirrus B scans or 2 consecutive Spectralis B scans, was determined. The associations of patient-specific and ocular features at baseline and follow-up with ORT were evaluated by univariate and multivariate analyses.

MAIN OUTCOME MEASURES: Outer retinal tubulations.

RESULTS: Seven of 69 eyes (10.1%) at 56 weeks and 64 of 368 eyes (17.4%) at week 104 had ORTs. Absence of diabetes, poor VA, blocked fluorescence, geographic atrophy, greater lesion size, and presence of subretinal hyperreflective material at baseline were associated independently with greater risk of ORT at 104 weeks ($P < 0.05$). Neither drug nor dosing regimen were associated significantly with ORT. The mean VA of eyes with ORT at week 104 (58.5 Early Treatment Diabetic Retinopathy Study letters) was worse than the mean VA of eyes without ORT (68.8 letters; $P < 0.0001$).

CONCLUSION: At 2 years after initiation of anti-VEGF therapy for neovascular AMD, ORTs are present in a substantial proportion of eyes. We identified baseline features that independently predict ORTs. It is important to identify ORTs because eyes with ORTs have worse VA outcomes than those without this finding.

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Other treatment & diagnosis

Br J Ophthalmol. 2014 Jul 30. pii: bjophthalmol-2014-305186. doi: 10.1136/bjophthalmol-2014-305186. [Epub ahead of print]

Intraretinal cysts are the most relevant prognostic biomarker in neovascular age-related macular degeneration independent of the therapeutic strategy.

Ritter M, Simader C, Bolz M, Deák GG, Mayr-Sponer U, Sayegh R, Kundi M, Schmidt-Erfurth UM.

BACKGROUND/AIMS: To investigate the impact of antiangiogenic monotherapy and photodynamic therapy (PDT) as add-on strategy on retinal morphology, and to analyse prognostic biomarkers for visual outcome and retreatment frequency in neovascular age-related macular degeneration (nAMD).

METHODS: 255 patients participating in the MONT BLANC study were evaluated. Patients were randomised to receive as-needed ranibizumab monotherapy or combination therapy (verteporfin PDT and ranibizumab). Outcome measures included visual acuity (VA), retinal morphology assessed by optical coherence tomography and retreatment frequency.

RESULTS: The proportion of scans showing intraretinal cysts (IRC) or subretinal fluid (SRF) decreased more intensively in the combination than in the monotherapy group. Pigment epithelial detachments (PED) decreased significantly only in the combination group. Patients with IRC presented the lowest initial VA, and IRC had the strongest negative predictive value for functional improvement in both groups. SRF showed a predictive value for a higher number of ranibizumab injections (combination, +0.9; monotherapy, +0.8) and a higher number of PDT treatments in the combination group (+0.3). PED was associated with a higher number of ranibizumab injections only in the monotherapy group (+1.2).

CONCLUSIONS: Combination and monotherapy showed a distinct response pattern for morphological parameters in nAMD. IRC was the only relevant prognostic parameter for functional outcome.

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Eye (Lond). 2014 Aug 1. doi: 10.1038/eye.2014.189. [Epub ahead of print]

Visual function assessment in simulated real-life situations in patients with age-related macular degeneration compared to normal subjects.

Barteselli G, Gomez ML, Doede AL, Chhablani J, Gutstein W, Bartsch DU, Dustin L, Azen SP, Freeman WR.

Purpose: To evaluate visual function variations in eyes with age-related macular degeneration (AMD) compared to normal eyes under different light/contrast conditions using a time-dependent visual acuity testing instrument, the Central Vision Analyzer (CVA).

Methods: Overall, 37 AMD eyes and 35 normal eyes were consecutively tested with the CVA after assessing best-corrected visual acuity (BCVA) using ETDRS charts. The CVA established visual thresholds for three mesopic environments (M1 (high contrast), M2 (medium contrast), and M3 (low contrast)) and three backlight-glare environments (G1 (high contrast, equivalent to ETDRS), G2 (medium contrast), and G3 (low contrast)) under timed conditions. Vision drop across environments was calculated, and repeatability of visual scores was determined.

Results: BCVA significantly reduced with decreasing contrast in all eyes. M1 scores for BCVA were greater than M2 and M3 (P<0.001); G1 scores were greater than G2 and G3 (P<0.01). BCVA dropped more in AMD eyes than in normal eyes between M1 and M2 (P=0.002) and between M1 and M3 (P=0.003). In AMD eyes, BCVA was better using ETDRS charts compared to G1 (P<0.001). The drop in visual function between ETDRS and G1 was greater in AMD eyes compared to normal eyes (P=0.004). Standard deviations of test-retest ranged from 0.100 to 0.139 logMAR.

Conclusion: The CVA allowed analysis of the visual complaints that AMD patients experience with different lighting/contrast time-dependent conditions. BCVA changed significantly under different lighting/contrast conditions in all eyes, however, AMD eyes were more affected by contrast reduction than normal eyes. In AMD eyes, timed conditions using the CVA led to worse BCVA compared to non-timed ETDRS charts.Eye advance online publication, 1 August 2014; doi:10.1038/eye.2014.189.

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Transl Vis Sci Technol. 2014 Jul 3;3(3):11. eCollection 2014.

Enhancing RPE Cell-Based Therapy Outcomes for AMD: The Role of Bruch's Membrane.

Heller JP, Martin KR.

Abstract: Age-related macular degeneration (AMD) is the leading cause of legal blindness in older people in the developed world. The disease involves damage to the part of the retina responsible for central vision. Degeneration of retinal pigment epithelial (RPE) cells, photoreceptors, and choriocapillaris may contribute to visual loss. Over the past decades, scientists and clinicians have tried to replace lost RPE cells in patients with AMD using cells from different sources. In recent years, advances in generating RPE cells from stem cells have been made and clinical trials are currently evaluating the safety and efficiency of replacing the degenerated RPE cell layer with stem cell-derived RPE cells. However, the therapeutic success of transplantation of stem cell-derived RPE cells may be limited unless the transplanted cells can adhere and survive in the long term in the diseased eye. One hallmark of AMD is the altered extracellular environment of Bruch's membrane to which the grafted cells have to adhere. Here, we discuss recent approaches to overcome the inhibitory environment of the diseased eye and to enhance the survival rate of transplanted RPE cells. Our aim is to highlight novel approaches that may have the potential to improve the efficacy of RPE transplantation for AMD in the future.

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Retina. 2014 Jul 28. [Epub ahead of print]

UNDERSTANDING INDOCYANINE GREEN ANGIOGRAPHY IN POLYPOIDAL CHOROIDAL VASCULOPATHY: The Group Experience With Digital Fundus Photography and Confocal Scanning Laser Ophthalmoscopy.

Cheung CM, Lai TY, Chen SJ, Chong V, Lee WK, Htoon H, Ng WY, Ogura Y, Wong TY.

PURPOSE: To evaluate the angiographic features in using fundus camera-based versus confocal scanning laser ophthalmoscope (cSLO)-based indocyanine green angiography in differentiating polypoidal choroidal vasculopathy (PCV) from typical age-related macular degeneration.

METHODS: Sixty-five eyes of 44 patients with exudative maculopathy due to PCV or typical age-related macular degeneration were prospectively imaged with indocyanine green angiography using fundus camera and cSLO. Images were graded independently by retinal specialists. The main outcome measure was agreement between cSLO and fundus camera for the diagnosis of PCV. The rate of detection and area under the receiver operating characteristic curve of 7 preselected individual features were also compared.

RESULTS: The diagnosis of PCV was made with the cSLO system in 36 eyes (55.4%) and typical age-related macular degeneration in 29 eyes (44.6%), whereas the fundus camera diagnosed PCV in 39 eyes (60.0%) and typical age-related macular degeneration in 26 eyes (40.0%). There was moderate agreement between the two indocyanine green angiography systems (Kappa = 0.53). Using cSLO as the gold standard, fundus camera has a sensitivity and specificity of 83.3% and 69.0%, respectively. Typical nodular appearance was the most commonly detected feature (median, 88.9% for cSLO, 80.6% for fundus camera, P = 0.63) and had the highest area under the curve for the diagnosis of PCV in both systems (median, 80.2% for cSLO, 73.2% for fundus camera, P = 0.13). Confocal scanning laser ophthalmoscope was more sensitive in detecting branching vascular network and late hyperfluorescent plaque.

CONCLUSION: Both systems detected >80% of PCV based on typical nodular appearance of polyps. However, the cSLO is superior in detecting additional features, particularly branching vascular network.

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Stem Cells Transl Med. 2014 Jul 28. pii: sctm.2014-0079. [Epub ahead of print]

ROCK Inhibition Extends Passage of Pluripotent Stem Cell-Derived Retinal Pigmented Epithelium.

Croze RH, Buchholz DE, Radeke MJ, Thi WJ, Hu Q, Coffey PJ, Clegg DO.

Abstract: Human embryonic stem cells (hESCs) offer a potentially unlimited supply of cells for emerging cell-based therapies. Unfortunately, the process of deriving distinct cell types can be time consuming and expensive. In the developed world, age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, with more than 7.2 million people afflicted in the U.S. alone. Both hESC-derived retinal pigmented epithelium (hESC-RPE) and induced pluripotent stem cell-derived RPE (iPSC-RPE) are being developed for AMD therapies by multiple groups, but their potential for expansion in culture is limited. To attempt to overcome this passage limitation, we examined the involvement of Rho-associated, coiled-coil protein kinase (ROCK) in hESC-RPE and iPSC-RPE culture. We report that inhibiting ROCK1/2 with Y-27632 allows extended passage of hESC-RPE and iPSC-RPE. Microarray analysis suggests that ROCK inhibition could be suppressing an epithelial-to-mesenchymal transition through various pathways. These include inhibition of key ligands of the transforming growth factor-β pathway (TGFB1 and GDF6) and Wnt signaling. Two important processes are affected, allowing for an increase in hESC-RPE expansion. First, ROCK inhibition promotes proliferation by inducing multiple components that are involved in cell cycle progression. Second, ROCK inhibition affects many pathways that could be converging to suppress RPE-to-mesenchymal transition. This allows hESC-RPE to remain functional for an extended but finite period in culture.

PMID: 25069775 [PubMed - as supplied by publisher]

Pathogenesis

Front Aging Neurosci. 2014 Jul 10;6:151. doi: 10.3389/fnagi.2014.00151. eCollection 2014.

Why AMD is a disease of ageing and not of development: mechanisms and insights.

Sharma K, Sharma NK, Anand A.

Abstract: Ageing disorders can be defined as the progressive and cumulative outcome of several defective cellular mechanisms as well as metabolic pathways, consequently resulting in degeneration. Environment plays an important role in its pathogenesis. In contrast, developmental disorders arise from inherited mutations and usually the role of environmental factors in development of disease is minimal. Age related macular degeneration (AMD) is one such retinal degenerative disorder which starts with the progression of age. Metabolism plays an important role in initiation of such diseases of ageing. Cholesterol metabolism and their oxidized products like 7-ketocholesterol have been shown to adversely impact retinal pigment epithelium (RPE) cells. These molecules can initiate mitochondrial apoptotic processes and also influence the complements factors and expression of angiogenic proteins like VEGF etc. In this review we highlight why and how AMD is an ageing disorder and not a developmental disease substantiated by disrupted cholesterol metabolism common to several age related diseases.

PMID: 25071560 [PubMed] PMCID: PMC4091411

Exp Anim. 2014;63(3):305-10.

Plasma proteome analysis on cynomolgus monkey (macaca fascicularis) pedigrees with early onset drusen formation.

Kobayashi H, Okamoto H, Murakami A, Iwata T.

Abstract: The central region of the primate retina is called macula. The fovea is located at the center of the macula, where the photoreceptors are concentrated to create neural network adapted for high visual acuity. Damage to the fovea by macular dystrophies and age-related macular degeneration (AMD) can reduce the central visual acuity. The molecular mechanisms leading to these diseases are most likely dependent on the proteins in macula differ from that in peripheral retina in expression level. Previously, we reported an early onset macular degeneration with drusen in cynomolgus monkey pedigrees. These monkeys show similar fundus findings of early stage of AMD at 2 years after birth. To elucidate mechanism of drusen formation and to find disease biomarkers for early stage of AMD, we performed plasma proteome analysis. Plasma samples were collected from four affected and control monkeys within the same pedigree. Successful fractionation of the plasma proteins by ProteoMiner and Gelfree8100 were confirmed by SDS-PAGE. Total of 245 proteins were identified from eight samples. From the results of spectral counting, we selected some proteins, Apolipoprotein E, Histidine-rich glycoprotein, and Retinol-binding protein 4 as candidate proteins that would be related with drusen formation. Candidate proteins would be potentially beneficial as biomarkers for human AMD. One of the identified proteins, Apolipoprotein E (ApoE), is structural component of drusen and also related with other neurodegenerative disease like Alzheimer disease. In this plasma proteome analysis, ApoE would be one of the possible factors of early drusen formation in these cynomolgus monkey pedigrees.

PMID: 25077760 [PubMed - in process]

Expert Opin Ther Targets. 2014 Jul 31:1-11. [Epub ahead of print]

Correlation of platelet activating factor and age-related macular degeneration.

Nitoda E, Koutsilieris M, Brouzas D, Koutsandrea C, Philippou A, Ladas D, Moschos MM.

Objective: To investigate the role of Platelet Activating Factor (PAF) in the pathogenesis and development of Age-Related Macular Degeneration (ARMD). Research design and methods: Fifty six patients with ARMD (24 patients with dry ARMD and 32 patients with wet ARMD) and 25 age-matched control participants underwent ophthalmological examination, including visual acuity measurement and evaluation of the retina. The participants were classified into three groups according to their retinal status, based on indirect fundoscopy, Optical Coherence Tomography and fluorescein angiography findings. In order to evaluate the concentrations of PAF in serum, blood samples were collected from all participants and were analyzed with ELISA technique. Results: The concentrations of PAF differed significantly according to macular lesions and were found to be lower in patients with ARMD than control participants. Conclusions: PAF levels are decreased along with the severity of ARMD. Understanding the role of PAF in pathogenesis of ARMD could be the impetus for the development of new therapies field of treatment of ARMD or even other retinal diseases.

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Invest Ophthalmol Vis Sci. 2014 Jul 29. pii: IOVS-14-14126. doi: 10.1167/iovs.14-14126. [Epub ahead of print]

Age-dependent changes in heparan sulfate in human Bruch's membrane: implications for age-related macular degeneration.

Keenan TD, Pickford CE, Holley RJ, Clark SJ, Lin W, Dowsey AW, Merry CL, Day AJ, Bishop PN.

Purpose: Heparan sulfate (HS) has been implicated in age-related macular degeneration (AMD), since it is the major binding partner for complement factor H (CFH) in human Bruch's membrane (BrM), and CFH has a central role in inhibiting complement activation on extracellular matrices. The aim was to investigate potential aging changes in HS quantity and composition in human BrM.

Methods: Post-mortem human ocular tissue was obtained from donors without known retinal disease. HS was purified from BrM and neurosensory retina, and after digestion to disaccharides, fluorescently labeled and analyzed by reverse-phase HPLC. HS and heparanase-1 were detected by immunohistochemistry in macular tissue sections from young and old donors, and binding of exogenously applied recombinant CCP6 -8 region of CFH (402Y and 402H variants) was compared.

Results: Disaccharide analysis demonstrated that the mean quantity of HS in BrM was 50% lower (p=0.006) in old vs. young donors (average 82 vs. 32 years). In addition, there was a small but significant decrease in HS sulfation in old BrM. Immunohistochemistry revealed approximately 50% (p=0.02) less HS in macular BrM in old vs. young donors, whereas heparanase-1 increased by 24% in old macular BrM (p=0.56). In young donor tissue the AMD-associated 402H CCP6-8 bound relatively poorly to BrM, compared to the 402Y form. In BrM from old donors, this difference was significantly greater (p=0.019).

Conclusions: The quantity of HS decreases substantially with age in human BrM, resulting fewer binding sites for CFH and especially affecting the ability of the 402H variant of CFH to bind BrM.

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Diabetes Metab Res Rev. 2014 Jul 27. doi: 10.1002/dmrr.2581. [Epub ahead of print]

Higher titers of anti Chalmydia pneumoniae IgG in diabetic retinopathy: a cross sectional study.

Banaee T, Daneshvar Kakhki R, Abrishami M, Mahmoudi M, Farzadnia M.

BACKGROUND: Chronic inflammation has a role in the pathogenesis of diabetic retinopathy (DR). Infection with intracellular organisms may incite chronic inflammation. This study was conducted to investigate the association between previous infection with C.pneumoniae (an intracellular microorganism) and DR.

METHODS: Patients with type 2 diabetes mellitus (30-60 years old) and age-matched normal controls were recruited. Patients with history of cardiovascular or cerebrovascular disease, recent pulmonary infection and the presence of age related macular degeneration were excluded from the study. Complete ophthalmic examinations were performed. Fasting blood sugar (FBS) and hemoglobin levels were measured in controls and HgbA1C, BUN, creatinine, and 24 hour urine protein were measured in diabetics. Anti-C.pneumoniae IgG (ELISA) was measured in the sera of all participants.

RESULTS: A total of 215 type 2 diabetic patients and 243 normal healthy controls were included. Anti-Chlamydia pneumoniae IgG titers were higher in patients affected by diabetic retinopathy than participants without retinopathy (74.78 ± 33.38 vs. 66.18 ± 31.40, p = 0.028). Diabetic patients with DR also had higher titers than diabetic patients without DR (74.78 ± 33.38 vs. 66.11 ± 33.41, p = 0.042). Of different variables including age, BMI, hemoglobin level, glycosylated hemoglobin level, FBS, mean arterial pressure, and BUN, only age (r = 0.17; p = 0.001) and BMI (r = 0.15; p = 0.003) were correlated with anti Chlamydia IgG levels. In regression analysis, the presence of DR was still a determinant of the antibody level (p = 0.03).

CONCLUSION: Anti C. pneumoniae IgG titers were higher in patients with diabetic retinopathy, which may indicate a role of this infection in the pathogenesis of diabetic retinopathy. This article is protected by copyright. All rights reserved.

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Invest Ophthalmol Vis Sci. 2014 Jul 15;55(8):4714-27. doi: 10.1167/iovs.14-14332.

Lack of paraoxonase 1 alters phospholipid composition, but not morphology and function of the mouse retina.

Oczos J, Sutter I, Kloeckener-Gruissem B, Berger W, Riwanto M, Rentsch K, Hornemann T, von

Eckardstein A, Grimm C.

PURPOSE: Biochemical and genetic analyses established a contribution of lipid metabolism to AMD pathology. Paraoxonase 1 (PON1) is an antioxidative protein involved in high density lipoprotein (HDL) function and was found to be associated with AMD. Here, we used Pon1(-/-) mice to study the influence of PON1 on retinal physiology and to reveal the potential impact of PON1 on AMD etiology.

METHODS: Laser capture microdissection served to isolate single retinal layers. Retinal function was assessed by ERG. Retinal and RPE morphology were monitored by fundus imaging, fluorescein angiography, light and transmission electron microscopy, and immunofluorescence microscopy. Levels of mRNA and composition of phospholipid species were determined by real-time PCR and LC-MS, respectively.

RESULTS: Adult (8 weeks old) Pon1(-/-) mice displayed normal retinal function and morphology, but their retinas contained reduced amounts of lysophosphatidylcholines (LPCs) compared to controls. Aged (12 months old) Pon1(-/-) animals did not show any morphologic or molecular signs of photoreceptor or RPE degeneration, or of accelerated aging. Photoreceptors of Pon1(-/-) and control mice were similarly susceptible to light damage.

CONCLUSIONS: Results indicated that PON1 is not essential for normal development, function, ageing, and the defense against light damage of the mouse retina. Reduced levels of LPCs in eyes of Pon1(-/-) mice may reflect a decreased activity of phospholipase A2 or altered antioxidative activity in aged eyes.

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Epidemiology

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Non-Genetic risk factors for late age-related macular degeneration.

Ristau T, Ersoy L, Hahn M, den Hollander AI, Kirchhof B, Liakopoulos S, Fauser S.

Purpose: To create a risk model for neovascular age-related macular degeneration (nAMD) based on non-genetic factors.

Methods: In this case-control study, 1459 individuals were included, 445 patients showed nAMD and 1014 were healthy controls. Participants were randomly assigned into a training set (containing 2/3 of individuals) and a validation set. Stepwise logistic regression analysis was performed for 25 environmental risk factors in the training set. The risk model with the remaining factors was then validated in the validation set using receiver-operating-characteristics (ROC) curve and Hosmer-Lemeshow-Test. Additionally, a genetic risk model including variants in the complement factor H gene (CFH, rs1061170) and the age-related maculopathy susceptibility 2 gene (ARMS2, rs10490924) was generated.

Results: The environmental risk model with the factors age, alcohol use, allergy, education, sunlight exposure, fish consumption and physical exercise showed an AUC of 0.80 (95%-CI: 0.76 - 0.84) in the training set. Validation of the model showed adequate calibration (Hosmer-Lemeshow p=0.81). The AUC for the genetic model was 0.77 (95%-CI: 0.730 - 0.808), for the combined environmental and genetic model 0.92 (95%-CI: 0.887 - 0.947).

Conclusions: Seven non-genetic factors are able to provide equivalent discrimination between nAMD patients and controls to genetic risk models. Most of them are modifiable and give the opportunity for counselling patients.

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Phenome-wide association studies (PheWASs) for functional variants.

Ye Z, Mayer J, Ivacic L, Zhou Z, He M, Schrodi SJ, Page D, Brilliant MH, Hebbring SJ.

Abstract: The genome-wide association study (GWAS) is a powerful approach for studying the genetic complexities of human disease. Unfortunately, GWASs often fail to identify clinically significant associations and describing function can be a challenge. GWAS is a phenotype-to-genotype approach. It is now possible to conduct a converse genotype-to-phenotype approach using extensive electronic medical records to define a phenome. This approach associates a single genetic variant with many phenotypes across the phenome and is called a phenome-wide association study (PheWAS). The majority of PheWASs conducted have focused on variants identified previously by GWASs. This approach has been efficient for rediscovering gene-disease associations while also identifying pleiotropic effects for some single-nucleotide polymorphisms (SNPs). However, the use of SNPs identified by GWAS in a PheWAS is limited by the inherent properties of the GWAS SNPs, including weak effect sizes and difficulty when translating discoveries to function. To address these challenges, we conducted a PheWAS on 105 presumed functional stop-gain and stop-loss variants genotyped on 4235 Marshfield Clinic patients. Associations were validated on an additional 10 640 Marshfield Clinic patients. PheWAS results indicate that a nonsense variant in ARMS2 (rs2736911) is associated with age-related macular degeneration (AMD). These results demonstrate that focusing on functional variants may be an effective approach when conducting a PheWAS.European Journal of Human Genetics advance online publication, 30 July 2014; doi:10.1038/ejhg.2014.123.

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Relationship between the complement system, risk factors and prediction models in age-related macular degeneration.

Bora NS, Matta B, Lyzogubov VV, Bora PS.

Abstract: Studies performed over the past decade in humans and experimental animals have been a major source of information and improved our understanding of how dysregulation of the complement system contributes to age-related macular degeneration (AMD) pathology. Drusen, the hall-mark of dry-type AMD are reported to be the by-product of complement mediated inflammatory processes. In wet AMD, unregulated complement activation results in increased production of angiogenic growth factors leading to choroidal neovascularization both in humans and in animal models. In this review article we have linked the complement system with modifiable and non-modifiable AMD risk factors as well as with prediction models of AMD. Understanding the association between the complement system, risk factors and prediction models will help improve our understanding of AMD pathology and management of this disease.

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Genetics

BMC Med Genomics. 2014;7 Suppl 1:S6. doi: 10.1186/1755-8794-7-S1-S6. Epub 2014 May 8.

IGENT: efficient entropy based algorithm for genome-wide gene-gene interaction analysis.

Kwon MS, Park M, Park T.

BACKGROUND: With the development of high-throughput genotyping and sequencing technology, there are growing evidences of association with genetic variants and complex traits. In spite of thousands of genetic variants discovered, such genetic markers have been shown to explain only a very small proportion of the underlying genetic variance of complex traits. Gene-gene interaction (GGI) analysis is expected to unveil a large portion of unexplained heritability of complex traits.

METHODS: In this work, we propose IGENT, Information theory-based GEnome-wide gene-gene iNTeraction method. IGENT is an efficient algorithm for identifying genome-wide gene-gene interactions (GGI) and gene-environment interaction (GEI). For detecting significant GGIs in genome-wide scale, it is important to reduce computational burden significantly. Our method uses information gain (IG) and evaluates its significance without resampling.

RESULTS: Through our simulation studies, the power of the IGENT is shown to be better than or equivalent to that of that of BOOST. The proposed method successfully detected GGI for bipolar disorder in the Wellcome Trust Case Control Consortium (WTCCC) and age-related macular degeneration (AMD).

CONCLUSIONS: The proposed method is implemented by C++ and available on Windows, Linux and MacOSX.

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POLYMORPHISMS IN THE APOE GENE AND THE LOCATION OF RETINAL FLUID IN EYES WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION.

Wickremasinghe SS, Sandhu SS, Amirul-Islam FM, Abedi F, Richardson AJ, Baird PN, Guymer RH.

BACKGROUND: Previous reports suggest that the outcome of age-related macular degeneration treatment is dependent on variants in the apolipoprotein E (APOE) gene. We wish to establish if variants in this gene are associated with anatomical location of fluid within the macula on optical coherence tomography imaging before and after three anti-vascular endothelial growth factor treatments.

METHODS: Patients with subfoveal choroidal neovascularization secondary to age-related macular degeneration were prospectively enrolled and monitored over a 12-month period. Main outcome measures were logMAR best-corrected visual acuity and correlation of qualitative optical coherence tomography features (intraretinal fluid [IRF] and/or subretinal fluid) at baseline and after three anti-vascular endothelial growth factor injections with genetic variants of the APOE gene.

RESULTS: One hundred and eighty-six eyes of 186 patients aged 79.4 years (range, 58-103 years). Subjects with an ε2 allele were more likely to have IRF at baseline compared with the eyes without (odds ratio: 2.98, 95% confidence interval: 1.22-7.29, P = 0.02). After 3 injections, 184 eyes remained. Of these, 114 of eyes (62.0%) were classified as "dry" on optical coherence tomography, whereas 48 eyes (26.1%) still had a component of IRF, and 22 (12.0%) had subretinal fluid alone. There was no statistically significant association between APOE variants and presence of persistent IRF, although there were almost double the number of subjects with ε2 (40%) who had persistent fluid compared with those with ε3/ε4 (23%) (P = 0.06).

CONCLUSION: In patients with neovascular age-related macular degeneration, the presence of the ε2 allele of the APOE gene was associated with having IRF at baseline. Larger studies are required to determine if a greater proportion of those with the ε2 allele retain this fluid after three initial injections.

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COMPARISON OF DRUSEN AND MODIFYING GENES IN AUTOSOMAL DOMINANT RADIAL DRUSEN AND AGE-RELATED MACULAR DEGENERATION.

Sohn EH, Wang K, Thompson S, Riker MJ, Hoffmann JM, Stone EM, Mullins RF.

BACKGROUND: Autosomal dominant radial drusen (ADRD), also termed Malattia Leventinese and Doyne honeycomb retinal dystrophy, causes early-onset vision loss because of mutation in EFEMP1. Drusen in an exceedingly rare ADRD human donor eye was compared with eyes affected with age-related macular degeneration (AMD). This study also elucidated whether variations in high-risk AMD genotypes modify phenotypic severity of ADRD.

METHODS: Morphologic and histochemical analyses of drusen in one ADRD donor and seven AMD donors. Evaluation of complement factor H (CFH) and ARMS2/HTRA1 alleles in a cohort of 25 subjects with ADRD.

RESULTS: Autosomal dominant radial drusen had unique onion skin-like lamination but otherwise shared many compositional features with hard, nodular drusen and/or diffuse soft drusen with basal deposits. Autosomal dominant radial drusen also possessed collagen type IV, an extracellular matrix protein that is absent in age-related drusen. Antibodies directed against the membrane attack complex showed robust labeling of ADRD. Vitronectin and amyloid P were present in drusen of both types. High-risk alleles in the CFH and ARMS2/HTRA1 genes were not associated with increasing ADRD severity.

CONCLUSION: Drusen from ADRD and AMD exhibit overlap of some major constituents, but ADRD exhibit distinct alterations in the extracellular matrix that are absent in AMD.

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Retinitis pigmentosa and macular degeneration in a patient with ataxia with isolated vitamin E deficiency with a novel c.717 del C mutation in the TTPA gene.

Iwasa K, Shima K, Komai K, Nishida Y, Yokota T, Yamada M.

Abstract: Ataxia with isolated vitamin E deficiency (AVED) is a neurodegenerative disease caused by a mutation in the α-tocopherol transfer protein gene (TTPA). The clinical features of the disease resemble Friedreich's ataxia. However, AVED is associated with low plasma vitamin E levels, which results in compromised antioxidant function. Dysregulation of this lipid-soluble antioxidant vitamin plays a major role in the neurodegeneration observed in AVED. Some AVED patients experience decreased visual acuity. Retinitis pigmentosa is thought to be the main cause of this visual impairment. Although antioxidant levels are important for the prevention of macular degeneration, there have been no reports of macular degeneration in AVED. Here, we describe a patient with AVED with progressive macular degeneration, who carried a novel truncating mutation-c.717 del C (p.D239EfsX25)-in exon 5 of the TTPA gene. These findings suggest that this newly identified mutation results in severely low serum vitamin E levels, which may be associated with the development of retinitis pigmentosa and macular degeneration.

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