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MD Research News

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Drug treatment

Ophthalmologica. 2015 May 13. [Epub ahead of print]

The Presence of Intra- or Subretinal Fluid during the Loading Phase in the Treatment of Exudative Age-Related Macular Degeneration with Intravitreal Ranibizumab Assessed by Optical Coherence Tomography.

Ebneter A, Gekkiev B, Chanana B, Wolf S, Zinkernagel MS.

PURPOSE: To assess intra- and subretinal fluid during the loading phase with intravitreal ranibizumab in exudative age-related macular degeneration and to quantify the accuracy of crosshair scan spectral-domain optical coherence tomography with regard to retinal fluid.

METHODS: This is a retrospective study of 31 treatment-naive patients who received 3 monthly intravitreal ranibizumab injections. Visual acuity and the presence of retinal fluid were assessed at each visit using volume and crosshair scan protocols.

RESULTS: Visual acuity improved and central retinal thickness decreased significantly during the loading phase. However, retinal fluid persisted in two thirds of the patients. The accuracy of the crosshair scan to detect fluid was 93%.

CONCLUSIONS: A substantial proportion of eyes had persistent fluid after 3 months of ranibizumab injections. However, visual improvement was independent of residual fluid. Message: Crosshair scans detect relevant collections of retinal fluid accurately and may be sufficient in daily clinical practice.

PMID: 25998752 [PubMed - as supplied by publisher]

Int Ophthalmol. 2015 May 20. [Epub ahead of print]

Aflibercept versus ranibizumab for treating persistent diabetic macular oedema.

Roa Vandekerckhove K.

Abstract: The purpose of this study was to compare the efficacy of intravitreal aflibercept versus ranibizumab for treating therapy-resistant diabetic macular oedema (DME). A 69-year-old man presented with persistent bilateral DME despite previous ranibizumab treatment. Bilateral study treatment comprised one cycle of three monthly ranibizumab injections (0.5 mg), followed by one cycle of three aflibercept injections (2.0 mg), a second ranibizumab cycle and a second aflibercept cycle. Baseline visual acuity (ETDRS score) was 60 letters for the right eye and 65 letters for the left eye. Baseline central foveal thickness (CFT) was 305 µm for the right eye and 453 µm for the left eye. Substantially improved outcomes were observed during the first aflibercept cycle. CFT was reduced by 150 µm (mean) in both the eyes and decreased below the lowest level achieved during the previous 2.5-year ranibizumab treatment. Visual

acuity was improved by 17.5 letters (mean) in both the eyes. Reintroduction of ranibizumab immediately worsened the status of both eyes back to the baseline level. During the final aflibercept cycle, visual acuity and CFT improved to the same levels achieved during the first aflibercept cycle. In this case study, we prospectively switched the treatment three times and observed a dramatic and consistent treatment advantage for aflibercept.

PMID: 25989873 [PubMed - as supplied by publisher]

Clinicoecon Outcomes Res. 2015 May 6;7:235-47. eCollection 2015.

Cost-effectiveness of ranibizumab versus aflibercept in the treatment of visual impairment due to diabetic macular edema: a UK healthcare perspective.

Régnier SA, Malcolm W, Haig J, Xue W.

BACKGROUND: Ranibizumab and aflibercept are alternative anti-vascular endothelial growth factor agents approved for the treatment of visual impairment (VI) due to diabetic macular edema (DME).

OBJECTIVE: To estimate, from a UK healthcare perspective, the cost-effectiveness of ranibizumab 0.5 mg pro re nata (PRN) and ranibizumab 0.5 mg treat and extend (T&E) compared with aflibercept 2 mg every 8 weeks after five initial monthly doses (2q8) in the treatment of VI due to DME.

METHODS: A Markov model previously reviewed by the National Institute for Health and Care Excellence was used to simulate the long-term outcomes and costs of treating DME. Health states were defined by increments of ten letters in best-corrected visual acuity (BCVA), with a 3-month cycle length. Patients could gain (or lose) a maximum of two health states between cycles. A 3-year treatment time frame and a lifetime horizon were used. Future costs and health outcomes were discounted at 3.5% per annum. Patient baseline characteristics and the efficacy of ranibizumab PRN were derived using data from the RESTORE study. The relative efficacies of ranibizumab PRN, ranibizumab T&E, and aflibercept were assessed with a network meta-analysis. Different utilities were assigned based on BCVA and whether the treated eye was the better- or the worse-seeing eye. Sensitivity analyses tested the robustness of the model.

RESULTS: Lifetime costs per patient of treating DME were £20,019 for ranibizumab PRN, £22,930 for ranibizumab T&E, and £25,859 for aflibercept 2q8. Ranibizumab was dominant over aflibercept, with an incremental gain of 0.05 quality-adjusted life-years (QALYs) and cost savings of £5,841 (PRN) and £2,930 (T&E) compared with aflibercept. Ranibizumab PRN and ranibizumab T&E had 79% and 67% probability, respectively, of being cost-effective relative to aflibercept at a willingness-to-pay threshold of £20,000/QALY. When assuming the higher end of PRN injection frequency (15.9 over 3 years), the cost savings associated with ranibizumab were £3,969.

CONCLUSION: From a UK healthcare perspective, ranibizumab provides greater health gains with lower overall costs than aflibercept in patients with VI due to DME.

PMID: 25999748 [PubMed] PMCID: PMC4427067

Ophthalmic Res. 2015 May 21;54(1):6-9. [Epub ahead of print]

Description of Ophthalmic Pharmaceutical and Device Start-Up Companies.

Sharpe RA, Austin JP, Kruft B, Nelson LA, Stewart JA, Stewart WC.

AIMS: To describe the number, type and location of ophthalmic companies and their associated product areas and indications.

METHODS: A retrospective, non-patient-based, observational review of ophthalmic pharmaceutical and device companies with a new product in development. Data was compiled by Internet searches.

RESULTS: We identified 190 companies currently developing ophthalmic products: 134 (71%) were privately held and 56 (29%) publicly held, while 136 (72%) were in the United States and 53 (28%) were outside the United States. There were 436 total products of which 338 (78%) were pharmaceuticals and 98 (22%) devices. With pharmaceuticals we identified 46 separate indications with age-related macular degeneration (n = 75), glaucoma (n = 52) and dry eye (n = 46) as most common; anti-vascular endothelial growth factor, hormone therapy and anti-inflammatory products were also common classes. With devices there were 30 indications with glaucoma (n = 26), age-related macular degeneration (n = 19) and dry eye (n = 6) as most common; drug delivery, ocular implants and prostheses were less common classes.

CONCLUSIONS: Ophthalmology as a specialty is benefited by a wide effort in new medicine and device development. However, a concentration of effort into relatively few indications suggests a potential lack of market analysis and possible difficulty for many companies in commercializing their product.

PMID: 25999058 [PubMed - as supplied by publisher]

Ophthalmology. 2015 May 13. [Epub ahead of print]

The REVEAL Study: Ranibizumab Monotherapy or Combined with Laser versus Laser Monotherapy in Asian Patients with Diabetic Macular Edema.

Ishibashi T, Li X, Koh A, Lai TY, Lee FL, Lee WK, Ma Z, Ohji M, Tan N, Cha SB, Shamsazar J, Yau CL; REVEAL Study Group.

OBJECTIVE: The primary study hypothesis was that ranibizumab 0.5 mg monotherapy or combined with laser is superior to laser monotherapy based on mean average change in best-corrected visual acuity (BCVA) over 12 months in Asian patients with visual impairment resulting from diabetic macular edema (DME).

DESIGN: A 12-month, randomized, double-masked, multicenter, laser-controlled, phase III study.

PARTICIPANTS: Three hundred ninety-six patients aged ≥18 years, with type 1 or 2 diabetes mellitus, BCVA of 78-39 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and visual impairment resulting from DME.

METHODS: Patients were randomized to ranibizumab + sham laser (n = 133), ranibizumab + active laser (n = 132), or sham injection + active laser (n = 131). Ranibizumab/sham injections were administered on day 1 and continued monthly. As of month 3, monthly injections were continued if stable vision was not reached. Treatment was reinitiated if BCVA decreased because of DME progression. Active/sham laser was administered on day 1 and thereafter according to ETDRS guidelines.

MAIN OUTCOME MEASURES: Average change in BCVA from baseline to months 1 through 12, central retinal subfield thickness (CRST), and safety over 12 months.

RESULTS: Ranibizumab monotherapy or combined with laser was superior to laser in improving mean average change in BCVA from baseline to months 1 through 12 (+5.9 and +5.7 vs +1.4 letters). At month 12, greater proportion of patients gained ≥15 letters with ranibizumab and ranibizumab + laser compared with laser (18.8% and 17.8% vs 7.8%). Mean CRST reduced significantly from baseline to month 12 with ranibizumab (-134.6 μm) and ranibizumab + laser (-171.8 μm) versus laser (-57.2 μm). Patients received a mean of 7.8 and 7.0 ranibizumab injections in the ranibizumab and ranibizumab + laser arms, respectively, and 1.5-1.9 active laser across treatment arms over 12 months. Conjunctival hemorrhage was the most common ocular, whereas nasopharyngitis and hypertension were the most common nonocular adverse events. Ranibizumab was not associated with any cases of cerebrovascular hemorrhage and cerebrovascular ischemia. No death related to study treatment was reported.

CONCLUSIONS: Ranibizumab monotherapy or combined with laser showed superior BCVA improvements over laser treatment alone in Asian patients with visual impairment resulting from DME. No new ocular or nonocular safety findings were observed and treatment was well tolerated over 12 months.

PMID: 25983216 [PubMed - as supplied by publisher]

Jpn J Ophthalmol. 2015 May 16. [Epub ahead of print]

Intravitreal aflibercept for ranibizumab-resistant exudative age-related macular degeneration with choroidal vascular hyperpermeability.

Nomura Y, Yanagi Y.

PURPOSE: To investigate anatomical responses and visual changes in cases of exudative age-related macular degeneration (AMD) with choroidal vascular hyperpermeability (CVH) that responded poorly to multiple ranibizumab injections and were treated with intravitreal aflibercept.

DESIGN: Retrospective comparative study.

PARTICIPANTS: Twenty-five consecutive patients attending the outpatient clinic of the University of Tokyo Hospital who showed an insufficient response to multiple intravitreal ranibizumab injections and were switched to intravitreal aflibercept injections between March and June 2013. All patients were treated with intravitreal aflibercept in a treat-and-extend regimen and followed up for at least 12 months.

METHODS: Presence or absence of CVH was determined by indocyanine green angiography. Changes of best-corrected visual acuity (BCVA) and central retinal thickness (CRT) at 12 months were compared between the CVH (+) AMD and CVH (-) AMD eyes.

RESULTS: The improvement in logMAR BCVA at 12 months was larger in the CVH (-) AMD eyes than in the CVH (+) AMD eyes (-0.18 vs -0.026; P = 0.0089, t-test). The changes in CRT did not differ significantly between the groups (-122 ± 101 μm in the CVH (-) AMD eyes and -159 ± 118 μm in the CVH (+) AMD eyes; P = 0.44, t-test). The proportion of the eyes without intraretinal or subretinal fluid or hemorrhage was 88 % in the CVH (-) AMD and 67 % in the CVH (+) AMD (P = 0.21, t-test).

CONCLUSIONS: Compared with AMD without CVH, AMD with CVH showed poorer visual gain resulting from intravitreal aflibercept treatment.

PMID: 25983109 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2015 May 18. [Epub ahead of print]

In reply to the comment of Dr Asaf Achiron to a paper: Circulating anti-retinal antibodies in response to anti-angiogenic therapy in exudative age-related macular degeneration.

Kubicka-Trząska A1, Wilańska J2, Romanowska-Dixon B1, Sanak M2.

PMID: 25988617 [PubMed - as supplied by publisher]

Other treatment & diagnosis

J Fr Ophtalmol. 2015 May 18. [Epub ahead of print]

[Interest of optical coherence tomography performed immediately before intravitreal injection of anti-VEGF in exudative AMD].[Article in French]

Moyal L, Cohen SY, Pedinielli A, Semoun O, Lalloum F, Jung C, Souied E.

INTRODUCTION: Two or three systematic intravitreal injections (IVT) may be prescribed in a PRN approach to treat an exudative recurrence of neovascular age-related macular degeneration (AMD), according to the phenotype. Optical coherence tomography (OCT) may be performed immediately before the 2nd or the 3rd scheduled IVT, making it possible to cancel the procedure in the absence of exudation. The aim of the study was to evaluate the usefulness of this OCT examination and to assess the percentage of IVT cancelled, in order to evaluate a potential medico-economic benefit.

METHODS: Monocentric retrospective study, in which were included 292 consecutive eyes with exudative recurrence of AMD, for which 2 or 3 IVT were scheduled between January 1st and April 30th, 2014. All patients received a first systematic IVT in the seven days following the diagnosis. Then, on the days of the 2nd and 3rd scheduled IVT, each patient had a visual acuity measurement and a Spectral domain-OCT (Spectralis, HRA Heidelberg Engineering). This measurement allowed for the IVT to be either performed as scheduled or cancelled. Both ranibizumab and aflibercept were used. A Chi2 test was used to compare the qualitative variables and an adjusted Wilcoxon test for the quantitative values.

RESULTS: Two hundred and ninety-two consecutive eyes were included; 172 in the "2 scheduled IVT" group (group A) and 120 in the "3 scheduled IVT" group (group B). At the first follow-up, 37.6% of scheduled IVT were cancelled after the OCT (44.1% in group A and 28.3% in group B). At the second follow-up, 33.3% of IVT were cancelled in group B. Overall, 150/412 (36.4%) IVT were avoided in this series. Presence of serous retinal detachment, retinal edema and increased central macular thickness were statistically correlated with confirmation of the scheduled IVT at the two follow-ups (P<0.001, P<0.001 and P=0.002, respectively). A savings of 429.80 € per patient was calculated during this short period of follow-up.

CONCLUSION: An average non-injection rate of 36.4% of scheduled IVT was found in this protocol of management of recurrences with OCT performed the day of IVT. This protocol allowed to avoid unnecessary IVT one-third of the time and appeared highly cost-effective.

PMID: 25997681 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 May 14. [Epub ahead of print]

Identification of Drusen Characteristics in Age-related Macular Degeneration by Polarization-Sensitive Optical Coherence Tomography.

Schlanitz FG, Sacu S, Baumann B, Bolz M, Platzer M, Pircher M, Hitzenberger CK, Schmidt-Erfurth U.

PURPOSE: To describe qualitative characteristics of drusen in eyes with non-advanced age-related macular degeneration (AMD) using polarization-sensitive optical coherence tomography (OCT).

DESIGN: Cross-sectional study METHODS: 25 eyes of 25 patients with early to intermediate (non-advanced) AMD were imaged with polarization-sensitive OCT using macular volume scans. All individual drusen in each B-scan were manually delineated by experts certified by a reading center and graded for six different morphological characteristics based on a defined classification scheme, including the presence of internal depolarizing structures and associated depolarizing foci. With the use of a custom-made software, the central B-scan of each individual druse was selected and used to analyze its location, diameter and characteristics and assess the prevalence of the different features and relations between.

RESULTS: Using the macular volume scans, 6224 individual drusen could be identified including their position within the retina, their characteristics and their association with any pigmentary alterations. The most common drusen type was a convex-shaped druse with homogeneous medium internal reflectivity and no depolarizing contents (55.3% of drusen). 30.5% of the drusen exhibited internal depolarizing material. 0.3% presented overlying hyperreflective foci, in 54.5%, the foci were also depolarizing. Significant correlations were found between the diameter of the drusen and their distribution throughout the retina, shape, homogeneity of internal reflectivity, presence of internal depolarizing characteristics and presence of overlying foci (p<0.001 each). Significant relations were found between reflectivity, homogeneity and polarization-sensitive internal characteristics (p<0.001).

CONCLUSIONS: Polarization-sensitive OCT reveals characteristic morphologic features of different druse types highlighting the pathophysiological spectrum of early to intermediate AMD.

PMID: 25982973 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2015 May 14. [Epub ahead of print]

Increased fundus autofluorescence and progression of geographic atrophy secondary to age-related macular degeneration. The GAIN study.

Biarnés M, Arias L, Alonso J, Garcia M, Hijano M, Rodríguez A, Serrano A, Badal J, Muhtaseb H, Verdaguer P, Monés J.

PMID: 25982972 [PubMed - as supplied by publisher]

Fibrogenesis Tissue Repair. 2015 May 15;8:9. eCollection 2015.

Prospects for clinical use of reprogrammed cells for autologous treatment of macular degeneration.

Alvarez Palomo AB, McLenachan S, Chen FK, Da Cruz L, Dilley RJ, Requena J, Lucas M, Lucas A, Drukker M, Edel MJ.

Abstract: Since the discovery of induced pluripotent stem cells (iPSC) in 2006, the symptoms of many human diseases have been reversed in animal models with iPSC therapy, setting the stage for future clinical development. From the animal data it is clear that iPSC are rapidly becoming the lead cell type for cell replacement therapy and for the newly developing field of iPSC-derived body organ transplantation. The first human pathology that might be treated in the near future with iPSC is age-related macular degeneration (AMD), which has recently passed the criteria set down by regulators for phase I clinical trials with allogeneic human embryonic stem cell-derived cell transplantation in humans. Given that iPSC are currently in clinical trial in Japan (RIKEN) to treat AMD, the establishment of a set of international criteria to make clinical-grade iPSC and their differentiated progeny is the next step in order to prepare for future autologous cell therapy clinical trials. Armed with clinical-grade iPSC, we can then specifically test for their threat of cancer, for proper and efficient differentiation to the correct cell type to treat human disease and then to determine their immunogenicity. Such a rigorous approach sets a far more relevant paradigm for their intended future use than non-clinical-grade iPSC. This review focuses on the latest developments regarding the first possible use of iPSC-derived retinal pigment epithelial cells in treating human disease, covers data gathered on animal models to date and methods to make clinical-grade iPSC, suggests techniques to ensure quality control and discusses possible clinical immune responses.

PMID: 25984235 [PubMed] PMCID: PMC4432516

Pathogenesis

Trends Immunol. 2015 May 13. [Epub ahead of print]

Immune mechanisms in inflammatory and degenerative eye disease.

Perez VL, Caspi RR.

Abstract: It has recently been recognized that pathology of age-associated degenerative eye diseases such as adult macular degeneration (AMD), glaucoma and diabetic retinopathy, have strong immunological underpinnings. Attempts have been made to extrapolate to age-related degenerative disease insights from inflammatory processes associated with non-infectious uveitis, but these have not yet been sufficiently informative. Here we review recent findings on the immune processes underlying uveitis and those that have been shown to contribute to AMD, discussing in this context parallels and differences between overt inflammation and para-inflammation in the eye. We propose that mechanisms associated with ocular immune privilege, in combination with paucity of age-related antigen(s) within the target tissue, dampen what could otherwise be overt inflammation and result in the para-inflammation that characterizes age-associated neurodegenerative disease.

PMID: 25981967 [PubMed - as supplied by publisher]

Curr Drug Targets. 2015 May 17. [Epub ahead of print]

Endogenous retroelements in cellular senescence and related pathogenic processes: promising drug targets in age-related diseases.

Cardelli M, Giacconi R, Malavolta M, Provinciali M.

Abstract: Endogenous retroelements (ERs) represent nearly half of the human genome. Considered up to recent years as "functionless" DNA sequences, they are now known to be involved in important cellular functions such as stress response and generation of non coding regulatory RNAs. Moreover, an increasing amount of data supports the idea of ERs as key players in cellular senescence and in different senescence-related pathogenic cellular processes, including those leading to inflammation, cancer and major age-related multifactorial diseases. The involvement of ERs in these biological mechanisms can suggest new therapeutic strategies in neoplasms, inflammatory/autoimmune diseases and in different age-related pathologies, such as macular degeneration, diabetes, cardiovascular diseases and major age-related neurodegenerative disorders. The therapeutic approaches which can be suggested range from a set of well -known, common drugs that have been shown to modulate ERs activity, to immune therapy against ER-derived tumor antigens, to more challenging strategies such as those based on anti-ERs RNA interference.

PMID: 25981608 [PubMed - as supplied by publisher]

Neuropharmacology. 2015 May 18. [Epub ahead of print]

Purinergic Signaling in Retinal Degeneration and Regeneration.

Reichenbach A, Bringmann A.

Abstract: Purinergic signaling is centrally involved in mediating the degeneration of the injured and diseased retina, the induction of retinal gliosis, and the protection of the retinal tissue from degeneration. Dysregulated calcium signaling triggered by overactivation of P2X7 receptors is a crucial step in the induction of neuronal and microvascular cell death under pathogenic conditions like ischemia-hypoxia, elevated intraocular pressure, and diabetes, respectively. Overactivation of P2X7 plays also a pathogenic role in inherited and age-related photoreceptor cell death and in the age-related dysfunction and degeneration of the retinal pigment epithelium. Gliosis of micro- and macroglial cells, which is induced and/or modulated by purinergic signaling and associated with an impaired homeostatic support to neurons, and the ATP-mediated propagation of retinal gliosis from a focal injury into the surrounding noninjured tissue are involved in inducing secondary cell death in the retina. On the other hand, alterations in the glial metabolism of extracellular nucleotides, resulting in a decreased level of ATP and an increased level of adenosine, may be neuroprotective in the diseased retina. Purinergic signals stimulate the proliferation of retinal glial cells which contributes to glial scarring which has protective effects on retinal degeneration and adverse effects on retinal regeneration. Pharmacological modulation of purinergic receptors, e.g., inhibition of P2X and activation of adenosine receptors, may have clinical importance for the prevention of photoreceptor, neuronal, and microvascular cell death in diabetic retinopathy, retinitis pigmentosa, age-related macular degeneration, and glaucoma, respectively, for the clearance of retinal edema, and the inhibition of dysregulated cell proliferation in proliferative retinopathies.

PMID: 25998275 [PubMed - as supplied by publisher]

J Acoust Soc Am. 2015 May;137(5):EL381.

Fine-resolution maps of acoustic properties at 250 MHz of unstained fixed murine retinal layers.

Rohrbach D, Lloyd HO, Silverman RH, Mamou J.

Abstract: Ex vivo assessment of microscale tissue biomechanical properties of the mammalian retina could offer insights into diseases such as keratoconus, and macular degeneration. A 250-MHz scanning acoustic

microscope (7-μm resolution) has been constructed to derive two-dimensional quantitative maps of attenuation (α), speed of sound (c), acoustic impedance (Z), bulk modulus (B), and mass density (ρ). The two-dimensional maps were compared to coregistered hematoxylin-and-eosin stained sections. This study is the first to quantitatively assess α, c, Z, B, and ρ of individual retinal layers of mammalian animals at high ultrasound frequencies. Significant differences in these parameters between the layers were demonstrated.

PMID: 25994737 [PubMed - in process] PMCID: PMC4425732

Mol Pharmacol. 2015 May 20. [Epub ahead of print]

Identification of a Dual Inhibitor of SRPK1 and CK2 that Attenuates Pathological Angiogenesis of Macular Degeneration in Mice.

Morooka S, Hoshina M, Kii I, et al

Abstract: Excessive angiogenesis contributes to numerous diseases, including cancer and blinding retinopathy. Antibodies against vascular endothelial growth factor (VEGF) have been approved, and are widely used in the clinical treatment. Our previous studies using SRPIN340, a small molecule inhibitor of SRPK1 (Serine-Arginine Protein Kinase 1), demonstrated that SRPK1 is a potential target for development of anti-angiogenic drug. In this study, we solved the structure of SRPK1 bound to SRPIN340 by X-ray crystallography. Using pharmacophore docking models followed by in vitro kinase assays, we screened a large-scale chemical library, and thus identified a new inhibitor of SRPK1. This inhibitor, SRPIN803, prevented VEGF production more effectively than SRPIN340 due to the dual inhibition of SRPK1 and CK2 (Casein Kinase 2). In a mouse model of age-related macular degeneration, topical administration of eye ointment containing SRPIN803 significantly inhibited choroidal neovascularization, suggesting a clinical potential of SRPIN803 as a topical ointment for ocular neovascularization. Thus SRPIN803 merits further investigation as a novel inhibitor of VEGF.

PMID: 25993998 [PubMed - as supplied by publisher]

Proc Natl Acad Sci U S A. 2015 May 19. [Epub ahead of print]

Regulation of age-related macular degeneration-like pathology by complement factor H.

Toomey CB, Kelly U, Saban DR, Bowes Rickman C.

Abstract: Complement factor H (CFH) is a major susceptibility gene for age-related macular degeneration (AMD); however, its impact on AMD pathobiology is unresolved. Here, the role of CFH in the development of AMD pathology in vivo was interrogated by analyzing aged Cfh+/- and Cfh-/- mice fed a high-fat, cholesterol-enriched diet. Strikingly, decreased levels of CFH led to increased sub-retinal pigmented epithelium (sub-RPE) deposit formation, specifically basal laminar deposits, following high-fat diet. Mechanistically, our data show that deposits are due to CFH competition for lipoprotein binding sites in Bruch's membrane. Interestingly and despite sub-RPE deposit formation occurring in both Cfh+/- and Cfh-/- mice, RPE damage accompanied by loss of vision occurred only in old Cfh+/- mice. We demonstrate that such pathology is a function of excess complement activation in Cfh+/- mice versus complement deficiency in Cfh-/- animals. Due to the CFH-dependent increase in sub-RPE deposit height, we interrogated the potential of CFH as a previously unidentified regulator of Bruch's membrane lipoprotein binding and show, using human Bruch's membrane explants, that CFH removes endogenous human lipoproteins in aged donors. Thus, advanced age, high-fat diet, and decreased CFH induce sub-RPE deposit formation leading to complement activation, which contributes to RPE damage and visual function impairment. This new understanding of the complicated interactions of CFH in AMD-like pathology provides an improved foundation for the development of targeted therapies for AMD.

PMID: 25991857 [PubMed - as supplied by publisher]

Cell Mol Neurobiol. 2015 May 20. [Epub ahead of print]

Up-Regulation of PKM2 Relates to Retinal Ganglion Cell Apoptosis After Light-Induced Retinal Damage in Adult Rats.

Yang X, Chen H, Zhu M, Zhu R, Qin B, Fang H, Dai M, Sang A, Liu X.

Abstract: Pyruvate kinase isozyme type M2 (PKM2), a key glycolytic enzyme, which is involved in ATP generation and pyruvate production, participates in tumor metabolism, growth, and other multiple cellular processes. However, one attractive biological function of PKM2 is that it translocates to the nucleus and induces cell apoptosis. Recently, increased PKM2 has been found in age-related macular degeneration (AMD), but little is known regarding its function in the AMD pathophysiology. To investigate whether PKM2 participated in retinal degeneration, we performed a light-induced retinal damage model in adult rats. Western blot and immunohistochemistry analysis showed a significant up-regulation of PKM2 in retinal ganglion cells (RGCs) layer (GCL) after light exposure. Immunofluorescent labeling indicated that PKM2 located mainly in RGCs. Co-localization of PKM2 and active caspase-3 as well as TUNEL in RGCs suggested that PKM2 might participate in RGC apoptosis. In addition, the expression patterns of cyclin D1 and phosphorylated extracellular signal-regulated kinase (p-ERK) were parallel with that of PKM2. Furthermore, PKM2, cyclin D1, and active caspase-3 protein expression decreased by intravitreal injection of U0126, a highly selective inhibitor of MAPK/ERK kinase. Collectively, we hypothesized that PKM2 might participate in RGC apoptosis after light-induced retinal damage medicated by p-ERK through cycle re-entry mechanism.

PMID: 25990228 [PubMed - as supplied by publisher]

Curr Mol Pharmacol. 2015 May 19. [Epub ahead of print]

The Role of Peptidyl Prolyl Isomerases in Aging and Vascular Diseases.

McClements L, Annett S, Yakkundi A, Robson T.

Abstract: Peptidyl prolyl isomerases (PPIases) are proteins belonging to the immunophilin family and are characterised by their cis-trans isomerization activity at the X-Pro peptide bond, in addition to their tetratricopeptide repeat (TPR) domain, important for interaction with the molecular chaperone, Hsp90. Due to this unique structure these proteins are able to facilitate protein-protein interactions which can impact significantly on a range of cellular processes such as cell signalling, differentiation, cell cycle progression, metabolic activity and apoptosis. Malfunction and/or dysregulation of most members of this class of proteins promotes cellular damage and tissue/organ failure, predisposing to ageing and age-related diseases. Many individual genes within the PPIase family are associated with several age-related diseases including cardiovascular diseases (CVDs), atherosclerosis, type II diabetes (T2D), chronic kidney disease (CDK), neurodegeneration, cancer and age-related macular degeneration (AMD), in addition to the ageing process itself. This review will focus on the different roles of PPIases, and their therapeutic/biomarker potential in these age-related vascular diseases.

PMID: 25986561 [PubMed - as supplied by publisher]

Exp Eye Res. 2015 May 13. [Epub ahead of print]

Subretinal transplantation of retinal pigment epithelium overexpressing fibulin-5 inhibits laser-induced choroidal neovascularization in rats.

Li F, Zeng Y, Xu H, Yin ZQ.

Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly. Choroidal neovascularization (CNV) is the abnormal angiogenesis that causes severe visual loss in AMD.

Fibulin-5 (Fbln5), which functions as an angiogenesis inhibitor, plays an important role in the pathogenesis of AMD. Here, we investigated whether subretinal transplantation of Fbln5-overexpressing retinal pigment epithelial (RPE) cells can inhibit CNV in vivo. Adult Long-Evans rats were used in this study. CNV was induced by laser photocoagulation. One week after laser-induced CNV, RPE cells expressing pZlen-Fbln5-IRES-GFP or the control pZlen-IRES-GFP vectors were transplanted into the subretinal space of the right and left eyes, respectively. CNV was evaluated using fundus photography, fundus fluorescein angiography (FFA), and hematoxylin and eosin staining. We found that CNV occurred at 1 week after photocoagulation, reaching peak activity at 3 weeks and remaining at a high level at 4-5 weeks after photocoagulation. Transplanted RPE cells survived for at least 4 weeks and migrated toward the retina. Subretinal transplantation of Fbln5-overexpressing RPE cells resulted in a significant reduction in the total area of leakage and the number of leakage spots compared with transplantation of RPE cells expressing only green fluorescent protein. Our findings suggest that subretinal transplantation of Fbln5-overexpressing RPE cells inhibits laser-induced CNV in rats and thus represents a promising therapy for the treatment of AMD.

PMID: 25983185 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2015 May 16. [Epub ahead of print]

Prevalence and Causes of Visual Impairment in a Chinese Adult Population: The Taizhou Eye Study.

Tang Y, Wang X, Wang J, Huang W, Gao Y, Luo Y, Lu Y.

PURPOSE: To study the current prevalence and causes of low vision and blindness in an adult Chinese population.

DESIGN: Population-based, cross-sectional study.

PARTICIPANTS: We used a random cluster sampling method and evaluated 10 234 eligible subjects ≥45 years old (response rate, 78.1%) in the Taizhou Eye Study.

METHODS: Examinations were performed from July 2012 through December 2013. Participants underwent a detailed examination, including uncorrected visual acuity, best-corrected visual acuity (BCVA), intraocular pressure, axial length, slit-lamp, and fundus examinations to evaluate the prevalence and primary causes of visual impairment (VI).

MAIN OUTCOME MEASURES: We defined low vision and blindness according to the World Health Organization (WHO) criteria (low vision: BCVA, <20/63-≥20/400; blindness: BCVA, <20/400 in the better eye) and United States criteria (low vision: BCVA, <20/40-≥20/200; blindness: BCVA, <20/200 in the better eye).

RESULTS: Using the WHO BCVA criteria, the standardized prevalence of bilateral low vision and blindness were 5.1% and 1.0%, respectively. Using the United States BCVA criteria, the standardized prevalence were 12.8% and 1.5%, respectively. Using the WHO criteria, the primary causes of bilateral low vision and blindness were cataract (59.1% and 48.5%, respectively), myopic macular degeneration (17.6% and 17.2%, respectively), and age-related macular degeneration (11.6% and 10.1%, respectively). The primary causes of monocular low vision were cataract (55.6%), age-related macular degeneration (12.6%), and myopic macular degeneration (8.9%), whereas those of monocular blindness were cataract (46.8%), atrophy of eyeball or prosthetic eye (10.2%), and cornea opacity (7.3%). A further analysis revealed that in adults 45-59 years old, myopic macular degeneration (59.6% and 27.2%, respectively) and cataract (13.8% and 23.4%, respectively) were the leading causes of bilateral and monocular VI. In adults ≥60 years old, cataract (66.8% and 61.2%, respectively) and age-related macular degeneration (12.6% and 11.8%, respectively) were the primary causes of bilateral and monocular VI.

CONCLUSIONS: The prevalence of low vision and blindness in Chinese adults remains a severe public

health problem. In the Taizhou Eye Study, cataract was the leading cause of low vision and blindness. Myopic macular degeneration and cataract were the primary causes of VI in adults 45-59 years and ≥60 years old, respectively.

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Association between psoriasis and neovascular age-related macular degeneration: A population-based study.

Kao LT, Wang KH, Lin HC, Tsai MC, Chung SD.

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ASSOCIATIONS BETWEEN AGE-RELATED MACULAR DEGENERATION, OSTEOARTHRITIS AND RHEUMATOID ARTHRITIS: Record Linkage Study.

Keenan TD, Goldacre R, Goldacre MJ.

PURPOSE: The epidemiologic relationship between age-related macular degeneration (AMD) and arthritis is unknown and has implications for understanding disease pathogenesis and treatment strategies.

METHODS: An AMD cohort of 245,912 people was constructed from English linked hospital episode statistics (1999-2011), principally comprising neovascular AMD patients undergoing anti-vascular endothelial growth factor therapy. We compared the AMD cohort with a reference cohort (2,134,771 people) for rates of subsequent osteoarthritis (OA) and rheumatoid arthritis. Osteoarthritis (2,032,472 people) and rheumatoid arthritis (261,232 people) cohorts were also constructed and compared with the reference cohort for rates of subsequent AMD.

RESULTS: Risk of arthritis after AMD was not elevated. The rate ratio for OA was 0.96 (95% confidence interval 0.95-0.97) and for rheumatoid arthritis was 0.98 (0.94-1.02). However, risk of AMD after arthritis was modestly raised. For OA, the rate ratio was 1.06 (1.04-1.08), but risk increased with longer OA duration, for example, 1.15 (1.08-1.23) for >10 years. For rheumatoid arthritis, the rate ratio was also modestly elevated at 1.15 (1.12-1.19).

CONCLUSION: Age-related macular degeneration and arthritis are degenerative aging conditions that share some disease mechanisms and extracellular matrix involvement. However, considering arthritis after AMD, they are not positively associated. By contrast, people with OA experience modestly increased AMD risk, perhaps owing to medical treatments for OA.

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EFFECT OF SYSTEMIC BETA-BLOCKERS, ACE INHIBITORS, AND ANGIOTENSIN RECEPTOR BLOCKERS ON DEVELOPMENT OF CHOROIDAL NEOVASCULARIZATION IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION.

Thomas AS, Redd T, Hwang T.

PURPOSE: Recent studies have suggested that the use of systemic beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can induce regression of choroidal neovascularization

in rodent models. The purpose of this study is to evaluate if these agents have a protective effect against the development of choroidal neovascularization in patients with age-related macular degeneration.

METHODS: In this single-center retrospective case-control study, the charts of 250 patients with neovascular age-related macular degeneration were compared with those of 250 controls with dry age-related macular degeneration. Charts were reviewed for current and past use of beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Frequency tables were generated, and associations were examined using chi-square tests, t-tests, and multivariate logistic regression.

RESULTS: There was no statistically significant difference between rates of beta-blocker use (P = 0.57), angiotensin-converting enzyme inhibitors use (P = 0.20), or angiotensin receptor blockers use (P = 0.61) between the 2 groups. Additionally, there was no statistically significant difference between rates of use of combinations of the above drugs between the two groups.

CONCLUSION: Although there is growing evidence that beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can induce regression of choroidal neovascularization in rodent models, these medications do not seem to confer a protective effect against the development of choroidal neovascularization in patients with age-related macular degeneration.

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Genetics

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The genetics of age-related macular degeneration (AMD) - Novel targets for designing treatment options?

Grassmann F, Fauser S, Weber BH.

Abstract: Age-related macular degeneration (AMD) is a progressive disease of the central retina and the main cause of legal blindness in industrialized countries. Risk to develop the disease is conferred by both individual as well as genetic factors with the latter being increasingly deciphered over the last decade. Therapeutically, striking advances have been made for the treatment of the neovas