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MD Research News

Issue 206

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Drug treatment

Br J Ophthalmol. 2014 Nov 6. [Epub ahead of print]

One year results of a phase 1 study of the safety and tolerability of combination therapy using sustained release intravitreal triamcinolone acetonide and ranibizumab for subfoveal neovascular AMD.

Lim JI, Niec M, Wong V.

PURPOSE: To investigate safety and evidence of efficacy of IBI-20089, an intravitreal, liquid, sustained drug delivery system formulated with triamcinolone acetonide (TA) in combination with ranibizumab (Lucentis) for neovascular age related macular degeneration.

METHODS: Patients received a single intravitreal injection of IBI-20089 containing either 6.9 mg (25 µL) TA or 13.8 mg (50 µL) TA followed a week later by intravitreal injection of 0.5 mg ranibizumab. Patients were followed monthly and underwent best corrected visual acuity testing, slit lamp biomicroscopy, dilated ophthalmoscopy, fundus photos and optical coherence tomography. Patients received pro re nata dosing of ranibizumab.

RESULTS: Patients ranged in age from 59 years to 81 years (mean 73.4 years) and all completed 1 year follow-up. No serious related adverse events occurred. Ocular adverse events included mild, transient, elevated intraocular pressure in eight patients and cataract progression in three of the five phakic patients. At 1 year, 30 of a total 120 (25%) possible pro re nata re-Rx's had been given. Combination therapy resulted in a median number of 3.5 re-treatments at and including month 12.

CONCLUSIONS: Combination therapy IBI-20089 and ranibizumab was well-tolerated and resulted in fewer ranibizumab retreatments. Transient intraocular pressure elevation and cataract progression occurred.

PMID: 25376617 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2014 Oct 17;8:2129-31.

Successful treatment of neovascular age-related macular degeneration following single bevacizumab failure using aflibercept in a vitrectomized eye.

Hahn P.

Abstract: Intravitreal anti-vascular endothelial growth factor (VEGF) pharmacotherapy in vitrectomized eyes remains a challenge due to the reduced half-life of these agents. Aflibercept may have stronger binding

activity and a longer intravitreal half-life compared to bevacizumab and ranibizumab, but its use in postvitrectomy eyes has not been reported. We present a case of an 89-year-old female, with recurrent choroidal neovascularization 10 years following prior macular translocation vitrectomy surgery for neovascular age-related macular degeneration, successfully treated with monthly aflibercept injections initiated following poor response to a single initial bevacizumab injection. This report suggests that aflibercept may be an important treatment option for vitrectomized eyes requiring anti-VEGF treatment.

PMID: 25378900 [PubMed]

Retin Cases Brief Rep. 2014 Fall;8(4):336-9.

Intraretinal fibrosis in exudative diabetic macular edema after ranibizumab treatments.

Chaikitmongkol V, Bressler NM.

PURPOSE: To describe the clinical and optical coherence tomography findings of an eye with diabetic macular edema that developed intraretinal fibrosis in an area previously occupied by lipid accumulating after the intravitreous ranibizumab treatment.

METHODS: Interventional case report.

RESULTS: An 85-year-old man presented with diabetic macular edema involving the center of the macula with a half disk area of lipid inferotemporal to the macula. He received ranibizumab treatments after the principles of the Diabetic Retinopathy Clinical Research Network retreatment guidelines. After 12 doses of intravitreous ranibizumab injections over 20 months, macular edema resolved, visual acuity improved from 20/63 to 20/40, and the central subfield thickness decreased from 404 μm to 234 μm. As the edema resolved, the area of lipid did not expand toward the fovea but was replaced by fibrosis occupying the area of lipid, only smaller in extent. Optical coherence tomography scans showed an intraretinal, dome-shaped hyperreflective area corresponding to the fibrosis.

CONCLUSION: This case report, to our knowledge, provides the first documentation of intraretinal fibrosis replacing an area of lipid associated with diabetic macular edema after anti-vascular endothelial growth factor therapy, as had been described previously following laser photocoagulation for diabetic macular edema. Unlike some previous reports of lipid accumulating within the fovea with subsequent fibrosis corresponding to the metaplastic retinal pigment epithelium on histopathology, with or without laser treatment, the lipid in this case did not expand into the fovea before the development of fibrosis, and optical coherence tomography confirmed that the fibrosis was located in the intraretinal rather than the subretinal pigment epithelium space.

PMID: 25372542 [PubMed - in process]

Retin Cases Brief Rep. 2014 Summer;8(3):230-4.

Late retinal neovascularization after central retinal vein occlusion: a case report and literature review.

Iordanous Y, Sheidow TG.

PURPOSE: To present the case of a 59-year-old man with central retinal vein occlusion with limited retinal ischemia who developed retinal neovascularization over a year after initial presentation.

METHODS: Retrospective case report.

RESULTS: On initial presentation, the patient had counting fingers vision in the affected eye and significant macular edema. After 4 intravitreal ranibizumab injections, his vision improved to 20/30. An intravenous

fluorescein angiography performed at presentation and at a 4-month follow-up revealed limited retinal ischemia and no neovascularization. Over a year after his initial presentation, the patient returned with visual symptoms and was found to have subhyaloid hemorrhage and areas of retinal neovascularization.

CONCLUSION: Anterior and posterior segment neovascularization after central retinal vein occlusion has traditionally been thought to occur within a few months of the inciting event. However, the use of antivascular endothelial growth factor agents may alter the angiogenic processes within an eye after central retinal vein occlusion, potentially delaying the onset of neovascularization. This suggests the need for enhanced monitoring in this patient population.

PMID: 25372446 [PubMed - in process]

Middle East Afr J Ophthalmol. 2014 Oct;21(4):296-301.

Comparative evaluation between ranibizumab combined with laser and bevacizumab combined with laser versus laser alone for macular oedema secondary to branch retinal vein occlusion.

Azad SV, Salman A, Mahajan D, Sain S, Azad R.

PURPOSE: To evaluate the anatomical and functional efficacy of combination therapy of intravitreal ranibizumab with laser or intravitreal bevacizumab with laser treatment compared to only laser treatment for macular edema due to branch retinal vein occlusion (BRVO).

MATERIALS AND METHODS: Thirty eyes of 30 patients with BRVO of at least 6 weeks duration were randomized into three groups: Group 1 received a single dose of intravitreal Ranibizumab followed by grid laser treatment, Group 2 received a single dose of intravitreal Bevacizumab followed by grid laser treatment, and Group 3 received grid laser alone. Outcomes at 6 months follow-up were reported. Data were collected on best corrected visual acuity (BCVA), central foveal thickness (CFT), and gain in lines of Snellen acuity.

RESULTS: At 6 month follow-up, the difference in the mean BCVA and CFT between the three treatment groups was not statistically significant ($P > 0.05$, all comparisons). Six eyes (60%) in Group 1, four eyes (40%) in Group 2 and two eyes (20%) in Group 3 had a statistically significant gain of ≥3 lines of Snellen acuity ($P < 0.05$).

CONCLUSION: Both ranibizumab and bevacizumab combined with laser photocoagulation, resulted in better outcomes than grid laser treatment.

PMID: 25371633 [PubMed - in process] PMCID: PMC4219219

Oman J Ophthalmol. 2014 Sep;7(3):112-5.

Vascular endothelial growth factor trap-eye and trap technology: Aflibercept from bench to bedside.

Al-Halafi AM.

Abstract: Anti-vascular endothelial growth factor (VEGF) currently used to treat eye diseases have included monoclonal antibodies, antibody fragments, and an aptamer. A different method of achieving VEGF blockade in retinal diseases includes the concept of a cytokine trap. Cytokine traps technology are being evaluated for the treatment of various diseases that are driven by excessive cytokine levels. Traps consist of two extracellular cytokine receptor domains fused together to form a human immunoglobulin G (IgG). Aflibercept/VEGF trap-eye (VTE) is a soluble fusion protein, which combines ligand-binding elements taken from the extracellular components of VEGF receptors 1 and 2 fused to the Fc portion of IgG. This protein contains all human amino acid sequences, which minimizes the potential for immunogenicity in human patients. This review presents the latest data on VTE in regard to the pharmacokinetics, dosage and safety,

preclinical and clinical experiences. Method of the literature search: A systematic search of the literature was conducted on PubMed, Scopus, and Google Scholar with no limitation on language or year of publication databases. It was oriented to articles published for VTE in preclinical and clinical studies and was focused on the pharmacokinetics, dosage and safety of VTE.

PMID: 25378873 [PubMed]

Curr Eye Res. 2014 Nov 7:1-9. [Epub ahead of print]

Transsclera Drug Delivery by Pulsed High-Intensity Focused Ultrasound (HIFU): An Ex Vivo Study.

Murugappan SK, Zhou Y.

Purpose/aim of study: Drug delivery to the ocular posterior segment is of importance, but it is a challenge in the treatment of irreversible blindness disease, such as age-related macular degeneration. Although some methods (i.e. intraocular injection, sustained release by polymer and iontophoresis) have been applied, some technical drawbacks, such as slow rate and damage to the eye, need to be overcome for wide use.

Materials and methods: In this study, the feasibility of high-intensity focused ultrasound (HIFU) to enhance the transsclera drug delivery was tested for the first time. One-hundred HIFU pulses with the driving frequency of 1.1 MHz, acoustic power of 105.6 W, pulse duration of 10-50 ms and pulse repetition frequency of 1 Hz were delivered to the fresh ex vivo porcine sclera specimen.

Results: In comparison to the passive diffusion (control), 50-ms HIFU can increase the penetration depth by 2.0 folds (501.7 ± 126.4 μm versus 252.4 ± 29.2 μm) using bicinchoninic acid assay and Rhodamine 6 G fluorescence intensity by 3.1 folds (22.4 ± 12.3 versus 7.1 ± 4.1) and coverage area by 2.6 folds (40.4 ± 9.1% versus 15.8 ± 2.9%). No morphological changes on the sonicated sclera samples were found using a surface electron microscope.

Conclusions: In summary, pulsed-HIFU may be an effective modality in the transsclera drug delivery with a high transporting rate and depth. In vivo studies are necessary to further evaluate its performance, including the drug penetration and its possible side effects.

PMID: 25380302 [PubMed - as supplied by publisher]

Retin Cases Brief Rep. 2014 Fall;8(4):342-4.

Anti-vascular endothelial growth factor injection technique for recurrent exudative macular degeneration in a telescope-implanted eye.

Joondeph BC.

PURPOSE: To describe the management of a patient with neovascular age-related macular degeneration and an implantable miniature telescope.

METHODS: Clinical case report.

RESULTS: The patient developed recurrent choroidal neovascularization after telescope implantation and was successfully managed with a series of anti-vascular endothelial growth factor injections and serial ocular coherence tomography through the telescope.

CONCLUSION: Intravitreal injections can be safely performed in an eye with a telescope using standard ocular coherence tomography imaging and taking into consideration the unique geometric dimensions of the telescope.

PMID: 25372544 [PubMed - in process]

Acta Ophthalmol. 2014 Nov 6. [Epub ahead of print]

Treatment of wet age-related macular degeneration by ranibizumab in "real life" in France: treatment behaviours and associated visual outcome.

Souied EH, Cohen SY, de Pouvourville G, Dupeyron G, Latour E, Ponthieux A, Weber M.

PMID: 25377519 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Retina. 2014 Nov 6. [Epub ahead of print]

COLOCALIZATION OF PSEUDODRUSEN AND SUBRETINAL DRUSENOID DEPOSITS USING HIGH-DENSITY EN FACE SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

Spaide RF.

PURPOSE: To determine if pseudodrusen seen in fundus photography, particularly infrared scanning laser ophthalmoscopy, colocalize with subretinal drusenoid deposits imaged by optical coherence tomography.

METHODS: The patients were scanned with spectral domain optical coherence tomography having an A-scan spacing of 5.9 μm and a B-scan spacing of 11 μm. En face slabs were derived from this data set at distances 50 μm to 90 μm above the Bruch membrane reference plane to image the subretinal drusenoid deposit and also 6 μm below Bruch membrane to image the level of the choriocapillaris. The corresponding infrared scanning laser ophthalmoscopy image was registered to the optical coherence tomography data by aligning the retinal blood vessels in each imaging modality through elastic warping.

RESULTS: All ten eyes of nine consecutively imaged patients showed a concordance between the pseudodrusen and the subretinal drusenoid deposit in every case. At their more internal aspects, subretinal drusenoid deposits were generally isolated foci of reflectivity and with decreasing distances above the reference plane appeared to become broader, reaching confluence with neighboring deposits analogous to a topographical map of mountains. In contrast to previous reports based on optical coherence tomography, and in keeping with histologic evaluation, no patient was seen to have widespread abnormalities in choriocapillaris imaging.

CONCLUSION: This study, using an unprecedented scan density, showed that pseudodrusen appearance can be attributed to subretinal drusenoid deposits. The results of this study have widespread applicability in the understanding of age-related macular degeneration and the associations of the lesions with other structures in the outer retinal neurovascular unit.

PMID: 25380066 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2014 Nov 5. [Epub ahead of print]

The accuracy of home monitoring to detect disease activity during maintenance therapy for neovascular ARMD.

McKibbin M, Baker L, Baxter P, Czoski-Muray C, Setty R.

PURPOSE: To report the reproducibility, sensitivity, specificity, and predictive value of home monitoring for disease activity in neovascular age-related macular degeneration (ARMD).

METHODS: Participants were trained to complete three separate home monitoring tasks, designed to identify subtle changes in visual function that may indicate increasing neovascular ARMD disease activity.

These included measurement of near acuity and assessments of environmental distortion and overall visual function. The need for repeat intra-vitreal injection, as predicted by home monitoring, was compared to standard clinical assessment involving ETDRS distance acuity, slit lamp examination, and spectral domain ocular coherence tomography.

RESULTS: Although all participants were able to complete the home monitoring tasks, the reproducibility of each of the three tasks was modest. Cohen's kappa was 0.118 (p = 0.54) for the comparison of the outcome of the home monitoring exercise with the gold standard of hospital assessment to determine disease activity. The sensitivity of the home monitoring exercise was 33.3 % (95 % CI 15.2-51.4) and the specificity was 77.8 % (95 % CI 61.8-93.8).

CONCLUSIONS: This study suggests that current tests of visual function, which are readily completed at home, cannot replace traditional clinic-based assessments for neovascular ARMD disease activity. Instead, such tests are likely to remain complementary to standard assessment in clinic.

PMID: 25367832 [PubMed - as supplied by publisher]

Indian J Ophthalmol. 2014 Sep;62(9):941-8.

Repeatability of retinal thickness and volume metrics in neovascular age-related macular degeneration using the topcon 3doct-1000.

Tah V, Keane PA, Esposti SD, Allimuthu J, Chen FK, Cruz LD, Tufail A, Patel PJ1.

INTRODUCTION: Optical coherence tomography (OCT) is a commonly used imaging modality that provides detailed cross-sectional retinal images. This has revolutionised management of neovascular age-related macular degeneration. The need for repeated anti-vascular endothelial growth factor injections has led to therapy being delivered using OCT-guided retreatment strategies with both qualitative OCT features of disease activity (e.g. macular fluid) and changes in retinal thickness as triggers for retreatment The purpose of this study is to determine the intra-session repeatability of retinal thickness and volume measurements using the Topcon 3DOCT-1000 spectral-domain optical coherence tomography (SDOCT) device in patients with neovascular age-related macular degeneration (nAMD). This is the largest study to date looking specifically at the Topcon 3DOCT-1000.

MATERIALS AND METHODS: Two SDOCT raster scans were performed by the same blinded observer in the same sitting in consecutive patients attending for nAMD treatment as part of standard validation of a new device. Retrospective analysis was undertaken, with retinal thickness and volume measurements automatically calculated by the onboard software for each Early Treatment of Diabetic Retinopathy Study subfield for each scan. Bland-Altman methods of analysis were used to assess repeatability.

RESULTS: Data from the 73 patients were analyzed with a mean age of 78 years (standard deviation 8). The 95% coefficient of repeatability (CR) was 64 μm and 0.050 mm 3 for retinal thickness and volume respectively in the central 1 mm macular subfield. The CR did not exceed 85 μm (0.30 mm 3) in any subfield. The revised CR for retinal thickness and volume for the subgroup of 37 patients with no segmentation error in the central 1 mm subfield was 53 μm and 0.050 mm 3 respectively.

DISCUSSION: We report relatively modest intra-sessional repeatability of SDOCT retinal thickness and volume metrics in patients with nAMD in a clinical setting. Though useful in detecting clinical change from measurement variability in clinical practice, these results suggest the precision of macular thickness measurement does not approach the theoretical resolution of SDOCT.

PMID: 25370398 [PubMed - in process]

ScientificWorldJournal. 2014;2014:536161. Epub 2014 Oct 14.

Wide-field fluorescein angiography in wet age-related macular degeneration.

Madhusudhan S, Beare N.

Purpose: The aim of our study was to investigate if peripheral retinal ischaemia contributed to the pathogenesis of neovascular AMD (NvAMD), using wide-field fluorescein angiography (WFFA).

Methods: This prospective study included 30 consecutive patients with newly diagnosed NvAMD in the index eye. Wide-field colour fundus images and fluorescein angiograms were obtained using P200C optomap FA and analysed using a grid with three concentric circles of 50°, 100°, and 200° centred on the fovea to define zones Z1, Z2, and Z3.

Results: Areas of peripheral retinal nonperfusion were seen in 2 (7%) eyes, peripheral vascular leakage in 5 (17%) eyes, and diffuse dye leakage close to the ora in 5 (17%) eyes. A total of one-third of the study eyes showed changes on WFFA in Z2 and Z3. On comparing index eyes to nonindex eyes in these patients, the presence of NvAMD was associated with peripheral FA changes (P = 0.009, Fisher's test).

Conclusion: Frank peripheral retinal non-perfusion does not appear to be associated with NvAMD. In some patients with active NvAMD there is degradation of the peripheral blood-retina barrier. Smoking was also found to be associated with the above-mentioned abnormalities.

PMID: 25379537 [PubMed - in process]

Stem Cells Transl Med. 2014 Nov 6. [Epub ahead of print]

Proceedings: Debilitating Eye Diseases.

Caras IW, Littman N, Abo A.

Abstract: Debilitating eye diseases such as age-related macular degeneration and retinitis pigmentosa currently represent a large unmet medical need that could potentially be addressed by stem cell therapy. A number of novel stem cell-based cellular therapies are now under development to treat a variety of eye diseases. The approaches being taken by the California Institute for Regenerative Medicine, together with its grantees, are discussed.

PMID: 25378652 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2014 Nov 7;9(11):e112450.

Metabolic Syndrome Triggered by High-Fructose Diet Favors Choroidal Neovascularization and Impairs Retinal Light Sensitivity in the Rat.

Thierry M, Pasquis B, Acar N, Grégoire S, Febvret V, Buteau B, Gambert-Nicot S, Bron AM, Creuzot-Garcher CP, Bretillon L.

Abstract: Diabetic retinopathy and age-related macular degeneration are the leading causes of blindness in Western populations. Although it is a matter of controversy, large-scale population-based studies have reported increased prevalence of age-related macular degeneration in patients with diabetes or diabetic retinopathy. We hypothesized that metabolic syndrome, one of the major risk factors for type 2 diabetes, would represent a favorable environment for the development of choroidal neovascularization, the main complication of age-related macular degeneration. The fructose-fed rat was used as a model for metabolic

syndrome in which choroidal neovascularization was induced by laser photocoagulation. Male Brown Norway rats were fed for 1, 3, and 6 months with a standard equilibrated chow diet or a 60%-rich fructose diet (n=24 per time point). The animals expectedly developed significant body adiposity (+17%), liver steatosis at 3 and 6 months, hyperleptinemia at 1 and 3 months (two-fold increase) and hyperinsulinemia at 3 and 6 months (up to two-fold increase), but remained normoglycemic and normolipemic. The fructose-fed animals exhibited partial loss of rod sensitivity to light stimulus and reduced amplitude of oscillatory potentials at 6 months. Fructose-fed rats developed significantly more choroidal neovascularization at 14 and 21 days post-laser photocoagulation after 1 and 3 months of diet compared to animals fed the control diet. These results were consistent with infiltration/activation of phagocytic cells and up-regulation of pro-angiogenic gene expression such as Vegf and Leptin in the retina. Our data therefore suggested that metabolic syndrome would exacerbate the development of choroidal neovascularization in our experimental model.

PMID: 25380250 [PubMed - as supplied by publisher]

Mol Biol Cell. 2014 Nov 5. [Epub ahead of print]

Cholesterol-mediated activation of acid sphingomyelinase disrupts autophagy in the retinal pigment epithelium.

Toops KA, Tan LX, Jiang Z, Radu RA, Lakkaraju A.

Abstract: Autophagy is an essential mechanism for clearing damaged organelles and proteins within the cell. As with neurodegenerative diseases, dysfunctional autophagy could contribute to blinding diseases like macular degeneration. However, precisely how inefficient autophagy promotes retinal damage is unclear. Here, we investigate innate mechanisms that modulate autophagy in the retinal pigment epithelium (RPE), a key site of insult in macular degenerations. High-speed live imaging of polarized adult primary RPE cells and data from a mouse model of early-onset macular degeneration identify a mechanism by which lipofuscin bisretinoids, visual cycle metabolites that progressively accumulate in the RPE, disrupt autophagy. We demonstrate that bisretinoids trap cholesterol and bis(monoacylglycero)phosphate, an acid sphingomyelinase cofactor, within the RPE. Acid sphingomyelinase activation increases cellular ceramide, which promotes tubulin acetylation on stabilized microtubules. Live imaging data show that autophagosome traffic and autophagic flux are inhibited in RPE with acetylated microtubules. Drugs that remove excess cholesterol or inhibit acid sphingomyelinase reverse this cascade of events and restore autophagosome motility and autophagic flux in the RPE. Since accumulation of lipofuscin bisretinoids and abnormal cholesterol homeostasis are implicated in macular degenerations, our studies suggest that acid sphingomyelinase could be a potential therapeutic target to ensure efficient autophagy that maintains RPE health.

PMID: 25378587 [PubMed - as supplied by publisher]

Front Immunol. 2014 Oct 22;5:523.

Evidence That Erythropoietin Modulates Neuroinflammation through Differential Action on Neurons, Astrocytes, and Microglia.

Bond WS, Rex TS.

Abstract: Neuroinflammation is a normal and healthy response to neuronal damage. However, excessive or chronic neuroinflammation exacerbates neurodegeneration after trauma and in progressive diseases such as Alzheimer's, Parkinson's, age-related macular degeneration, and glaucoma. Therefore, molecules that modulate neuroinflammation are candidates as neuroprotective agents. Erythropoietin (EPO) is a known neuroprotective agent that indirectly attenuates neuroinflammation, in part, by inhibiting neuronal apoptosis.

In this review, we provide evidence that EPO also modulates neuroinflammation upstream of apoptosis by acting directly on glia. Further, the signaling induced by EPO may differ depending on cell type and context possibly as a result of activation of different receptors. While significant progress has been made in our understanding of EPO signaling, this review also identifies areas for future study in terms of the role of EPO in modulating neuroinflammation.

PMID: 25374571 [PubMed]

Cutan Ocul Toxicol. 2014 Nov 6:1-6. [Epub ahead of print]

Intravitreal administration of known phototoxicants in the rabbit fails to produce phototoxicity: implications for phototoxicity testing of intravitreally administered small molecule therapeutics.

Thackaberry EA, Farman C, Bantseev V, Schuetz C, Baker JF, Brown MH, Learn DB.

Abstract Context: Intravitreal (ITV) dosing has become a clinically important route of administration for the treatment of uveitis, endophthalmitis, retinal vein occlusion, diabetic macular edema and age-related macular degeneration. Despite this, there are no validated non-clinical models of phototoxicity for ITV products.

Objective: The objective of this study was to develop an ITV rabbit model of phototoxicity for use in assessing the photosafety of small molecules therapeutics.

Materials and methods: Dutch Belted rabbits were intravitreally injected bilaterally with four known phototoxicants: 8-methoxypsoralen, lomefloxacin, doxycycline and stannsoporfrin. Triescence®, a non-phototoxic triamcinolone acetonide steroid formulation designed for ITV administration, was used as a negative control. One eye was then irradiated with solar-simulated ultraviolet radiation for 30 min, 1 h after dosing, while the other eye was occluded, serving as a non-irradiated control.

Results: Despite the direct administration of known phototoxicants into the vitreous, no evidence of ocular phototoxicity was observed in any dose group. Direct (non-phototoxic) retinal toxicity was observed in the doxycycline dose group only.

Conclusion: These data suggest that the posterior segment of the rabbit eye is protected against phototoxicity by anatomical and/or physiological mechanisms, and is not a useful model for the assessment of phototoxicity of intravitreally administered molecules.

PMID: 25373486 [PubMed - as supplied by publisher]

J Mol Model. 2014 Nov;20(11):2472. Epub 2014 Nov 1.

Conformational analysis of a polyconjugated protein-binding ligand by joint quantum chemistry and polarizable molecular mechanics. Addressing the issues of anisotropy, conjugation, polarization, and multipole transferability.

Goldwaser E, de Courcy B, Demange L, Garbay C, Raynaud F, Hadj-Slimane R, Piquemal JP, Gresh N.

Abstract: We investigate the conformational properties of a potent inhibitor of neuropilin-1, a protein involved in cancer processes and macular degeneration. This inhibitor consists of four aromatic/conjugated fragments: a benzimidazole, a methylbenzene, a carboxythiourea, and a benzene-linker dioxane, and these fragments are all linked together by conjugated bonds. The calculations use the SIBFA polarizable molecular mechanics procedure. Prior to docking simulations, it is essential to ensure that variations in the ligand conformational energy upon rotations around its six main-chain torsional bonds are correctly represented (as compared to high-level ab initio quantum chemistry, QC). This is done in two successive calibration stages and one validation stage. In the latter, the minima identified following independent

stepwise variations of each of the six main-chain torsion angles are used as starting points for energy minimization of all the torsion angles simultaneously. Single-point QC calculations of the minimized structures are then done to compare their relative energies ΔE conf to the SIBFA ones. We compare three different methods of deriving the multipoles and polarizabilities of the central, most critical moiety of the inhibitor: carboxythiourea (CTU). The representation that gives the best agreement with QC is the one that includes the effects of the mutual polarization energy E pol between the amide and thioamide moieties. This again highlights the critical role of this contribution. The implications and perspectives of these findings are discussed.

PMID: 25367040 [PubMed - in process]

Biol Pharm Bull. 2014;37(11):1838-42.

Anti-angiogenic Effects of Mammalian Target of Rapamycin Inhibitors in a Mouse Model of Oxygen-Induced Retinopathy.

Yagasaki R, Nakahara T, Ushikubo H, Mori A, Sakamoto K, Ishii K.

Abstract: Ocular pathologic angiogenesis is a causative factor for retinopathy of prematurity, diabetic retinopathy, and age-related macular degeneration. In the present study, we examined the effects of rapamycin and everolimus, inhibitors of mammalian target of rapamycin (mTOR), on retinal pathologic angiogenesis in mice with oxygen-induced retinopathy (OIR), an animal model of proliferative ischemic retinopathy. Mice were exposed to 80% oxygen from postnatal day (P) 7 to P10, and were then brought into room air and subcutaneously injected with rapamycin and everolimus. The neovascular tufts, the size of the central avascular zone, and the immunoreactivity for phosphorylated ribosomal protein S6 (pS6), a downstream indicator of mTOR activity, were evaluated in flat-mounted retinas. Retinal neovascular tufts and vascular growth in the avascular zone were observed in P15 mice with OIR. In addition, intense immunoreactivity for pS6 was detected in the neovascular tufts and in endothelial cells located at the vascular-avascular border. Both rapamycin and everolimus reduced the extent of retinal neovascular tufts and pS6 immunoreactivity, but they also increased the size of the avascular zone. Thus, activation of the mTOR pathway in endothelial cells contributes to retinal pathologic angiogenesis, and mTOR inhibitors that target proliferating endothelial cells are promising candidates as anti-angiogenic agents for the treatment of vasoproliferative retinal diseases.

PMID: 25366488 [PubMed - in process]

Acta Ophthalmol. 2014 Nov 2. [Epub ahead of print]

Early and exudative age-related macular degeneration is associated with increased plasma levels of soluble TNF receptor II.

Faber C, Jehs T, Juel HB, Singh A, Falk MK, Sørensen TL, Nissen MH.

PURPOSE: We have recently identified homeostatic alterations in the circulating T cells of patients with age -related macular degeneration (AMD). In cultures of retinal pigment epithelial cells, we have demonstrated that T-cell-derived cytokines induced the upregulation of complement, chemokines and other proteins implicated in AMD pathogenesis. The purpose of this study was to test whether increased plasma levels of cytokines were present in patients with AMD.

METHODS: We conducted a case-control study. Age-related macular degeneration status was assessed using standardized multimodal imaging techniques. Plasma was isolated from freshly drawn peripheral venous blood samples and analysed for interleukin (IL)15, IL18, interferon (IFN)γ, soluble tumour necrosis factor (TNF) receptor II (sTNFRII) and complement factor H (CFH) Y402H genotype.

RESULTS: We included 136 individuals with early or late forms of AMD and 74 controls. Significantly increased levels of sTNFRII were observed in patients with early or exudative AMD ($p < 0.01$). After adjusting for CFH Y402H genotype, age, sex and smoking history, the level of sTNFRII remained a significant predictor for prevalence of AMD with odds ratios at 3.0 in the middle and 3.6 in the highest tertiles. Levels of IL15, IL18 and IFNγ were low and not associated with AMD.

CONCLUSIONS: Increased plasma level of sTNFRII is found to be associated with AMD. The data supports the observations of low-grade, systemic inflammatory alterations in patients with AMD. However, it remains to be determined whether increased levels of TNFα can be found, which directly reflects an increased activity of macrophages and T cells.

PMID: 25363549 [PubMed - as supplied by publisher]

Chem Res Toxicol. 2014 Nov 7. [Epub ahead of print]

Detection and Biological Activities of Carboxyethylpyrrole Ethanolamine Phospholipids: a Correlation with Age-related Macular Degeneration.

Wang H, Guo J, West X, Bid HK, Lu L, Hong L, Jang GF, Zhang L, Crabb JW, Linetsky MD, Salomon RG.

Abstract: Oxidation of docosahexaenoate phospholipids produces 4-hydroxy-7-oxo-hept-5-eonyl phospholipids (HOHA)-PLs that react with protein lysyl ε-amino residues to generate 2-ω-carboxyethylpyrrole (CEP) derivatives, endogenous factors that induce angiogenesis in the retina and tumors. It seemed likely but remained unproven that HOHA-PLs react with ethanolamine phospholipids (EPs) in vivo to generate CEP-EPs. We now show that CEP-EPs are present in human blood at 4.6-fold higher levels in age-related macular degeneration plasma than in normal plasma. We also show that a CEP -EPs are pro-angiogenic, inducing tube formation by human umbilical vein endothelial cells by activating the Toll-like receptor 2. CEP-EP levels may be a useful biomarker for clinical assessment of AMD risk and CEP -associated tumor progression and a tool for monitoring the efficacy of therapeutic interventions.

PMID: 25380349 [PubMed - as supplied by publisher]

Genetics

Cold Spring Harb Perspect Med. 2014 Nov 6. [Epub ahead of print]

Highly Penetrant Alleles in Age-Related Macular Degeneration.

den Hollander AI, de Jong EK.

Abstract: Age-related macular degeneration (AMD) is a complex disease caused by a combination of genetic and environmental factors. Genome-wide association studies have identified several common genetic variants associated with AMD, which together account for 15%-65% of the heritability of AMD. Multiple hypotheses to clarify the unexplained portion of genetic variance have been proposed, such as gene-gene interactions, gene-environment interactions, structural variations, epigenetics, and rare variants. Several studies support a role for rare variants with large effect sizes in the pathogenesis of AMD. In this work, we review the methods that can be used to detect rare variants in common diseases, as well as the recent progress that has been made in the identification of rare variants in AMD. In addition, the relevance of these rare variants for diagnosis, prognosis, and treatment of AMD is highlighted.

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Visual Impairment and Hip Fractures: A Case-Control Study in Elderly Patients.

Loriaut P, Loriaut P, Boyer P, Massin P, Cochereau I.

Aims: To investigate the relationship between visual impairment and fall-related hip fracture and to determine the etiology of visual impairment in a population of elderly patients with hip fracture.

Methods: A case-control study compared 96 patients diagnosed with hip fracture to a randomly selected control group of 103 patients without hip fracture. Inclusion criteria for the case group were as follows: patients aged 60 years and over with a hip fracture. Clinical assessment included visual acuity and ophthalmic examination.

Results: Forty-three patients with hip fracture had a visual impairment compared to only 12 patients in the control group. Visual impairment was a significant risk factor for hip fracture (OR = 6.15; 95% CI 2.98-12.69). Twenty-seven hip fracture patients had an uncorrected refractive error compared to only 15 controls (OR = 2.78; 95% CI 0.92-8.35). There was no significant difference of dense cataract between both groups (OR = 2.28; 95% CI 0.75-6.93). Fourteen hip fracture patients had a macular degeneration compared to only 8 controls (OR = 5.63; 95% CI 1.57-20.18), and 10 patients had suspicion of glaucoma compared to only 5 controls (OR = 10.65; 95% CI 2.21-51.3).

Conclusion: Visual impairment was significantly associated with an increased risk of hip fracture in elderly people. There are many etiologies that may contribute to hip fractures, most notably refractive error, cataract, macular degeneration and glaucoma. © 2014 S. Karger AG, Basel.

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Perceptual learning in patients with macular degeneration.

Plank T, Rosengarth K, Schmalhofer C, Goldhacker M, Brandl-Rühle S, Greenlee MW.

Abstract: Patients with age-related macular degeneration (AMD) or hereditary macular dystrophies (JMD) rely on an efficient use of their peripheral visual field. We trained eight AMD and five JMD patients to perform a texture-discrimination task (TDT) at their preferred retinal locus (PRL) used for fixation. Six training sessions of approximately one hour duration were conducted over a period of approximately 3 weeks. Before, during and after training twelve patients and twelve age-matched controls (the data from two controls had to be discarded later) took part in three functional magnetic resonance imaging (fMRI) sessions to assess training-related changes in the BOLD response in early visual cortex. Patients benefited from the training measurements as indexed by significant decrease ($p = 0.001$) in the stimulus onset asynchrony (SOA) between the presentation of the texture target on background and the visual mask, and in a significant location specific effect of the PRL with respect to hit rate ($p = 0.014$). The following trends were observed: (i) improvement in Vernier acuity for an eccentric line-bisection task; (ii) positive correlation between the development of BOLD signals in early visual cortex and initial fixation stability ($r = 0.531$); (iii) positive correlation between the increase in task performance and initial fixation stability ($r = 0.730$). The first two trends were non-significant, whereas the third trend was significant at $p = 0.014$, Bonferroni corrected. Consequently, our exploratory study suggests that training on the TDT can enhance eccentric vision in patients with central vision loss. This enhancement is accompanied by a modest alteration in the BOLD response in early visual cortex.

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Sipjeondaebo-tang, a traditional herbal formula, inhibits retinal neovascularization in a mouse model of oxygen-induced retinopathy.

Lee YM, Kim CS, Sohn E, Jo K, Lim HR, Kim SK, Kim JS, Kim J.

Abstract: Retinal neovascularization is a common pathology in age-related macular degeneration, retinopathy of prematurity and proliferative diabetic retinopathy. Platelet derived growth factor (PDGF) is a vasoactive factor and has been implicated in proliferative retinopathies. Oxygen-induced retinopathy in the mouse is the standard experimental model of proliferative retinopathies. Sipjeondaebo-tang (SDT) is the most widely used traditional herbal formula in East Asia, also known as Shi-Quan-Da-Bu-Tang in Chinese and Juzen-taiho-to in Japanese. SDT has been known to exert anti-angiogenic activities in several tumor models, but the role of SDT in proliferative retinopathies remains unclear. Thus, the object of the present study is to examine the mechanism of action and efficacy of SDT on retinal neovascularization in oxygen-induced ischemic retinopathy (OIR) mice. Neonatal mice at postnatal day 7 (P7) were exposed to 75% concentration of oxygen for 5 days (P7-P12), and then returned to room air from P12 to P17 to induce retinal neovascularization. SDT were administered once per day for 5 consecutive days (P12-P16) by intraperitoneal injection. Retinal neovascularization was measured at P17. We used a protein array to evaluate the expression levels of angiogenic factors. Inhibitory activity of SDT on PDGF-BB/PDGFRβ interaction was evaluated in vitro. Retinal neovascularization in the OIR mice was significantly decreased by SDT. SDT decreased the expression levels of PDGF-BB protein and VEGF mRNA. Moreover, SDT dose -dependently inhibited PDGF-BB/PDGFRβ interaction (IC50 = 388.82 ± 7.31 μg/ml). In conclusion, SDT is a potent inhibitor of retinal neovascularization through inhibiting the pro-angiogenic effect of PDGF-BB.

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