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MD Research News

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Drug treatment

Ophthalmology. 2012 Feb 4. [Epub ahead of print]

HORIZON: An Open-Label Extension Trial of Ranibizumab for Choroidal Neovascularization Secondary to Age-Related Macular Degeneration.

Singer MA, Awh CC, Sadda S, Freeman WR, Antoszyk AN, Wong P, Tuomi L.

Medical Center Ophthalmology Associates, San Antonio, Texas.

OBJECTIVE: To evaluate the long-term safety and efficacy of multiple intravitreal ranibizumab injections (Lucentis, Genentech, Inc., South San Francisco, CA) administered at the investigator's discretion in patients with choroidal neovascularization secondary to age-related macular degeneration.

DESIGN: An open-label, multicenter, extension study.

PARTICIPANTS: Patients who completed the controlled treatment phase of 1 of 3 prospective, randomized, 2-year clinical trials of ranibizumab were eligible for enrollment. Analyses were performed for 3 groups: (1) patients treated with ranibizumab in the initial study (ranibizumab treated-initial; n = 600); (2) patients randomized to control who crossed over to receive ranibizumab (ranibizumab treated-XO; n = 190); and (3) ranibizumab-naïve patients (ranibizumab untreated; n = 63).

METHODS: Ranibizumab 0.5 mg was administered at the investigator's discretion. Adverse events (AEs) and Early Treatment Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA) assessments were conducted at study visits every 3 to 6 months.

MAIN OUTCOME MEASURES: Incidence and severity of AEs.

RESULTS: There was 1 occurrence of mild endophthalmitis per 3552 HORIZON injections in the ranibizumab treated-initial/ranibizumab treated-XO groups. There were no serious AE reports of lens damage, retinal tears, or rhegmatogenous retinal detachments in the study eyes. The proportion of patients with any single postdose intraocular pressure ≥30 mmHg was 9.2%, 6.6%, and 0%, and the proportion of patients with glaucoma was 3.2%, 4.2%, and 3.2% in the ranibizumab treated-initial, ranibizumab treated-XO, and ranibizumab untreated groups, respectively. Cataract AEs were less frequent in the ranibizumab untreated group: 6.3% versus 12.5% and 12.1% in the ranibizumab treated-initial and ranibizumab treated-XO groups, respectively. The proportion of patients with arterial thromboembolic events as defined by the Antiplatelet Trialists' Collaboration was 5.3% in the ranibizumab treated-initial and ranibizumab treated-XO groups, and 3.2% in the ranibizumab untreated group. At month 48 (2 years of HORIZON), the mean change in BCVA (ETDRS letters) relative to the initial study baseline was 2.0 in the ranibizumab treated-initial group versus -11.8 in the pooled ranibizumab treated-XO and ranibizumab untreated groups.

CONCLUSIONS: Multiple ranibizumab injections were well tolerated for ≥4 years. With less frequent follow-up leading to less treatment, there was an incremental decline of the visual acuity (VA) gains achieved with monthly treatment.

PMID: 22306121 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Feb 7. [Epub ahead of print]

Treatment Patterns for Neovascular Age-Related Macular Degeneration: Analysis of 284 380 Medicare Beneficiaries.

Curtis LH, Hammill BG, Qualls LG, Dimartino LD, Wang F, Schulman KA, Cousins SW.

Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina; Department of Medicine, Duke University School of Medicine, Durham, North Carolina.

PURPOSE: To examine trends in the treatment of newly diagnosed neovascular age-related macular degeneration (AMD).

DESIGN: Retrospective cohort study.

METHODS: Among 284 380 Medicare beneficiaries with a new diagnosis between 2006 and 2008, we used the cumulative incidence function to estimate procedure rates and the mean frequency function to estimate the cumulative mean number of intravitreous injections. We used Cox log-binomial regression to estimate predictors of the use of vascular endothelial growth factor (VEGF) antagonists within 1 year after diagnosis. Discontinuation of anti-VEGF therapy was defined by absence of treatment for 12 months. Discontinuation rates were calculated using the Kaplan-Meier method.

RESULTS: The proportion of patients receiving anti-VEGF therapy increased from 60.3% to 72.7%, photodynamic therapy decreased from 12.8% to 5.3%, and thermal laser treatment decreased from 5.5% to 3.2%. Black patients (hazard ratio, 0.77; 95% confidence interval, 0.75-0.79) and patients of other/unknown race (0.83; 0.81-0.84) were less likely than white patients to receive anti-VEGF therapy. Patients with dementia were less likely to receive anti-VEGF therapy (0.88; 0.88-0.89). Among patients who received anti-VEGF therapy, the mean number of injections within 1 year of the first injection was 4.3 per treated eye. Anti-VEGF therapy was discontinued in 53.6% of eyes within 1 year, and in 61.7% of eyes within 18 months.

CONCLUSIONS: Treatment of new neovascular AMD changed significantly between 2006 and 2008, most notably in the increasing use of anti-VEGF therapies. However, few patients treated with anti-VEGF medications received monthly injections, and discontinuation rates were high.

PMID: 22321802 [PubMed - as supplied by publisher]

Expert Opin Biol Ther. 2012 Feb 6. [Epub ahead of print]

Ranibizumab for age-related macular degeneration.

Dhoot DS, Kaiser PK.

Cole Eye Institute , 9500 Euclid Avenue, Desk i3, Cleveland, OH 44195 , USA +1 216 444 6702 ; pkkaiser@aol.com.

Introduction: Age-related macular degeneration (AMD) is the leading cause of blindness in patients over 50 years in the developed world. The wet form of AMD is responsible for the majority of severe vision loss. VEGF-A is a key component in the development of wet AMD. Ranibizumab is an anti-VEGF agent that has

established itself as the gold standard in the treatment of neovascular AMD. Herein, we review the pharmacology, pharmacokinetics, efficacy and safety of ranibizumab.

Areas covered: Since its approval in 2006, ranibizumab has revolutionized the treatment of wet AMD. In two pivotal Phase III trials, MARINA and ANCHOR, ranibizumab (0.5 mg) prevented moderate visual loss in 90 and 96% of patients, respectively, and improved vision by 15 letters or more in 33 and 40% of patients, respectively. Fixed monthly dosing regimens were compared with quarterly dosing regimens in PIER and EXCITE studies and support the superiority of fixed monthly dosing. The CATT trial revealed that bevacizumab was not inferior to ranibizumab when dosed monthly. As-needed treatment regimens of ranibizumab were also found to be non-inferior to monthly ranibizumab after 1 year of follow-up.

Expert opinion: Ranibizumab has positively altered the treatment of wet AMD and offers hope for millions of patients.

PMID: 22309606 [PubMed - as supplied by publisher]

Eye (Lond). 2012 Feb 10. doi: 10.1038/eye.2012.7. [Epub ahead of print]

Microperimetric changes in neovascular age-related macular degeneration treated with ranibizumab.

Alexander P, Mushtaq F, Osmond C, Amoaku W.

Department of Ophthalmology, Queen's Medical Centre, Nottingham University Hospitals, Nottingham, UK.

Purpose: To assess the value of microperimetry in eyes with neovascular age-related macular degeneration previously treated with ranibizumab and now in the maintenance phase of therapy.

Methods: A total of 21 eyes (14 patients) were included. Microperimetry was performed using the Macular Integrity Assessment Device on at least three occasions for each eye. Intravitreal ranibizumab was administered if visual acuity (VA) or optical coherence tomography (OCT) showed signs of active disease.

Results: Five eyes showed no change in VA or OCT findings, and required no intravitreal injections. In these eyes, mean threshold sensitivity (TS) decreased by 13% (paired t-test, P=0.05) during the study period, but fixation stability (FS) was unchanged. In all, 16 eyes showed signs of disease activity, and therefore required ranibizumab injections during the study. In these eyes, VA, central retinal thickness (CRT), FS, and TS remained unchanged during follow-up. Peak TS was noted when CRT was 210 μm; above or below 210 μm, there was a gradual reduction in TS.

Conclusion: This study has provided novel information on the relationship between macular sensitivity, CRT, and VA in the maintenance phase of ranibizumab therapy. Patients with stable VA and CRT may still have deteriorating retinal sensitivity. This is usually a late manifestation and may indicate subclinical CNV activity.

Eye advance online publication, 10 February 2012; doi:10.1038/eye.2012.7.

PMID: 22322998 [PubMed - as supplied by publisher]

Biomaterials. 2012 Feb 7. [Epub ahead of print]

The movement of self-assembled amphiphilic polymeric nanoparticles in the vitreous and retina after intravitreal injection.

Koo H, Moon H, Han H, Na JH, Huh MS, Park JH, Woo SJ, Park KH, Chan Kwon I, Kim K, Kim H.

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Abstract

The purpose of this study is to determine the correlation between the distribution of nanoparticles in the vitreous and retina and their surface properties after intravitreal injection. For this purpose, we synthesized seven kinds of nanoparticles through self-assembly of amphiphilic polymer conjugates in aqueous condition. They showed similar size but different surface properties. They were labeled with fluorescent dyes for efficient tracking. After intravitreal injection of these nanoparticles into a rodent eye, their time-dependent distribution in the vitreous and retina was determined in stacking tissue images by confocal microscopy. The results demonstrated that the surface property of nanoparticles is a key factor in determining their distribution in the vitreous and retina after intravitreal injection. In addition, immunohistochemistry and TEM images of retina tissues suggested the important mechanism related with Müller cells for intravitreally administered nanoparticles to overcome the physical barrier of inner limiting membrane and to penetrate into the deeper retinal structures. Therefore, we expect that this study can provide valuable information for biomedical researchers to develop optimized nanoparticles as drug or gene carriers for retinal and optic nerve disorders such as glaucoma, age-related macular degeneration, and diabetic retinopathy.

PMID: 22322197 [PubMed - as supplied by publisher]

Retina. 2012 Feb 2. [Epub ahead of print]

BILATERAL SAME-DAY INTRAVITREAL INJECTIONS USING A SINGLE VIAL AND MOLECULAR BACTERIAL SCREENING FOR SAFETY SURVEILLANCE.

Woo SJ, Han JM, Ahn J, Heo JW, Yu HG, Chung H, Song J, Park KU, Park KH.

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PURPOSE: To evaluate the safety of bilateral same-day intravitreal injections using a single vial and to introduce a molecular surveillance system to screen bacterial drug contamination using eubacterial polymerase chain reaction (PCR).

METHODS: Retrospective review of the medical records of 135 patients who received 574 bilateral same-day intravitreal injections for various retinal diseases in 2 tertiary referral hospitals between January 2008 and March 2010 was performed. Data were obtained regarding the diagnosis, kinds of drugs injected, postinjection complications, and the result of molecular bacterial screening of the injected drugs. Drugs for bilateral intravitreal injections were drawn from a single vial and injected using separate syringes or needles. Molecular bacterial screening was performed using the remaining drug in the syringe by 16S ribosomal DNA real-time PCR.

RESULTS: A total of 574 injections (384 bevacizumab, 154 ranibizumab, and 36 triamcinolone) were administered on bilateral eyes of 135 patients. There were no complications, including endophthalmitis, uveitis, retinal tear, or retinal detachment. Of the 278 injections screened for bacterial contamination using eubacterial PCR, no cases (0%) showed drug contamination by bacteria. The sensitivity of eubacterial PCR for molecular bacterial screening was 10 colony-forming units (CFUs)/mL or lower.

CONCLUSION: Bilateral same-day intravitreal injections drawn from a single vial using separate syringes or needles are well tolerated by patients, and its safety profile may be equivalent to unilateral injections. The bacterial molecular surveillance system using eubacterial PCR demonstrated the safety of bilateral same-day intravitreal injections and may be used for safety surveillance and for timely intervention of possible drug-related endophthalmitis.

PMID: 22307220 [PubMed - as supplied by publisher]

Klin Oczna. 2011;113(7-9):233-6.

[Combined photodynamic therapy and intravitreal injection of triamcinolone acetonide in patients with wet form of AMD. Introductory report].

[Article in Polish]

Mozolewska-Piotrowska K, Krzystolik K, Karczewicz D, Drobek-Słowik M, Kubasik-Kładna K.

Z Katedry i Kliniki Okulistyki Pomorskiej Akademii Medycznej w Szczecinie. kmp@ams.edu.pl

PURPOSE: To evaluate the efficacy of combined PDT and 4 mg intravitreal triamcinolone acetonide injection, performed 48-72 hours after PDT, in patients with wet form of AMD.

MATERIAL AND METHODS: Nonrandomised, interventional case series, 13 eyes of 13 patients with subfoveal CNV due to AMD that did not respond to PDT monotherapy - 7 females, 6 males - at the age of 65-85 (average age 76.6 +/- 6.7 years); standard PDT was performed in all patients followed by a 4 mg intravitreal injection of triamcinolone acetonide given 48-72 hours after PDT. Follow up visits were scheduled 1 and 7 days after the injection and then every 3 months afterwards and included: BVCA (Snellen chart), IOP measurements, FA, OCT, slit lamp and eye fundus examination. Lesions with active CNV leakage in FA were retreated every 3 months.

RESULTS: Average observation time was 10.8 +/- 3.5 months. Baseline visual acuity before PDT monotherapy was applied (Vo) was 0.17 +/- 0.12 (0.06-0.5), and after the therapy decreased to (V1) 0.14 +/- 0.13 (0.05-0.2). After combined PDT and Tc treatment BVCA increased to (V2) 0.21 +/- 0.13 (0.06-0.5), p<0,03. 76,9% of patients gained or maintained visual acuity after combined therapy in the observation time. In 70% of eyes no signs of active CNV was observed in AF and OCT after 1 session of combined PDT and Tc treatment. Only 4 patients required 1 repeated treatment session.

CONCLUSIONS: 1. Combination of PDT and IVTA may be effective in patients with wet AMD with no response to PDT alone and significantly reduces the repeated treatment rate. 2. Intravitreal Tc injection performed 48-72 hours after PDT may improve the final functional effects in treated eyes as compared with PDT monotherapy. Our results need further investigation.

PMID: 22256564 [PubMed - indexed for MEDLINE]

Retina. 2012 Feb 2. [Epub ahead of print]

Comparison of Age-Related Macular Degeneration Treatment Trials: What did we Learn?

Csaky KG.

Retina Foundation of the Southwest, Dallas, Texas.

PMID: 22307221 [PubMed - as supplied by publisher]

Other treatment and diagnosis

Am J Ophthalmol. 2012 Feb 7. [Epub ahead of print]

Microperimetric Correlations of Autofluorescence and Optical Coherence Tomography Imaging in Dry Age-Related Macular Degeneration.

Querques L, Querques G, Forte R, Souied EH.

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Creteil, France; Department of Ophthalmology, Hospital San Raffaele, University Vita Salute San Raffaele, Milan, Italy.

PURPOSE: To investigate the microperimetric correlations of autofluorescence imaging and optical coherence tomography (OCT) in dry age-related macular degeneration (AMD).

DESIGN: Retrospective, observational, cross-sectional study.

METHODS: Consecutive patients with dry AMD underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA), blue fundus autofluorescence (FAF), near-infrared autofluorescence, and spectral-domain (SD)-OCT with integrated microperimetry.

RESULTS: A total of 58 eyes of 29 patients (21 women; mean age 73 ± 9 years) were included. Mean BCVA was 0.28 ± 0.3 logarithm of the minimal angle of resolution (logMAR). Overall, 2842 points were analyzed as regards FAF and near-infrared autofluorescence patterns, the status of inner segment/outer segment (IS/OS) interface, and retinal sensitivity. We observed a good correlation between the FAF and near-infrared autofluorescence patterns for all the points graded (increased FAF/near-infrared autofluorescence, Pearson rho = 0.6, P = .02; decreased FAF/near-infrared autofluorescence, Pearson rho = 0.7, P = .01; normal FAF/near-infrared autofluorescence, Pearson rho = 0.7, P = .01). Mean retinal sensitivity was significantly reduced in cases of decreased FAF (4.73 ± 2.23 dB) or increased FAF (4.75 ± 2.39 dB) compared with normal FAF (7.44 ± 2.34 dB) (P = .001). Mean retinal sensitivity was significantly reduced in case of decreased near-infrared autofluorescence (3.87 ± 2.28 dB), compared with increased near-infrared autofluorescence (5.76 ± 2.44 dB) (P = .02); mean retinal sensitivity in case of increased near -infrared autofluorescence was significantly reduced compared with normal near-infrared autofluorescence (7.15 ± 2.38 dB) (P = .002). On SD-OCT, there was a high inverse correlation between retinal sensitivity and rate of disruptions in IS/OS interface (Pearson rho = -0.72, P = .001).

CONCLUSION: A reduced retinal sensitivity consistently correlates with decreased FAF/near-infrared autofluorescence and a disrupted IS/OS interface. Increased near-infrared autofluorescence may represent a useful method for detection of retinal abnormalities early in dry AMD development.

PMID: 22321805 [PubMed - as supplied by publisher]

J Glaucoma. 2012 Feb 5. [Epub ahead of print]

Influence of Age-related Macular Degeneration on Macular Thickness Measurement Made With Fourier-domain Optical Coherence Tomography.

Garas A, Papp A, Holló G.

Department of Ophthalmology, Semmelweis University, Budapest, Hungary.

PURPOSE: To evaluate the influence of age-related macular degeneration (AMD) on macular thickness measurement made with Fourier-domain optical coherence tomography (RTVue-OCT) to detect glaucoma.

METHODS: One nonglaucomatous eye of 79 white persons was imaged. This comprised 25 healthy eyes, 19 eyes with early/intermediate AMD (geographic atrophy excluded), 16 eyes with subfoveal choroidal neovascularization (CNV), and 19 CNV eyes after intravitreal antiangiogenic treatment [CNV-antivascular endothelial growth factor (VEGF)].

RESULTS: Compared with the age-matched controls, no difference in any nerve fiber layer and optic disc parameter was seen for any AMD group. No macular retinal segmentation error was detected in the control group. Localized inner retinal image segmentation errors topographically related to AMD were detected in 8 eyes with drusen (42.1%), all 16 CNV eyes (100%) and 17 eyes in the CNV-anti-VEGF group (89.5%; χ test, $P<0.001$ for all comparisons). The average macular thickness parameters did not differ between the control and the AMD groups (analysis of variance, $P>0.05$). In contrast, all pattern-based ganglion cell

complex (GCC) parameters were significantly higher (more abnormal) in the CNV and CNV-anti-VEGF group than in the control eyes (Mann-Whitney test, Bonferroni correction, P<0.001). For GCC focal loss volume, the only pattern-based parameter classified by the software, the frequency of "borderline" and "outside normal limits" classifications was significantly greater in each AMD group than in the control group (χ test, Bonferroni correction, P≤0.03).

CONCLUSIONS: In nonglaucomatous eyes, AMD significantly influences the pattern-based inner macular thickness parameters of the RTVue optical coherence tomograph and the software-provided classification of GCC focal loss volume, for detection of glaucoma.

PMID: 22314250 [PubMed - as supplied by publisher]

Pathogenesis

Clin Experiment Ophthalmol. 2012 Feb;40(1):18-26. doi: 10.1111/j.1442-9071.2011.02581.x.

Therapeutic targeting of the complement system in age-related macular degeneration: a review.

Troutbeck R, Al-Qureshi S, Guymer RH.

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Abstract

The last decade has produced pivotal change in our understanding of the molecular mechanisms underlying age-related macular degeneration (AMD), a leading cause of global blindness. In this time, the complement system has featured as a unifying theme for several elements of new evidence: initially, the discovery of complement proteins within drusen and subsequently, the association between AMD and mutations in various complement pathway genes, most notably complement factor H. Increasingly, a wealth of data are pointing towards a role for chronic local inflammation and complement activation in the patho-aetiology of AMD. These findings have paved the way for the exploration of a new paradigm of therapy in AMD management; targeting of specific molecular constituents in the complement pathway thus producing dampening or inhibition of the inflammatory response. Such an approach has the potential to intervene earlier in the disease process and ideally before vision is compromised. In this review we discuss the role of the complement system in AMD, novel therapies in preclinical evaluation and clinical trial, and whether these have a part to play in reducing the burden of disease.

PMID: 22304025 [PubMed - in process]

Mol Vis. 2012;18:234-40. Epub 2012 Jan 28.

TCCR/WSX-1 is a novel angiogenic factor in age-related macular degeneration.

Sung HJ, Han JI, Lee JW, Uhm KB, Heo K.

PURPOSE: Age-related macular degeneration (AMD) is the major cause of blindness among persons aged 60 years and older. The current approved therapies for AMD are exclusively limited to inhibiting vascular endothelial growth factor. However, substantial improvement in vision occurs in only one-third of patients treated with vascular endothelial growth factor antagonists, and one-sixth of treated patients still progress to legal blindness. Therefore, more specific targets are needed to treat AMD. Our goal was to find secretory proteins that change in number in the aqueous humor and that cause exudative AMD disease.

METHODS: The number of molecules changed in the aqueous humor of patients with AMD compared to the control group was determined using antibody array analysis. The levels of angiopoietin-2 and insulin-

like growth factor binding protein-related protein 7 were measured using enzyme-linked immunosorbent assay. The levels of T-cell cytokine receptor (TCCR/WSX-1) were determined using western blot. Potential TCCR/WSX-1-mediated effects on tube formation as well as phosphorylation of extracellular signal-regulated kinase in human umbilical vein endothelial cells were determined.

RESULTS: We found that the numbers of several molecules were changed in the aqueous humor of patients with AMD compared to the control group. Among them, angiopoietin-2 was reduced by 20% and TCCR/WSX-1 was increased twofold. Moreover, exogenous TCCR protein induced tube formation and phosphorylation of extracellular signal-regulated kinase in human umbilical vein endothelial cells.

CONCLUSIONS: Our study suggests that TCCR/WSX-1 is closely associated with angiogenesis and could serve as a novel therapeutic target in patients with AMD.

PMID: 22312192 [PubMed - in process] PMCID: PMC3272058

Invest Ophthalmol Vis Sci. 2012 Feb 9. [Epub ahead of print]

Complement and UV-irradiated photoreceptor outer segments increase the cytokine secretion by retinal pigment epithelial cells.

Lueck K, Hennig M, Lommatzsch A, Pauleikhoff D, Wasmuth S.

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Purpose: Age-related macular degeneration (AMD) is accompanied by increased complement activation, and by lipofuscin accumulation in retinal pigment epithelial (RPE) cells due to incomplete degradation of photoreceptor outer segments (POS). The influence of POS, ultraviolet-irradiated (UV)-POS and human complement sera (HCS) on cytokine secretion from RPE cells was therefore examined.

Methods: RPE cells were incubated with POS or UV-POS every other day for one week. The autofluorescence (AF) was measured photometrically and by flow cytometry. Senescence-associated genes were analysed by RT-PCR. Internalisation and degradation of POS were determined using phagocytosis and degradation assays, and lysosomal function by neutral red up-take. RPE cells in transwell inserts were incubated apically with POS or UV-POS and afterwards basally with HCS. C7-deficient HCS was used as control. The integrity of the cell monolayer was assessed by measuring the transepithelial electrical resistance (TER) and the permeability. Interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1 and vascular endothelial growth factor were quantified by ELISA.

Results: POS treatment led to an increased AF and senescence marker expression, which were further elevated in response to UV-POS. UV-POS were preferentially accumulated over POS and the lysosomal function was impaired due to UV-POS. HCS intensified the cytokine production compared to controls. POS had no effect, though UV-POS combined with HCS induced a significant increase in all cytokines.

Conclusions: RPE cultivation with UV-POS might serve as a model to investigate the accumulation of lipofuscin-like structures. The enhanced cytokine secretion due to UV-POS with HCS may account for an increased susceptibility for lipofuscin-loaded cells to complement, inducing a pro-inflammatory environment as observed in AMD.

PMID: 22323489 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2012 Feb 9. [Epub ahead of print]

Anti-angiogenic activity of Aganirsen in non-human primate and rodent models of retinal neovascular disease following topical administration.

Cloutier F, Lawrence M, Goody R, Lamoureux S, Al-Mahmood S, Colin S, Ferry A, Conduzorgues JP, Hadri A, Cursiefen C, Udaondo P, Viaud E, Thorin E, Chemtob S.

Université de Montréal, Department of Pediatrics, Ophthalmology, Pharmacology, hôpital Ste-Justine, 3175, Chemin de la Côte-Sainte-Catherine Montreal H3T 1C5 Quebec, Canada, and.

Purpose: Aganirsen, an antisense oligonucleotide inhibiting insulin receptor substrate-1 (IRS-1) expression, has been shown to promote regression of pathological corneal neovascularization in patients. In this study, we aimed to demonstrate the antiangiogenic activity of Aganirsen in animal models of retinal neovascularization.

Methods: Eye drops of Aganirsen were applied daily in non-human primates following laser-induced choroidal neovascularization (CNV; model of wet age-related macular degeneration [AMD]), and in newborn rats following oxygen-induced retinopathy (OIR; model of ischemic retinopathy). Retinal Aganirsen concentrations were assessed in rabbits and monkeys following topical delivery (21.5, 43 or 86 µg). Clinical significance was further evaluated by determination of IRS-1 expression in monkey and human retinal biopsies.

Results: Topical corneal application of Aganirsen attenuated neovascular lesion development dose-dependently in African green monkeys: incidence of high grade CNV lesions (grade IV) decreased from 20.5% in vehicle-treated animals to 1.7% ($p<0.05$) at the 86 µg dose. Topical Aganirsen inhibited retinal neovascularization following OIR in rats ($p<0.05$); furthermore, a single intravitreal injection of Aganirsen reduced OIR as effectively as Ranibizumab, and their effects were additive. Significantly, topical applications of Aganirsen did not interfere with physiological retinal vessel development in newborn rats. Retinal delivery following topical administration was confirmed, and retinal expression of IRS-1 was demonstrated to be elevated in patients with sub-retinal neo-vascularization and AMD.

Conclusions: Topical application of Aganirsen offers a safe and effective therapy for both choroidal and retinal neovascularization, without preventing its normal vascularization. Together, our findings support clinical testing of Aganirsen for human retinal neovascular diseases.

PMID: 22323484 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2012 Feb 6. [Epub ahead of print]

Systemic Human CR2-Targeted Complement Alternative Pathway Inhibitor Ameliorates Mouse Laser-Induced Choroidal Neovascularization.

Rohrer B, Coughlin B, Holers VM.

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Purpose: Genetic associations and the presence of complement components within pathological structures of age-related macular degeneration (AMD) have generated the hypothesis that AMD is caused by chronic local complement activation. Since the majority of activity in the common terminal pathway results from engagement of the amplification loop, the alternative pathway has been proposed as a logical therapeutic target. We recently generated a factor H (fH)-based complement inhibitor (CR2-fH) with the capacity to be "targeted" to sites of complement C3 activation. We asked whether the human therapeutic (TT30) is effective in a mouse model of AMD.

Methods: Choroidal neovascularization (CNV) was induced by argon laser photocoagulation of Bruch's

membrane. Every other day, mice received intravenous injections of TT30 or vehicles, and after 6 days, the presence or absence of CNV and CNV-related changes were evaluated. Area of CNV, photoreceptor cell function, gene expression for complement components and cytokines, vascular endothelial growth factor (VEGF) protein levels, and TT30 bioavailability were determined.

Results: CNV development, which has previously been shown to require local complement activation, could be reduced by intravenous TT30 delivery. Specific inhibition of the alternative pathway not only reduced angiogenesis in CNV, but also ameliorated changes in several associated disease-related biomarkers, including diminished retinal function and molecular events known to be involved in AMD such as VEGF production. After intravenous injection, TT30 localized to CNV lesion sites in the retinal pigmented epithelium-choroid.

Conclusion: Systemic administration of TT30 was found to reduce CNV pathology. These data may open new avenues for novel systemic AMD treatment strategies.

PMID: 22309197 [PubMed - as supplied by publisher]

Biochim Biophys Acta. 2012 Jan 28. [Epub ahead of print]

The innate immune response to products of phospholipid peroxidation.

Weismann D, Binder CJ.

Abstract

Lipid peroxidation occurs in the context of many physiological processes, but is greatly increased in various pathological situations. A consequence of phospholipid peroxidation is the generation of "oxidation-specific" epitopes, such as phosphocholine of oxidized phospholipids and malondialdehyde, which form neo-self determinants on dying cells and oxidized low density lipoprotein. In this review we discuss evidence demonstrating that pattern recognition receptors of the innate immune system recognize OSEs as endogenous damage-associated molecular patterns, allowing the host to identify dangerous biological waste. Oxidation-specific epitopes are important targets of both cellular and soluble pattern recognition receptors, including toll-like and scavenger receptors, C-reactive protein, complement factor H, and innate natural IgM antibodies. This recognition allows the innate immune system to mediate important physiological house keeping functions, for example by promoting the removal of dying cells and oxidized molecules. Once this system is malfunctional or overwhelmed the development of diseases, such as atherosclerosis and age-related macular degeneration is favored. Understanding the molecular components and mechanisms involved in this process, will help the identification of individuals with increased risk of developing chronic inflammation, and indicate novel points for therapeutic intervention. This article is part of a Special Issue entitled: Oxidized phospholipids-their properties and interactions with proteins.

PMID: 22305963 [PubMed - as supplied by publisher]

Proc Natl Acad Sci U S A. 2012 Jan 30. [Epub ahead of print]

Reentrant spiral waves of spreading depression cause macular degeneration in hypoglycemic chicken retina.

Yu Y, Santos LM, Mattiace LA, Costa ML, Ferreira LC, Benabou K, Kim AH, Abrahams J, Bennett MV, Rozental R.

Departments of Cell Biology and Anatomy, Otolaryngology, and Neurosurgery, New York Medical College, Valhalla, NY 10595.

Abstract

Spreading depression (SD), a slow diffusion-mediated self-sustained wave of depolarization that severely disrupts neuronal function, has been implicated as a cause of cellular injury in a number of central nervous system pathologies, including blind spots in the retina. Here we show that in the hypoglycemic chicken retina, spontaneous episodes of SD can occur, resulting in irreversible punctate lesions in the macula, the region of highest visual acuity in the central region of the retina. These lesions in turn can act as sites of origin for secondary self-sustained reentrant spiral waves of SD that progressively enlarge the lesions. Furthermore, we show that the degeneration of the macula under hypoglycemic conditions can be prevented by blocking reentrant spiral SDs or by blocking caspases. The observation that spontaneous formation of reentrant spiral SD waves leads to the development of progressive retinal lesions under conditions of hypoglycemia establishes a potential role of SD in initiation and progression of macular degeneration, one of the leading causes of visual disability worldwide.

PMID: 22308470 [PubMed - as supplied by publisher]

Genetics

Mol Biol Rep. 2012 Feb 4. [Epub ahead of print]

Pooled-analysis of the associations between three polymorphisms in the VEGF gene and age-related macular degeneration.

Lu Y, Shi Y, Xue C, Yin J, Huang Z.

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Abstract

The vascular endothelial growth factor (VEGF) gene has been suggested to play an important role in the pathogenesis of age-related macular degeneration (AMD). However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the associations between VEGF polymorphisms and AMD risk across different populations. Published literature from PubMed and EMBASE were retrieved. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using fixed- or random-effects model. Five studies (1,280 cases and 715 controls) for rs833061 polymorphism, five studies (1,033 cases and 807 controls) for rs1413711 polymorphism, and four studies (1,217 cases and 4,079 controls) for rs2010963 polymorphism were identified. No statistically significant association was found for rs833061, rs1413711 and rs2010963 polymorphisms, although there were significant associations for rs833061 polymorphism under a homogeneous co-dominant model (CC vs. TT: OR = 1.59, 95%CI 1.14-2.23) and for rs1413711 polymorphism under a recessive model (TT vs. CT + CC: OR = 1.50, 95%CI 1.08-2.08), the results were not robust by sensitivity analysis. However, there was a significant association for rs833061 among European and East Asian populations, and for rs1413711 among Europeans. The present meta-analyses indicated that there were no significantly associations between VEGF polymorphisms (rs833061, rs1413711, rs2010963) and the risk of AMD, although the association was different for each polymorphism among different populations.

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Retina Expression and Cross-Species Validation of Gene Silencing by PF-655, a Small Interfering RNA Against RTP801 for the Treatment of Ocular Disease.

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Abstract Purpose: PF-655, a synthetic 19-mer siRNA, targeting the RTP801 gene is currently in clinical trials for the treatment of wet age-related macular degeneration and diabetic macular edema. Preclinical studies have shown a dose-related suppression of RTP801 expression in rat disease models. Investigative studies were conducted with PF-655 to validate the Dutch-Belted rabbit as a biologically relevant species for gene silencing to support nonclinical ocular toxicity and continual dosing studies.

Methods: Cross-species comparison and DNA sequencing was done to determine the level of homology between PF-655 and rabbit RTP801. Human (HEK 293) and rabbit (SIRC cornea) cell lines were stimulated with CoCl(2) to mimic hypoxic stress (an inducer of RTP801 expression) and treated with PF-655. Taqman-polymerase chain reaction and immunoblot analysis were performed to gauge RTP801 expression in cell culture and rabbit retinas.

Results: Sequence analysis showed a 1-base mismatch in the PF-655 targeting site from genomic DNA of Dutch-Belted rabbit and the SIRC cell line, a cornea cell derived from the New Zealand White rabbit. HEK and SIRC CoCl(2)-stressed cells induced RTP801 expression 10-20-fold above control conditions. Treatment with 20 or 100 nM PF-655 showed a decrease in gene expression, 40%-50% relative to appropriate controls. RTP801 mRNA was detectable in primary rabbit retina tissues, with cycle threshold values showing a large linear range for the assay.

Conclusion: These results support our investigation into cross-species validation of gene suppression by a therapeutic siRNA designed to a human gene. The SIRC cell line was utilized as a surrogate to test the degree of RTP801 gene silencing induced by PF-655 in vitro. With a 1-base mismatch, the level of silencing in a rabbit ocular cell line was comparable to that of a human cell line. Sequence analysis and expression data confirmed the relevance of the RTP801 target gene in rabbits and the utility of this species as a relevant animal model. Additionally, our work outlines a tractable method that validates relevant larger non-rodent species for ophthalmic drug testing.

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Gene delivery nanoparticles specific for human microvasculature and macrovasculature.

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Abstract

Endothelial cell dysfunction is a critical component of ocular diseases such as age-related macular degeneration and diabetic retinopathy. An important limitation in endothelial cell research is the difficulty in achieving efficient transfection of these cells. A new polymer library was synthesized and utilized to find polymeric nanoparticles that can transfect macrovascular (human umbilical vein, HUVECs) and microvascular (human retinal, HRECs) endothelial cells. Nanoparticles were synthesized that can achieve transfection efficiency of up to 85% for HRECs and 65% for HUVECs.These nanoparticle systems enable high levels of expression while avoiding problems associated with viral gene delivery. The polymeric nanoparticles also show cell-specific behavior, with a high correlation between microvascular and macrovascular transfection (R(2) = 0.81), but low correlation between retinal endothelial and retinal epithelial transfection (R(2) = 0.21). These polymeric nanoparticles may be used in vitro as experimental tools and potentially in vivoto target and treat vascular-specific diseases.

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Diet

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Spirulina is an effective dietary source of zeaxanthin to humans.

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Abstract

Zeaxanthin is a predominant xanthophyll in human eyes and may reduce the risk of cataracts and age-related macular degeneration. Spirulina is an algal food that contains a high concentration of zeaxanthin. In order to determine the zeaxanthin bioavailability of spirulina for dietary supplementation in humans, spirulina was grown in nutrient solution with 2H2O for carotenoid labelling. Single servings of 2H-labelled spirulina (4·0-5·0 g) containing 2·6-3·7 mg zeaxanthin were consumed by fourteen healthy male volunteers (four Americans and ten Chinese) with 12 g dietary fat. Blood samples were collected over a 45 d period. The serum concentrations of total zeaxanthin were measured using HPLC, and the enrichment of labelled zeaxanthin was determined using LC-atmospheric pressure chemical ionisation-MS (LC-APCI-MS). The results showed that intrinsically labelled spirulina zeaxanthin in the circulation was detected at levels as low as 10 % of the total zeaxanthin for up to 45 d after intake of the algae. A single dose of spirulina can increase mean serum zeaxanthin concentration in humans from 0·06 to 0·15 μmol/l, as shown in our study involving American and Chinese volunteers. The average 15 d area under the serum zeaxanthin response curve to the single dose of spirulina was 293 nmol × d/μmol (range 254-335) in American subjects, and 197 nmol × d/μmol (range 154-285) in Chinese subjects. It is concluded that the relative bioavailability of spirulina zeaxanthin can be studied with high sensitivity and specificity using 2H labelling and LC-APCI-MS methodology. Spirulina can serve as a rich source of dietary zeaxanthin in humans.

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