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MD Research News

Issue 231

Monday 11 May, 2015

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Drug treatment

Ophthalmology. 2015 Apr 29. [Epub ahead of print]

The Cost-Effectiveness of Ranibizumab for the Treatment of Diabetic Macular Edema.

Brown GC, Brown MM, Turpcu A, Rajput Y.

PURPOSE: To assess the incremental, comparative effectiveness (patient value gain) and cost effectiveness (financial value gain) associated with 0.3-mg intravitreal ranibizumab injection therapy versus sham therapy for diabetic macular edema (DME).

DESIGN: Value-Based Medicine (Center for Value-Based Medicine, Flourtown, PA) 14-year, cost-utility analysis using patient preferences and 2012 United States real dollars.

PARTICIPANTS: Published data from the identical Ranibizumab Injection in Subjects with Clinically Significant Macular Edema with Center Involvement Secondary to Diabetes Mellitus (RISE and RIDE) clinical trials.

METHODS: An incremental cost-utility analysis was performed using societal and third-party insurer cost perspectives. Costs and outcomes were discounted with net present value analysis at 3% per annum.

MAIN OUTCOME MEASURES: The incremental comparative effectiveness was measured in: (1) quality-adjusted life year (QALY) gain and (2) percent patient value (quality-of-life) gain. Cost effectiveness was quantified with the cost-utility ratio (CUR) measured as $/QALY.

RESULTS: The 14-year, incremental patient value gain conferred by intravitreal ranibizumab therapy for diabetic maculopathy was 0.9981 QALY, equating to an 11.6% improvement in quality of life. The direct, ophthalmic medical cost for ranibizumab therapy in 1 eye was $30 116, whereas for 2 eyes it was $56 336. The direct, nonophthalmic, medical costs saved from decreased depression, injury, skilled nursing facility admissions, nursing home admissions, and other vision-associated costs totaled $51 758, resulting in an overall direct medical cost of $4578. The net mean societal cost for bilateral ranibizumab therapy was -$30 807. Of this total, decreased caregiver costs accrued a $31 406 savings against the direct medical costs, whereas decreased wage losses accrued a $3978 savings. The third-party insurer CUR for bilateral ranibizumab therapy was $4587/QALY. The societal cost perspective for bilateral therapy was -$30 807/QALY, indicating that ranibizumab therapy dominated sham therapy because it conferred both a positive QALY gain of 0.9981 and a financial value gain (positive financial return on investment) of $30 807 referent to the direct ophthalmic medical costs expended.

CONCLUSIONS: Intravitreal ranibizumab therapy for the treatment of DME confers considerable patient (human) value gain. It also accrues financial value to patients, public and private insurers, and society.

PMID: 25935787 [PubMed - as supplied by publisher]

BMJ Open. 2015 May 5;5(5):e006535.

The cost-effectiveness of initiating ranibizumab therapy in eyes with neovascular AMD with good vision: an economic model using real-world outcomes.

Butt T, Lee A, Lee C, Tufail A; UK AMD EMR Study Group.

OBJECTIVES: To evaluate the cost-effectiveness of immediate treatment with ranibizumab in patients with neovascular age-related macular degeneration (nAMD) with good (better than 6/12) starting visual acuity compared with current UK clinical guidance of waiting until vision falls below 6/12 to begin treatment, using real-world outcomes data.

DESIGN: A patient-level health economic state transition model based on levels of visual acuity in the better seeing eye was constructed to simulate the costs and consequences of treating patients with nAMD with ranibizumab.

SETTING: The model took the perspective of the UK National Health Service (NHS).

PARTICIPANTS: The model was populated with real-world outcomes and resource use from a prospective multicentre national nAMD database study containing 92 976 ranibizumab treatment episodes.

INTERVENTIONS: Two treatment approaches were compared: immediate intervention with 0.5 mg ranibizumab pro re nata, PRN (on detection of nAMD) or delayed intervention (waiting until vision fell to 6/12 before beginning treatment).

MAIN OUTCOME MEASURES: Quality-adjusted life years (QALYs) for health states and healthcare costs were accrued for each strategy, and an incremental cost-effectiveness ratio (ICER) was calculated. One-way and probabilistic sensitivity analyses were employed to test the uncertainty of the model.

RESULTS: Over a 2-year time horizon, based on 10 000 Monte Carlo simulations, the early treatment arm accumulated 1.59 QALYs and £8469.79 cost. The delayed treatment arm accumulated 1.35 QALYs and £7460.21 cost. The central ICER estimate was £4251.60.

CONCLUSIONS: A model based on real-world data is likely to be a realistic reflection of the health gains and resource use of ranibizumab for nAMD in the UK NHS. Initiating treatment immediately with ranibizumab PRN regimen is a cost-effective strategy compared with current guidance of initiating treatment at a level of 6/12 or worse vision.

PMID: 25943370 [PubMed - in process]

Int J Ophthalmol. 2015 Apr 18;8(2):315-20. eCollection 2015.

Effects of three consecutive monthly intravitreal injection of ranibizumab for polypoidal choroidal vasculopathy in Korea.

Park YG, Kang S, Roh YJ.

AIM: To evaluate the efficacy and safety of three consecutive monthly injections of intravitreal ranibizumab for the treatment of polypoidal choroidal vasculopathy (PCV) in Korea.

METHODS: A retrospective chart review of 25 patients (27 eyes) with PCV was conducted. Patients received three initial monthly intravitreal injections (0.5 mg) of ranibizumab and were monitored monthly for 12mo between January 2010 and October 2011. Reinjection of ranibizumab after three initial monthly loading was administered on an as-needed basis, guided by the optical coherence tomography (OCT), fluorescein angiography (FA) and indocyanine green angiography (ICGA). The main outcomes were the changes of the mean best corrected Snellen visual acuity (VA), central macular thickness (CMT) by OCT, the changes of polyps and branching vascular network by FA and ICGA, and total number of injections received by patients during the 12mo.

RESULTS: The mean best corrected Snellen visual acuities at baseline, 1, 3, 6 and 12mo after primary injection were 0.77±0.59, 0.76±0.53, 0.70±0.47, 0.63±0.43, 0.61±0.43, 0.62±0.42 logMAR, respectively, and showed significant improvement at 3, 6, 12mo (P=0.003, P=0.002, P=0.018, Wilcoxon signed-rank test). The mean CMT at baseline, 1, 2, 3, 6, and 12mo was 312.41±66.38 μm, 244.59±71.47 μm, 232.32±69.41 μm, 226.69±69.03 μm, 228.62±37.07 μm, 227.59±51.01 μm respectively, and showed significant reduction (all P<0.001, Wilcoxon signed-rank test). Polypoidal lesions resolved on ICGA in 3 eyes (11.1%) and a branching vascular network remained in all 24 eyes (88.9%). A total of 106 injections were given in the 12-month period, which equaled to a mean of 3.92 (range, 3-6) times. Sixteen of the 27 treated eyes had additional 1.56±0.91 injections. The others (11 eyes) had just 3 consecutive injections.

CONCLUSION: An initial loading dose of three monthly ranibizumab injections is a safe and effective method in treating PCV, with visual and anatomical improvement over one year follow-up.

PMID: 25938048 [PubMed] PMCID: PMC4413578

BMJ Open. 2015 May 3;5(4):e007746.

Anti-VEGF therapies in the treatment of choroidal neovascularisation secondary to non-age-related macular degeneration: a systematic review.

Stuart A, Ford JA, Duckworth S, Jones C, Pereira A.

OBJECTIVES: The aim of this study is to systematically review the evidence for anti-vascular endothelial growth factor (VEGF) therapy in choroidal neovascularisation secondary to conditions other than age-related macular degeneration.

DATA SOURCES: MEDLINE, MEDLINE in-process, EMBASE and CENTRAL databases and conference abstracts were searched (from inception to Jan 2014).

STUDY ELIGIBILITY CRITERIA, PARTICIPANTS AND INTERVENTIONS:

Randomised and non-randomised comparative studies with follow-up of at least 6 months were included and were used to assess clinical effectiveness.

STUDY APPRAISAL AND SYNTHESIS METHOD: Risk of bias was assessed using the Cochrane risk of bias tool and modified Newcastle-Ottawa Scale. Meta-analysis was not possible due to methodological heterogeneity.

RESULTS: 16 studies met the inclusion criteria (1091 eyes; 963 pathological myopia, 74 other conditions). There was large variation in risk of bias across studies. An improvement in best-corrected visual acuity in anti-VEGF arms over comparators was reported in all studies. The proportion of patients improving by at least 15 letters in anti-VEGF arms ranged from 27.3% to 70%. There were no significant differences between bevacizumab and ranibizumab.

LIMITATIONS: Owing to the rarity of choroidal neovascularisation secondary to conditions other than age-related macular degeneration or pathological myopia, there are unlikely to ever be sufficiently powered trials in these populations.

CONCLUSIONS: Bevacizumab and ranibizumab appear to be effective in improving visual acuity for patients with choroidal neovascularisation secondary to conditions other than age-related macular degeneration. The evidence base is strongest for choroidal neovascularisation secondary to pathological myopia, however, based on current evidence and likely pharmacological pathways, clinicians should consider treatment with either bevacizumab or ranibizumab for rarer causes.

PMID: 25941188 [PubMed - in process]

Retina. 2015 May 5. [Epub ahead of print]

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY FOR NEOVASCULAR AGE-RELATED MACULAR DEGENERATION: Outcomes in Eyes With Poor Initial Vision.

Toth LA, Stevenson M, Chakravarthy U.

PURPOSE: To assess the effect of anti-vascular endothelial growth factor treatment on visual acuity outcome in patients with neovascular age-related macular degeneration presenting with very low vision.

METHODS: Retrospective analysis of electronic patient care record of 420 eyes treated with ranibizumab between March 2010 and June 2013. The authors classified the extracted sample into 3 categories based on the initial best-corrected visual acuity (BCVA) as measured on the Early Treatment Diabetic Retinopathy Study charts: 0 to 35 letters, 36 to 69 letters, and ≥70 letters. Best BCVA achieved in Year 1, and average BCVA over 36 months was computed. The neovascular lesion type, area of lesion, the presence or absence of hemorrhage, retinal pigment epithelium tear, and atrophy were systematically graded as was extent of fibrosis on a categorical scale of 0 to 4. Regression analysis was performed with the best BCVA achieved in Year 1 as the outcome variable and initial BCVA, person, and lesion characteristics as explanatory variables.

RESULTS: The mean change in BCVA from the initial visit to the best-attained BCVA during Year 1 was highly statistically significant with an improvement of 9.95 letters. The improvement from initial BCVA to average BCVA over 36 months was 4.01 letters. Regression analysis identified atrophy and fibrosis as predictors of best BCVA, with the model having an r of 0.71.

CONCLUSION: Our study supports the use of anti-vascular endothelial growth factor agents even in eyes with low visual acuity particularly when fibrosis and atrophy are absent and suggests algorithms to predict outcome for combinations of visual acuity and lesion characteristics across the full visual acuity range.

PMID: 25946692 [PubMed - as supplied by publisher]

Arq Bras Oftalmol. 2015 Mar-Apr;78(2):105-9.

Optical coherence tomography and multifocal electroretinography of patients with advanced neovascular age-related macular degeneration before, during, and after treatment with ranibizumab.

Almeida IN, Almeida LN, Almeida Sobrinho EF, Gomes BD, Souza Gda S, Rosa AA, Silveira LC.

PURPOSE: To evaluate retinal morphology and function of patients with advanced neovascular age-related macular degeneration (AMD) before, during, and after treatment with ranibizumab.

METHODS: Twenty-one eyes diagnosed with advanced AMD were studied with optical coherence tomography (OCT) and multifocal electroretinography (mfERG). Three intravitreal injections of ranibizumab were administered at 1-month intervals. Evaluations were performed before the first injection (D0) and at 30 (D30), 60 (D60), and 90 days (D90) after the first injection and compared to an age-matched control group (n=21 eyes).

RESULTS: The thickness of macular retinal layers increased before treatment due to the presence of intraretinal fluid. A thick retinal pigment epithelium-choriocapillaris complex (RPE-CC) suggested the presence of choroidal neovascular membrane. Intraretinal edema decreased after treatment (P<0.01), but persisting RPE-CC thickness resulted in a subretinal scar. Three different annular retinal areas were studied with mfERG (from center to periphery: rings R1, R2, and R3). The amplitude of the first negative component (N1) decreased in R1, R2, and R3 at D30, D60, and D90 when compared with that in controls (P<0.05); the N1 implicit time was delayed in R3 at D30 (P<0.05). The amplitude of the first positive component (P1) was reduced in R1 and R2 at D30, D60, and D90 when compared with that in controls (P<0.01); the P1 implicit time was delayed in R1 at D0 and D60 (P<0.05), in R2 at D0, D30, and D90 (P<0.01), and in R3 at D30 and D60 (P<0.05).

CONCLUSION: Ranibizumab reduces intraretinal edema, even in advanced cases. Central macular activity appeared to increase after the initiation of treatment, improving over time.

PMID: 25945532 [PubMed - in process]

Other treatment & diagnosis

Middle East Afr J Ophthalmol. 2015 Apr-Jun;22(2):186-91.

Quantitative Analysis of Segmented Fluorescein Angiography Images for the Follow-up of Choroidal Neovascular Membrane.

Ghosh S, Haldar P, Ravindran P, Chatterjee J, Paranjape SV, Bhaduri G.

PURPOSE: The aim of this study was to evaluate choroidal neovascular (CNV) lesions with fluorescein angiography (FA) and to identify quantitative parameters and correlate these parameters to treatment outcomes.

SUBJECTS AND METHODS: This institution based cross-sectional study evaluated 30 eyes with active sub-foveal predominantly classic CNV treated with bevacizumab. Pre- and post-injection segmented FA images were analyzed. Lesion area and CNV lesion were manually delineated. Outcome measure was the change 1-month after each injection in different intensity values (0-255 divided in eight regions A [lowest intensity] to H [highest intensity] on a linear scale) in lesion area, perimeter, greatest linear dimension (GLD), area, visual acuity (VA) and central macular thickness (CMT).

RESULTS: At month 3, statistically significant changes from baseline occurred in VA, CMT, lesion area, GLD and perimeter ($P < 0.05$ all comparisons). Change in CMT from baseline to 3 months postinjection was correlated with change in VA ($P = 0.009$, $r = 0.469$) and intensity regions B ($P = 0.001$, $r = -0.565$), D ($P = 0.001$, $r = 0.560$), E ($P = 0.035$, $r = 0.386$). At month 3, change in intensity values 0-63 (A + B) was negatively correlated with CMT ($P = 0.001$, $r = -0.575$) and lesion area ($P = 0.019$, $r = -0.427$); change in intensity values 64-223 (C-G) was positively correlated with CMT ($P = 0.000$, $r = 0.636$) and lesion area ($P = 0.002$, $r = 0.551$).

CONCLUSIONS: Decrease in area, GLD, perimeter and area with intensity ≥ 64 on segmented FA were associated with a favorable outcome of treatment. These parameters may be useful adjuncts to existing evaluation techniques during follow-up of CNV.

PMID: 25949076 [PubMed - in process]

Stem Cell Reports. 2015 Apr 29. pii: S2213-6711(15)00105-8. [Epub ahead of print]

Treatment of Macular Degeneration Using Embryonic Stem Cell-Derived Retinal Pigment Epithelium: Preliminary Results in Asian Patients.

Song WK, Park KM, Kim HJ, Lee JH, Choi J, Chong SY, Shim SH, Del Priore LV, Lanza R.

Abstract: Embryonic stem cells hold great promise for various diseases because of their unlimited capacity for self-renewal and ability to differentiate into any cell type in the body. However, despite over 3 decades of research, there have been no reports on the safety and potential efficacy of pluripotent stem cell progeny in Asian patients with any disease. Here, we report the safety and tolerability of subretinal transplantation of human embryonic-stem-cell (hESC)-derived retinal pigment epithelium in four Asian patients: two with dry age-related macular degeneration and two with Stargardt macular dystrophy. They were followed for 1 year. There was no evidence of adverse proliferation, tumorigenicity, ectopic tissue formation, or other serious safety issues related to the transplanted cells. Visual acuity improved 9-19 letters in three patients and remained stable (+1 letter) in one patient. The results confirmed that hESC-derived cells could serve as a potentially safe new source for regenerative medicine.

PMID: 25937371 [PubMed - as supplied by publisher]

Atheroscler Suppl. 2015 May;18:140-5.

Changes of the complement system and rheological indicators after therapy with rheohemapheresis.

Blaha M, Andrys C, Langrova H, Studnicka J, Drsata J, Lanska M, Blaha V, Zak P.

INTRODUCTION: In the last 10 years, many studies have been published on the role of the complement system in microcirculation disorders. However, as for the changes of complement components after rheohemapheresis, there is still a lack of detailed data in the literature. Complement changes may play an important role in pathogenesis of some microcirculation disorders, such as age-related macular degeneration and acute hearing loss. The objective of this study was to investigate the effect of rheohemapheresis on the basic complement pathways.

PATIENTS AND METHODS: 32 patients were treated with rheohemapheresis, including 16 patients (10 men and 6 women) for age-related macular degeneration (AMD), mean age 69.7 ± 6.06 years (range 62-87 years) and 16 patients (11 men and 5 women) aged 56.4 ± 11.5 (range 34-73 years) for acute hearing loss.

RESULTS: Rheohemapheresis led to a significant drop of all three complement-activation pathways in both groups of patients. Moreover, complement factor H was also reduced.

CONCLUSION: The observed reduction in all three basic complement activation pathways after rheohemapheresis could be clinically important. The search continues both to find substances which influence complement systems and to develop more effective new drugs that require less frequent administration and that provide improved intraocular therapy for AMD patients.

PMID: 25936318 [PubMed - in process]

Optom Vis Sci. 2015 May 7. [Epub ahead of print]

Teleretinal Imaging for Detection of Referable Macular Degeneration.

Duchin KS, Asefzadeh B, Poulaki V, Rett D, Marescalchi P, Cavallerano A.

PURPOSE: The purpose of this study was to determine the sensitivity and specificity for detection of referable age-related macular degeneration (AMD) using an existing nonmydriatic telemedicine pathway for diabetic retinopathy screening with comparison to same-day face-to-face examination by a retina specialist.

METHODS: Subjects in this study underwent nonmydriatic and mydriatic digital retinal imaging on the same day as stereoscopic dilated examination of the macula by a retina specialist and the level of AMD was recorded for each eye. Images were graded by two trained readers as nonreferable or referable (AREDS [Age-Related Eye Disease Study] grading of level 3 or greater). Sensitivity and specificity were calculated by comparing referral recommendations between each reader and the retina specialist ("gold standard").

RESULTS: There were 47 subjects (94 eyes) enrolled in the study. Sensitivity for nonreferable AMD with nonmydriatic imaging was 1.0 (reader 1) and 1.0 (reader 2), whereas specificity was 0.75 (reader 1) and 0.91 (reader 2). Sensitivity for referable AMD with nonmydriatic imaging was 0.84 (reader 1) and 0.88 (reader 2), whereas specificity was 0.81 (reader 1) and 0.81 (reader 2).

CONCLUSIONS: Our study showed that nonmydriatic digital retinal imaging had excellent sensitivity and specificity in identifying referable and nonreferable AMD using an existing validated telemedicine pathway for diabetic retinopathy screening.

PMID: 25955641 [PubMed - as supplied by publisher]

Pathogenesis

J Neurosci. 2015 May 6;35(18):7304-11.

Investigating mitochondria as a target for treating age-related macular degeneration.

Terluk MR, Kapphahn RJ, Soukup LM, Gong H, Gallardo C, Montezuma SR, Ferrington DA.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness among older adults in the developed world. Although the pathological mechanisms have not been definitively elucidated, evidence suggests a key role for mitochondrial (mt) dysfunction. The current study used our unique collection of human retinal samples graded for the donor's stage of AMD to address fundamental questions about mtDNA damage in the retina. To evaluate the distribution of mtDNA damage in the diseased retina, damage in the retinal pigment epithelium (RPE) and neural retina from individual donors were compared. To directly test a long-held belief that the macula is selectively damaged with AMD, RPE mtDNA damage was measured in the macula and peripheral sections from individual donors. Small segments of the entire mt genome were examined to determine whether specific regions are preferentially damaged. Our results show that mtDNA damage is limited to the RPE, equivalent mtDNA damage is found in the macular and peripheral RPE, and sites of damage are localized to regions of the mt genome that may impact mt function. These results provide a scientific basis for targeting the RPE mitochondria with therapies that protect and enhance mt function as a strategy for combating AMD.

PMID: 25948278 [PubMed - in process]

J Neurosci. 2015 May 6;35(18):6987-96.

Upregulation of P2RX7 in Cx3cr1-Deficient Mononuclear Phagocytes Leads to Increased Interleukin-1β Secretion and Photoreceptor Neurodegeneration.

Hu SJ, Calippe B, Lavalette S, Roubeix C, Montassar F, Housset M, Levy O, Delarasse C, Paques M, Sahel JA, Sennlaub F, Guillonneau X.

Abstract: Photoreceptor degeneration in age-related macular degeneration (AMD) is associated with an infiltration and chronic accumulation of mononuclear phagocytes (MPs). We have previously shown that Cx3cr1-deficient mice develop age- and stress- related subretinal accumulation of MPs, which is associated with photoreceptor degeneration. Cx3cr1-deficient MPs have been shown to increase neuronal apoptosis through IL-1β in neuroinflammation of the brain. The reason for increased IL-1β secretion from Cx3cr1-deficient MPs, and whether IL-1β is responsible for increased photoreceptor apoptosis in Cx3cr1-deficient mice, has not been elucidated. Here we show that Cx3cr1-deficient MPs express increased surface P2X7 receptor (P2RX7), which stimulates IL-1β maturation and secretion. P2RX7 and IL-1β inhibition efficiently blunted Cx3cr1-MP-dependent photoreceptor apoptosis in a monocyte/retina coculture system and in light-induced subretinal inflammation of Cx3cr1-deficient mice in vivo. Our results provide an explanation for increased CX3CR1-dependent IL-1β secretion and suggest that IL-1β or P2RX7 inhibition can help inhibit the inflammation-associated photoreceptor cell loss in late AMD, including geographic atrophy, for which no efficient treatment currently exists.

PMID: 25948251 [PubMed - in process]

Phys Chem Chem Phys. 2015 May 8. [Epub ahead of print]

Phospholipid-based self-assembled mesophase systems for light-activated drug delivery.

Du JD, Fong WK, Salentinig S, Caliph SM, Hawley A, Boyd BJ.

Abstract: The manipulation of the structure of phospholipid-based mesophases to induce a slow to fast drug release profile has potential for use in therapeutic situations where continuous absorption of drug is not

desirable and reduce the frequency of injection for short acting or rapidly cleared drugs in treatments for diseases such as macular degeneration. This study had two aims; firstly to confirm the phase behaviour of 20 mol% cholesterol in 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoethanolamine (POPE), which was previously reported to transition from lamellar (slow release) to bicontinuous cubic (fast release) phase with increasing temperature. Contrary to the literature, no bicontinuous cubic phase was observed but a transition to the inverse hexagonal phase occurred at all POPE : cholesterol ratios investigated. The second aim was to render these mesophases responsive to near-infrared laser (NIR) irradiation by incorporation of gold nanorods (GNR) incorporated into the POPE system to induce photothermal heating. The inclusion of 3 nM GNR in POPE systems induced reversible disruption of lipid packing equivalent to increasing the temperature to 55 °C when irradiated for 30 s. This study confirmed that although the previously published phase behavior was not correct, GNR and NIR can be used to manipulate the self-assembled mesophases in phospholipid-based systems and highlights the potential for a phospholipid-based light-activated drug delivery system.

PMID: 25953620 [PubMed - as supplied by publisher]

Biosens Bioelectron. 2015 Apr 25;71:445-455. [Epub ahead of print]

Real-time quantitative monitoring of hiPSC-based model of macular degeneration on Electric Cell-substrate Impedance Sensing microelectrodes.

Gamal W, Borooah S, Smith S, Underwood I, Srsen V, Chandran S, Bagnaninchi PO, Dhillon B.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the developed world. Humanized disease models are required to develop new therapies for currently incurable forms of AMD. In this work, a tissue-on-a-chip approach was developed through combining human induced pluripotent stem cells, Electric Cell-substrate Impedance Sensing (ECIS) and reproducible electrical wounding assays to model and quantitatively study AMD. Retinal Pigment Epithelium (RPE) cells generated from a patient with an inherited macular degeneration and from an unaffected sibling were used to test the model platform on which a reproducible electrical wounding assay was conducted to model RPE damage. First, a robust and reproducible real-time quantitative monitoring over a 25-day period demonstrated the establishment and maturation of RPE layers on the microelectrode arrays. A spatially controlled RPE layer damage that mimicked cell loss in AMD disease was then initiated. Post recovery, significant differences ($P<0.01$) in migration rates were found between case (8.6±0.46μm/h) and control cell lines (10.69±0.21μm/h). Quantitative data analysis suggested this was achieved due to lower cell-substrate adhesion in the control cell line. The ECIS cell-substrate adhesion parameter (α) was found to be 7.8±0.28Ω1/2cm for the case cell line and 6.5±0.15Ω1/2cm for the control. These findings were confirmed using cell adhesion biochemical assays. The developed disease model-on-a-chip is a powerful platform for translational studies with considerable potential to investigate novel therapies by enabling real-time, quantitative and reproducible patient-specific RPE cell repair studies.

PMID: 25950942 [PubMed - as supplied by publisher]

PLoS One. 2015 May 7;10(5):e0125548. eCollection 2015.

Netrin-1 - DCC Signaling Systems and Age-Related Macular Degeneration.

SanGiovanni JP, Chen J, Gupta AS, Smith LE, Sapieha P, Lee PH.

Abstract: We conducted a nested candidate gene study and pathway-based enrichment analysis on data from a multi-national 77,000-person project on the molecular genetics of age-related macular degeneration (AMD) to identify AMD-associated DNA-sequence variants in genes encoding constituents of a netrin-1 (NTN1)-based signaling pathway that converges on DNA-binding transcription complexes through a 3'-5'-cyclic adenosine monophosphate-calcineurin (cAMP-CN)-dependent axis. AMD-associated single nucleotide polymorphisms (SNPs) existed in 9 linkage disequilibrium-independent genomic regions; these

included loci overlapping NTN1 (rs9899630, P ≤ 9.48 x 10-5), DCC (Deleted in Colorectal Cancer)-the gene encoding a primary NTN1 receptor (rs8097127, P ≤ 3.03 x 10-5), and 6 other netrin-related genes. Analysis of the NTN1-DCC pathway with exact methods demonstrated robust enrichment with AMD-associated SNPs (corrected P-value = 0.038), supporting the idea that processes driven by NTN1-DCC signaling systems operate in advanced AMD. The NTN1-DCC pathway contains targets of FDA-approved drugs and may offer promise for guiding applied clinical research on preventive and therapeutic interventions for AMD.

PMID: 25950802 [PubMed - in process]

Int J Ophthalmol. 2015 Apr 18;8(2):385-94. eCollection 2015.

Association between SERPING1 rs2511989 polymorphism and age-related macular degeneration: Meta-analysis.

Dong Y, Li ZD, Fang XY, Shi XF, Chen S, Tang X.

AIM: To investigate the association between SERPING1 rs2511989 (G>A) polymorphism and age-related macular degeneration (AMD).

METHODS: A number of electronic databases (up to July 15, 2014) were searched independently by two investigators. A Meta-analysis was performed on the association between SERPING1 rs2511989 polymorphism and AMD. Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated.

RESULTS: Eight studies with 16 cohorts consisting of 9163 cases and 6813 controls were included in this Meta-analysis. There was no significant association between rs2511989 polymorphism and AMD under all genetic models in overall estimates (A vs G: OR= 0.938, 95%CI =0.858-1.025; AA vs GG:OR =0.871, 95% CI =0.719-1.056; AG vs GG: OR =0.944, 95%CI =0.845-1.054; AA+AG vs GG: OR =0.927, 95% CI =0.823-1.044; AA vs AG+GG: OR =0.890, 95%CI =0.780-1.034). Cumulative Meta-analyses also showed a trend of no association between rs2511989 polymorphism and AMD as information accumulated by year. Subgroup analysis and Meta-regression analysis indicated that age-matching status was the main source of heterogeneity. Sensitivity analysis found the results in overall comparisons and subgroup comparisons of white subjects under the allele model were found to have significantly statistical differences after studies deviating from Hardy-Weinberg equilibrium (HWE) were excluded (overall: OR=0.918, 95%CI = 0.844-0.999, P =0.049; whites: OR =0.901, 95%CI = 0.817-0.994, P =0.038). However, the results were not sufficiently robust for further sensitivity analysis and statistical differences disappeared on applying Bonferroni correction (with a significance level set at 0.05/25).

CONCLUSION: This Meta-analysis indicates that SERPING1 rs2511989 polymorphism and AMD tend to have no association with each other. Age matching status is a big confounding factor, and more studies with subtle designs are warranted in future.

PMID: 25938061 [PubMed] PMCID: PMC4413591

Int J Mol Med. 2015 May 5. [Epub ahead of print]

3,3'-Diindolylmethane inhibits VEGF expression through the HIF-1α and NF-κB pathways in human retinal pigment epithelial cells under chemical hypoxic conditions.

Park H, Lee DS, Yim MJ, Choi YH, Park S, Seo SK, Choi JS, Jang WH, Yea SS, Park WS, Lee CM, Jung WK, Choi IW.

Abstract: Oxidative stress in the retinal pigment epithelium (RPE) can lead to the pathological causes of age-related macular degeneration (AMD). Hypoxia induces oxidative damage in retinal pigment epithelial cells (RPE cells). In this study, we investigated the capacity of 3,3'-diindolylmethane (DIM) to reduce the expression of vascular endothelial growth factor (VEGF) under hypoxic conditions, as well as the molecular

mechanisms involved. Human RPE cells (ARPE-19 cells) were treated with cobalt chloride (CoCl2, 200 μM) and/or DIM (10 and 20 μM). The production of VEGF was measured by enzyme-linked immunosorbent assay. The translocation of hypoxia-inducible factor-1α (HIF-1α) and nuclear factor-κB (NF-κB) was determined by western blot analysis. The binding activity of HIF-1α and NF-κB was analyzed by electrophoretic mobility shift assay. The phosphorylation levels of mitogen-activated protein kinases (MAPKs) were measured by western blot analysis. The levels of mitochondrial reactive oxygen species (ROS) were detected by fluorescence microplate assay. The results revealed that DIM significantly attenuated the CoCl2-induced expression of VEGF in the ARPE-19 cells. The CoCl2-induced translocation and activation of HIF-1α and NF-κB were also attenuated by treatment with DIM. In addition, DIM inhibited the CoCl2-induced activation of p38 MAPK in the ARPE-19 cells. Pre-treatment with YCG063, a mitochondrial ROS inhibitor, led to the downregulation of the CoCl2-induced production of VEGF by suppressing HIF-1α and NF-κB activity. Taken together, the findings of our study demonstrate that DIM inhibits the CoCl2-induced production of VEGF by suppressing mitochondrial ROS production, thus attenuating the activation of HIF-1α and p38 MAPK/NF-κB.

PMID: 25955241 [PubMed - as supplied by publisher]

J Mol Med (Berl). 2015 May 8. [Epub ahead of print]

Attenuation of EMT in RPE cells and subretinal fibrosis by an RAR-γ agonist.

Kimura K, Orita T, Liu Y, Yang Y, Tokuda K, Kurakazu T, Noda T, Yanai R, Morishige N, Takeda A, Ishibashi T, Sonoda KH.

Abstract: Subretinal fibrosis contributes to the loss of vision associated with age-related macular degeneration (AMD). Retinal pigment epithelial (RPE) cells play a key role in the pathogenesis of AMD including the fibrotic reaction. We examined the role of retinoic acid receptor-γ (RAR-γ) in the epithelial-mesenchymal transition (EMT) and other fibrosis-related processes in mouse RPE cells cultured in a type I collagen gel. Transforming growth factor-β2 (TGF-β2)-induced collagen gel contraction mediated by the RPE cells was inhibited by the RAR-γ agonist R667 in a concentration- and time-dependent manner. Expression of the mesenchymal markers α-smooth muscle actin and fibronectin, the release of interleukin-6, and the phosphorylation of paxillin, mitogen-activated protein kinases (ERK, p38, and JNK), Smad2, and AKT induced by TGF-β2 were also suppressed by the RAR-γ agonist. Furthermore, gelatin zymography and immunoblot analysis revealed that the TGF-β2-induced release of matrix metalloproteinase (MMP)-2, MMP-3, MMP-8, and MMP-9 from RPE cells was inhibited by R667, and the MMP inhibitor GM6001 attenuated TGF-β2-induced RPE cell contraction. Finally, immunohistofluorescence analysis with antibodies to glial fibrillary acidic protein showed that R667 inhibited the development of subretinal fibrosis in a mouse model in vivo. Our results thus suggest that RAR-γ agonists may prove effective for the treatment of subretinal fibrosis associated with AMD.

KEY MESSAGE: RAR-γ agonist R667 suppressed collagen gel contraction mediated by RPE cells. Epithelial-mesenchymal transition (EMT) in RPE cells was inhibited by RAR-γ agonist R667. RAR-γ agonist R667 inhibited fibrosis-related processes in RPE cells. RAR-γ agonists may attenuate AMD-associated fibrosis.

PMID: 25947075 [PubMed - as supplied by publisher]

Cell Mol Life Sci. 2015 May 6. [Epub ahead of print]

Deletion of myosin VI causes slow retinal optic neuropathy and age-related macular degeneration (AMD)-relevant retinal phenotype.

Schubert T, Gleiser C, Heiduschka P, Franz C, Nagel-Wolfrum K, Sahaboglu A, Weisschuh N, Eske G, Rohbock K, Rieger N, Paquet-Durand F, Wissinger B, Wolfrum U, Hirt B, Singer W, Rüttiger L,

Zimmermann U, Knipper M.

Abstract: The unconventional myosin VI, a member of the actin-based motor protein family of myosins, is expressed in the retina. Its deletion was previously shown to reduce amplitudes of the a- and b-waves of the electroretinogram. Analyzing wild-type and myosin VI-deficient Snell's Waltzer mice in more detail, the expression pattern of myosin VI in retinal pigment epithelium, outer limiting membrane, and outer plexiform layer could be linked with differential progressing ocular deficits. These encompassed reduced a-waves and b-waves and disturbed oscillatory potentials in the electroretinogram, photoreceptor cell death, retinal microglia infiltration, and formation of basal laminar deposits. A phenotype comprising features of glaucoma (neurodegeneration) and age-related macular degeneration could thus be uncovered that suggests dysfunction of myosin VI and its variable cargo adaptor proteins for membrane sorting and autophagy, as possible candidate mediators for both disease forms.

PMID: 25939269 [PubMed - as supplied by publisher]

Crit Rev Eukaryot Gene Expr. 2015;25(1):23-32.

Role of autophagy in photoreceptor cell survival and death.

Bo Q, Ma S, Han Q, Wang FE, Li X, Zhang Y

Abstract: Autophagy, a highly conserved self-degradation process that occurs under both physiological and pathological conditions, provides the raw material and energy for cell regeneration under normal circumstances. Dysregulated autophagy under diseased conditions may cause protein accumulation, organelle dysfunction, and even cell death. Recent studies have shown that autophagy regulates the structural integrity and physiological functions of retinal photoreceptor cells and contributes to the pathogenesis of retinopathies such as retinal detachment, age-related macular degeneration, retinitis pigmentosa, and Leber's congenital amaurosis. In this review, we discuss the role of autophagy in photoreceptor cell survival and death in retinal physiology and diseases, and suggest the possibility that autophagy-targeting therapy may be a new strategy for retinal diseases marked by photoreceptor cell death.

PMID: 25955815 [PubMed - in process]

Epidemiology

J Am Geriatr Soc. 2015 May 4. [Epub ahead of print]

Age-Related Macular Degeneration and Mortality in Older Women: The Study of Osteoporotic Fractures.

Pedula KL, Coleman AL, Yu F, Cauley JA, Ensrud KE, Hochberg MC, Fink HA, Hillier TA; Study of Osteoporotic Fractures Research Group.

OBJECTIVES: To examine the association between age-related macular degeneration (AMD) and all-cause and cause-specific mortality in a population of older women.

DESIGN: Prospective cohort study.

SETTING: Four U.S. clinical centers.

PARTICIPANTS: A random sample of 1,202 women with graded fundus photographs at the Year 10 visit of the Study of Osteoporotic Fractures (mean age 79.5).

MEASUREMENTS: Forty-five-degree stereoscopic fundus photographs were graded for presence and severity (early vs late) of AMD. Vital status was adjudicated from death certificates. Cox proportional

hazards models, adjusted for appropriate confounders, were used to estimate mortality hazards ratios.

RESULTS: Prevalence of any AMD was 40.5% at baseline, with 441 (36.7%) having early AMD and 46 (3.8%) having late AMD. Cumulative mortality was 51.6% over 15 years of follow-up. Overall, there was no significant association between AMD presence or severity and all-cause or cause-specific mortality. Because there was a significant interaction between AMD and age in predicting mortality ($P < .05$ for each mortality type), analyses were stratified according to age group. In women younger than 80, after adjusting for covariates, late AMD was associated with cardiovascular disease (CVD) mortality (hazard ratio (HR) = 2.61, 95% confidence interval (CI) = 1.05-6.46). In women aged 80 and older, early AMD was associated with all-cause (HR = 1.39, 95% CI = 1.11-1.75) and non-CVD, noncancer (HR = 1.45, 95% CI = 1.05-2.00) mortality. Any AMD was associated with all-cause (HR = 1.42, 95% CI = 1.13-1.78) and CVD (HR = 1.45, 95% CI = 1.01-2.09) mortality in women aged 80 and older.

CONCLUSION: AMD is a predictor of poorer survival in women, especially those aged 80 and older. Determination of shared risk factors may identify novel pathways for intervention that may reduce the risk of both conditions.

PMID: 25941039 [PubMed - as supplied by publisher]

Chin Med J (Engl). 2015 5th May;128(9):1154-1159.

Single-site Baseline and Short-term Outcomes of Clinical Characteristics and Life Quality Evaluation of Chinese Wet Age-related Macular Degeneration Patients in Routine Clinical Practice.

Wang LL, Liu WJ, Liu HY1, Xu X.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss among the older population. In China, treatment of age-related ocular diseases is becoming a priority in eye care services. This study was to investigate the clinical characteristics and quality of life of Chinese patients with wet AMD and current treatment types, to evaluate short-term gains in different treatments, and to investigate associations between visual function and vision-related quality of life (VRQoL).

METHODS: A prospective, observational, noninterventional study was conducted. Basic data were collected from patients with clinical diagnoses of wet AMD before clinical assessments at baseline. VRQoL was measured with the Chinese version of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25). Correlations of the NEI VFQ-25 subscale scores with best-corrected visual acuity (BCVA) and between-group differences were analyzed.

RESULTS: A total of 80 wet AMD patients were enrolled, with the mean age of 68.40 years. About one-quarter of wet AMD patients received intravitreal (IVT) ranibizumab treatment, and 67% of them were treated on a pro re nata basis. The visual acuity of patients treated with IVT ranibizumab at month 3 after treatment was significantly increased, whereas patients treated with traditional Chinese medicine achieved no significant improvement. Cronbach's α for the NEI VFQ-25 subscales ranged from 0.697 to 0.843. Eight subscale and overall composite scores were moderately correlated with the BCVA of the better-seeing eye. Significant differences in the overall NEI VFQ-25 scores and other subscales were observed between patients with BCVA in the better-seeing eye of less than 50 letters and the others.

CONCLUSIONS: Patients treated with IVT ranibizumab experienced better vision improvement at short-term follow-up. The Chinese version of the NEI VFQ-25 is a valid and reliable tool for assessing the VRQoL of Chinese wet AMD patients.

PMID: 25947396 [PubMed - as supplied by publisher]

Genetics

Arq Bras Oftalmol. 2015 Mar-Apr;78(2):85-8.

Association of high-density lipoprotein and apolipoprotein E genetic variants with age-related macular degeneration.

Cezario SM, Calastri MC, Oliveira CI, Carmo TS, Pinhel MA, Godoy MF, Jorge R, Cotrim CC, Souza DR, Siqueira RC.

PURPOSE: This study aimed to evaluate the association of age-related macular degeneration (AMD) with apolipoprotein E (APOE) variants and serum lipid profiles, including levels and fractions of total serum cholesterol (TC), low-density lipoprotein cholesterol (LDLc), and high-density lipoprotein cholesterol (HDLc), and triglycerides (TG).

METHODS: Genotyping of APOE-HhaI was performed in 134 patients (study group, SG) and 164 individuals without AMD (control group, CG), aged 50-89 years. Lipid profiles were analyzed in a subgroup of 30 subjects of both groups, matched according to age and sex. The significance level was set at P<0.05.

RESULTS: APOE E3/E3 was more prevalent (SG=74.6%; CG=77.4%), with no difference between both groups (P=0.667). The same result was observed for risk genotypes (APOE E -/2: SG=7.4%; CG=10.3%, P=0.624). Serum levels of TC, LDLc, and TG revealed similar median values between SG (193.5, 116, and 155 mg/dL, respectively) and CG (207.5, 120, and 123.5 mg/dL, respectively; P >0.05). For HDLc, a higher median value was observed in SG (53.3 mg/dL) versus CG (42.5 mg/dL; P=0.016). Logistic regression analysis showed the same value, and the HDLc/TC ratio was -11.423 (P=0.014), as also confirmed by an increase in HDLc in SG. The association between lipid profiles and apolipoprotein E genotypes was similar in both groups (P>0.05).

CONCLUSION: APOE-HhaI is not associated with AMD. However, an increase in serum HDLc level appears to exert a protective effect against the disease, irrespective of the genetic variants of apoE.

PMID: 25945528 [PubMed - in process]

Diet, lifestyle and low vision

Int Ophthalmol. 2015 May 5. [Epub ahead of print]

Visual function affects prosocial behaviors in older adults.

Teoli DA, Smith MD, Leys MJ, Jain P, Odom JV.

Abstract: Eye-related pathological conditions such as glaucoma, diabetic retinopathy, and age-related macular degeneration commonly lead to decreased peripheral/central field, decreased visual acuity, and increased functional disability. We sought to answer if relationships exist between measures of visual function and reported prosocial behaviors in an older adult population with eye-related diagnoses. The sample consisted of adults, aged ≥60 years old, at an academic hospital's eye institute. Vision ranged from normal to severe impairment. Medical charts determined the visual acuities, ocular disease, duration of disease (DD), and visual fields (VF). Measures of giving help were via validated questionnaires on giving formal support (GFS) and giving informal support; measures of help received were perceived support (PS) and informal support received (ISR). ISR had subscales: tangible support (ISR-T), emotional support (ISR-E), and composite (ISR-C). Visual acuities of the better and worse seeing eyes were converted to LogMAR values. VF information converted to a 4-point rating scale of binocular field loss severity. DD was in years. Among 96 participants (mean age 73.28; range 60-94), stepwise regression indicated a relationship of visual variables to GFS ($p < 0.05$; Multiple R 2 = 0.1679 with acuity-better eye, VF rating, and DD), PS ($p < 0.05$; Multiple R 2 = 0.2254 with acuity-better eye), ISR-C ($p < 0.05$; Multiple R 2 = 0.041 with acuity-better

eye), and ISR-T ($p < 0.05$; Multiple R 2 = 0.1421 with acuity-better eye). The findings suggest eye-related conditions can impact levels and perceptions of support exchanges. Our data reinforces the importance of visual function as an influence on prosocial behavior in older adults.

PMID: 25939988 [PubMed - as supplied by publisher]

RelaBr J Ophthalmol. 2015 Apr 30. [Epub ahead of print]

Patient-reported outcomes in randomised controlled trials on age-related macular degeneration.

Krezel AK, Hogg RE, Azuara-Blanco A.

BACKGROUND/AIMS: The purpose of this systematic review was to identify the frequency and type of patient-reported outcome measures (PROMs) used in recent randomised controlled trials (RCTs) for age-related macular degeneration (AMD).

METHODS: The authors conducted a systematic search between January 2010 and November 2013 in MEDLINE, EMBASE, Scopus, Cochrane Library (Central) and the clinical trials registries (http://www.controlled-trials.com and http://www.ClinicalTrials.gov) according to defined inclusion criteria (RCTs on AMD in English). Two independent reviewers evaluated studies for inclusion. One reviewer extracted data of included studies, and a second masked reviewer assessed 10% to confirm accuracy in data collection. Reference lists of included papers and appendices of relevant Cochrane systematic reviews were scanned to identify other relevant RCTs. Information collected on extracted outcomes was analysed using descriptive statistics.

RESULTS: Literature and registry search yielded 3816 abstracts of journal articles and 493 records from trial registries. A total of 177 RCTs were deemed to have met inclusion criteria. Of the 858 outcomes reported, 38 outcomes were identified as PROMs (4.4%). Of the 177 RCTs examined, PROMs were used in 25 trials (14.1%). The National Eye Institute Visual Function Questionnaire-25 was the most frequently used PROM instrument (64% of RCTs with PROMs included).

CONCLUSIONS: This review highlights that a small proportion of AMD RCTs included PROMs as outcome measures and that there was a variety in the instruments used.

PMID: 25934846 [PubMed - as supplied by publisher]

Front Psychol. 2015 Apr 21;6:491. eCollection 2015.

Editorial: Improving visual deficits with perceptual learning.

Campana G, Maniglia M.

PMID: 25954239 [PubMed]