Macular Degeneration Foundation
Our focus is your vision

MD Research News

Issue 111

Monday December 17, 2012

This free weekly bulletin lists the latest published research articles on macular degeneration (MD) as indexed in the NCBI, PubMed (Medline) and Entrez (GenBank) databases. These articles were identified by a search using the key term “macular degeneration”.

If you have not already subscribed, please email Rob Cummins at **research@mdfoundation.com.au** with ‘Subscribe to MD Research News’ in the subject line, and your name and address in the body of the email.

You may unsubscribe at any time by an email to the above address with your ‘unsubscribe’ request.

Drug treatment

Cochrane Database Syst Rev. 2012 Dec 12;12:CD007419. doi: 10.1002/14651858.CD007419.pub3.

Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for diabetic macular oedema.

Virgili G, Parravano M, Menchini F, Brunetti M.

Department of Specialised Surgical Sciences, University of Florence, Via le Morgagni 85, Florence, Italy, 50134.

BACKGROUND: Diabetic macular oedema (DMO) is a common complication of diabetic retinopathy. Although grid or focal laser photocoagulation has been shown to reduce the risk of visual loss in DMO or clinically significant macular oedema (CSMO), vision is rarely improved. Antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) modalities has recently been proposed for improving vision in people with DMO.

OBJECTIVES: To assess the effectiveness, safety and cost-effectiveness of anti-VEGF therapy for preserving or improving vision in people with DMO.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 6), MEDLINE (January 1946 to June 2012), EMBASE (January 1980 to June 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 13 June 2012.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) comparing any antiangiogenic drugs with an anti-VEGF mechanism of action versus another treatment, sham treatment, or no treatment in patients with DMO. We also included economic evaluations to assess cost-effectiveness.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted the data. The risk ratio (RR) of visual loss and visual gain of three or more lines was estimated at least six months after treatment. Each economic analysis was described narratively using a structured format.

MAIN RESULTS: Eleven studies provided data on three comparisons of interest in this review. We based our conclusions on the RR of gain or loss of three or more lines of vision at about one year, which was more consistently reported as follow-up.Compared with sham treatment, there was evidence of moderate

quality in three studies (497 participants, follow-up 8 to 12 months) that antiangiogenic therapy (pegaptanib: two studies, 246 participants; ranibizumab: one study, 151 participants) doubled and, respectively, halved, the chance of gaining or losing three or more lines of vision (RR: 2.19, 95% confidence interval (CI) 1.36 to 3.53; RR: 0.28, 95% CI: 0.13 to 0.59). In meta-analyses, the benefit was larger for ranibizumab compared to pegaptanib, but no significant subgroup difference could be demonstrated regarding our primary outcome.Compared with grid laser photocoagulation, there was evidence of moderate quality that antiangiogenic therapy (bevacizumab: two studies, 167 participants; ranibizumab: two studies, 300 participants; aflibercept: one study, 221 participants, 89 used for data extraction) more than doubled and, respectively, reduced by at least two thirds, the chance of gaining or losing three or more lines of vision (RR: 3.20, 95% CI 2.07 to 4.95 and RR: 0.13, 95% CI: 0.05 to 0.34, respectively). In meta-analyses, no significant subgroup difference could be demonstrated between bevacizumab, ranibizumab and aflibercept regarding our primary outcome, but, again, there was little power to detect a difference.Compared with grid laser photocoagulation alone, there was high quality evidence that ranibizumab plus photocoagulation (three studies, 783 participants) doubled and, respectively, at least halved, the chance of gaining or losing three or more lines of vision (RR: 2.11, 95% CI 1.67 to 2.67; RR: 0.29, 95% CI: 0.15 to 0.55).Systemic and ocular adverse events were rare in the included studies. Meta-analyses conducted for all antiangiogenic drugs compared with either sham or photocoagulation (nine studies, 104 events in 2159 participants) did not show a significant difference regarding arterial thromboembolic events (RR: 0.85 (0.56 to 1.28). Similarly, no difference was suggested regarding overall mortality (53 events, RR: 0.95 (0.52 to 1.74), but clinically significant differences could not be ruled out.

AUTHORS' CONCLUSIONS: There is moderate quality evidence that antiangiogenic drugs provide a definite, but small, benefit compared to current therapeutic options for DMO, i.e. grid laser photocoagulation, or no treatment when laser is not an option. The quality and quantity of the evidence was larger for ranibizumab, but there was little power to investigate drug differences. Most data were obtained at one year, and a long-term confirmation is needed, since DMO is a chronic condition. Safety of both drug and the intravitreal injection procedure were good in the trials, but further long-term data are needed to exclude small, but clinically important differences regarding systemic adverse events.

PMID: 23235642 [PubMed - in process]

Retina. 2012 Dec 5. [Epub ahead of print]

CURRENT KNOWLEDGE AND TRENDS IN AGE-RELATED MACULAR DEGENERATION: Today's and Future Treatments.

Velez-Montoya R, Oliver SC, Olson JL, Fine SL, Mandava N, Quiroz-Mercado H.

*Department of Ophthalmology, University of Colorado Health and Science Center, Rocky Mountain Lions Eye Institute, University of Colorado School of Medicine, Aurora, Colorado †Department of Ophthalmology, Denver Health Medical Center, University of Colorado School of Medicine, Denver, Colorado.

PURPOSE: To address the most dynamic and current issues concerning today's treatment options and promising research efforts regarding treatment for age-related macular degeneration. This review is aimed to serve as a practical reference for more in-depth reviews on the subject.

METHODS: An online review of the database PubMed and Ovid were performed, searching for the key words age-related macular degeneration, AMD, VEGF, treatment, PDT, steroids, bevacizumab, ranibizumab, VEGF-trap, radiation, combined therapy, as well as their compound phrases. The search was limited to articles published since 1985. All returned articles were carefully screened, and their references were manually reviewed for additional relevant data. The web page www.clinicaltrials.gov was also accessed in search of relevant research trials.

RESULTS: A total of 363 articles were reviewed, including 64 additional articles extracted from the references. At the end, only 160 references were included in this review.

CONCLUSION: Treatment for age-related macular degeneration is a very dynamic research field. While current treatments are mainly aimed at blocking vascular endothelial growth factor, future treatments seek to prevent vision loss because of scarring. Promising efforts have been made to address the dry form of the disease, which has lacked effective treatment.

PMID: 23222393 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2012 Dec 8. [Epub ahead of print]

Short-term outcome after intravitreal ranibizumab injections for the treatment of retinopathy of prematurity.

Castellanos MA, Schwartz S, García-Aguirre G, Quiroz-Mercado H.

Asociación para Evitar la Ceguera en México, Hospital "Luis Sanchez Bulnes" I.A.P., Mexico City, Mexico.

PURPOSE: To evaluate ocular outcome in premature infants treated with intravitreal ranibizumab injections for retinopathy of prematurity (ROP) over a period of 3 years.

METHODS: An interventional case series. Premature infants with high-risk prethreshold or threshold ROP with plus disease received an off label monotherapy with intravitreal injections of ranibizumab. The primary outcome was treatment success defined as regression of neovascularisation (NV) and absence of recurrence. The secondary outcomes were ocular and systemic adverse events and visual acuity.

RESULTS: Six eyes were included in the study and treated with intravitreal injections of ranibizumab. All showed complete resolution of NV after a single injection. The anti-angiogenic intravitreal injections allowed for continued normal vessel growth into the peripheral retina, without any signs of disease recurrence or progression during the follow up period. No ocular or systemic adverse effects were observed.

CONCLUSIONS: Three years of follow up in a small series suggest that intravitreal ranibizumab injections for ROP result in apparently preserved ocular outcome. Further large scale studies are needed to address the long-term safety and efficacy.

PMID: 23221964 [PubMed - as supplied by publisher]

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

Bevacizumab and Triamcinolone Acetonide for Choroidal Neovascularization Due to Age-Related Macular Degeneration Unresponsive to Antivascular Endothelial Growth Factors.

Veritti D, Sarao V, Lanzetta P.

Department of Ophthalmology, University of Udine , Udine, Italy .

Abstract Purpose: To evaluate the safety and efficacy of a combined approach using an antivascular endothelial growth factor (VEGF) agent (bevacizumab) and a steroid (triamcinolone acetonide) for treating choroidal neovascularization (CNV) due to age-related macular degeneration (AMD) unresponsive to anti-VEGF monotherapy.

Methods: Retrospective case series. We analyzed 25 eyes with CNV due to AMD who received a combination of intravitreal bevacizumab (1 mg) and triamcinolone (4 mg). Results were assessed at 7 days, 1, 3, 6, 9, and 12 months by best-corrected visual acuity (BCVA) measurement, fluorescein angiography, indocyanine green angiography, and optical coherence tomography (OCT). Retreatment with intravitreal bevacizumab or combination therapy was considered at investigator discretion at every follow-up visit.

Results: A mean BCVA improvement of 0.18 (95% CI: 0.05; 0.3) logMAR was reported between baseline

and the 12-month measurement (P<0.01). An opposite trend toward progressive loss of BCVA, from 1.08 to 1.31 logMAR, had been observed in the 6 months before starting the combination therapy, in spite of regular treatment with anti-VEGFs (P<0.0001). OCT measurements showed a 139-µm (95% CI: 76; 203) decrease in mean central retinal thickness (P<0.01). On average, patients required 1.8 additional treatments. Five (20%) cases of intraocular pressure elevation were successfully treated with medications.

Conclusions: Combination therapy with intravitreal bevacizumab and triamcinolone acetonide proved to be a safe and effective option for CNV unresponsive to anti-VEGF monotherapy. The combined treatment reversed the preoperative trend toward losing vision, and a significant anatomic improvement was seen by OCT.

PMID: 23215753 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2012 Dec 5. [Epub ahead of print]

Intravitreal Tumor Necrosis Factor-Alpha Inhibitors for Neovascular Age-Related Macular Degeneration Suboptimally Responsive to Antivascular Endothelial Growth Factor Agents: A Pilot Study from the Pan American Collaborative Retina Study Group.

Wu L, Arevalo JF, Hernandez-Bogantes E, Regatieri CV, Roca JA, Farah ME.

Instituto de Cirugia Ocular , San José, Costa Rica .

Abstract Purpose: To compare the short-term visual and anatomic outcomes after intravitreal injections of 2 different tumor necrosis factor-α inhibitors to continued antivascular endothelial growth factor (VEGF) therapy in eyes with choroidal neovascularization (CNV) secondary to age-related macular degeneration that responded suboptimally to anti-VEGF agents.

Methods: Retrospective comparative case series of 26 eyes. Eyes were injected intravitreally with 1 mg infliximab, 2 mg infliximab, 2 mg adalimumab, or 1.25 mg bevacizumab. The main outcomes measured were the best-corrected visual acuity (BCVA) and the central macular thickness (CMT) at 3 months of follow-up.

Results: The mean log minimal angle of resolution BCVA changed from 1.04±0.23 at baseline to 1.06±0.51 at 3 months (P=0.9455) in the 1-mg infliximab group; 0.94±0.48 at baseline to 0.85±0.43 in the 2-mg infliximab group (P=0.2802); 1.58±0.50 at baseline to 1.38±0.43 in the adalimumab group (P=0.1116); and 1.08±0.1 at baseline to 1.03±0.16 in the bevacizumab group (P=0.9928). The mean CMT changed from 387±54 µm at baseline to 342±108 µm (P=0.1053) in the 1-mg infliximab group; 301±42 µm at baseline to 284±73 µm (P=0.4854) in the 2-mg infliximab group; remained unchanged at 348±106 µm (P=0.308) in the adalimumab group; and 362±66 µm to 340±27 µm in the bevacizumab group (P=0.4622). Adverse events included uveitis in 37.5% (6/16) of eyes injected with infliximab.

Conclusion: Intravitreal infliximab and adalimumab do not appear to benefit eyes with CNV that responded suboptimally to anti-VEGF agents. Intravitreal injections of infliximab may elicit a severe intraocular inflammatory reaction.

PMID: 23215543 [PubMed - as supplied by publisher]

J Fr Ophtalmol. 2012 Dec 3. pii: S0181-5512(12)00340-3. doi: 10.1016/j.jfo.2012.04.013. [Epub ahead of print]

Intravitreal ranibizumab for type 3 choroidal neovascularization complicating adult onset foveomacular vitelliform dystrophy.

Querques G, Querques L, Leveziel N, Bandello F, Souied EH.

Department of Ophthalmology, University Paris XII, Centre Hospitalier Intercommunal de Créteil, 40 Avenue de Verdun, 94000 Créteil, France. Electronic address: giuseppe.querques@hotmail.it.

PURPOSE: To describe the results obtained with intravitreal ranibizumab injections in a patient with adult onset foveomacular vitelliform dystrophy (AOFVD) complicated by Type 3 choroidal neovascularization (CNV).

METHODS: A 78-year old man diagnosed with AOFVD presented at our department for decreased vision in his left eye (LE) (20/80). Upon a complete ophthalmologic examination, including fluorescein angiography, indocyanine green angiography, and spectral-domain optical coherence tomography, the patient was diagnosed with Type 3 CNV. Three monthly injections of ranibizumab 0.05ml/0.5mg were administered intravitreally without complications.

RESULTS: After the first injection, visual acuity of the LE improved (20/64) and regression of the Type 3 CNV was observed by fluorescein angiography, indocyanine green angiography and OCT. Six months after the final ranibizumab injection, a more-or-less complete resolution of the exudative retinal changes was observed.

CONCLUSIONS: Type 3 CNV may be associated with AOFVD. Intravitreal ranibizumab may represent a possible therapeutic option in this unusual context.

PMID: 23218864 [PubMed - as supplied by publisher]

Ophthalmologe. 2012 Dec 8. [Epub ahead of print]

[Therapy of stage III retinal angiomatous proliferation : Intravitreal ranibizumab injections.]

[Article in German]

Maier M, Perz C, Bockmaier J, Feucht N, Lohmann CP.

Augenklinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675, München, Deutschland, Mathias.Maier@mri.tum.de.

Abstract: Retinal angiomatous proliferation (RAP) is a subtype of exudative age-related macular degeneration which is characterized by an intraretinal origin of the lesion and a particularly poor prognosis. In this retrospective case study 33 eyes from 33 patients with stage III RAP lesions were included and initially treated with 3 intravitreal injections of 0.5 mg ranibizumab at monthly intervals. Criteria for extended treatment were visual deterioration, fresh bleeding, residual fluid or increase of the central retinal thickness in optical coherence tomography (OCT) as well as persisting activity in fluorescence angiography (FLA). The follow-up period was 8 months. The mean best corrected visual acuity (BCVA) increased insignificantly from logMAR 0.71 at the start of therapy to logMAR 0.67 after the first 3 intravitreal treatment injections and remained stable up to 8 months. The mean decrease of the central retinal thickness after 4 months (-90 µm) and after 8 months (-70 µm) was significant. Of the patients included in the study 67 % were treated repeatedly and the mean frequency of reinjections was 2.27 injections after 8 months. The intravitreal injection of ranibizumab in patients with stage III RAP lesions resulted in functional and anatomical stabilization. In most cases repeated treatment is necessary which underlines the urgent need for close surveillance in follow-up.

PMID: 23224129 [PubMed - as supplied by publisher]

Ophthalmologe. 2012 Dec 8. [Epub ahead of print]

[Treatment of recurrent neovascular age-related macular degeneration with ranibizumab according to the PrONTO scheme.] [Article in German]

Wolf A, Reznicek L, Muhr J, Ulbig M, Kampik A, Haritoglou C.

Augenklinik, Ludwig-Maximilians-Universität, Klinikum der Universität München Campus Innenstadt, Mathildenstr. 8, 80336, München, Deutschland, Armin.Wolf@med.uni-muenchen.de.

BACKGROUND: The goal of this retrospective study was to evaluate the development of visual acuity before and after recurrence treatment of neovascular age-related macular degeneration (AMD) in a university eye clinic with referring ophthalmologists.

METHODS: Data from patients with recurrent neovascular AMD who initially had been treated for neovascular AMD and followed by referring ophthalmologists were analyzed. An intravitreal recurrence treatment with ranibizumab using the same PrONTO scheme as used in the "upload" phase followed.

RESULTS: Mean best corrected visual acuity (BCVA) of all 100 patients included in the study was - 0.61 ± 0.33 LogMAR before treatment and improved to - 0.36 ± 0.24 LogMAR ($p < 0.001$) after "upload" therapy. Mean central retinal thickness (CRT) was 291.5 ± 85.3 µm before treatment and decreased to 200.1 ± 63.7 µm after "upload" therapy ($p < 0.001$). At the time of recurrence the mean BCVA was - 0.63 ± 0.33 LogMAR and improved significantly to - 0.52 ± 0.28 LogMAR ($p < 0.001$) after recurrence treatment. At the time of recurrence the mean CRT was 281.2 ± 94.4 µm and decreased significantly to 202.7 ± 59.9 µm after recurrence treatment ($p < 0.001$).

CONCLUSIONS: Retreatment criteria according to the PrONTO scheme showed good morphological and functional results in the patients with recurrent neovascular AMD treated but seemed to be defined too broadly for everyday clinical use with an irreversible loss under those conditions in cases of a recurrent episode. Accordingly, the latest recurrence criteria of the DOG/BVA/DOC recommendations should be applied.

PMID: 23224125 [PubMed - as supplied by publisher]

Hong Kong Med J. 2012 Dec;18(6):488-95.

Intravitreal bevacizumab: safety of multiple doses from a single vial for consecutive patients.

Ng DS, Kwok AKh, Chan CW, Li WW.

Department of Ophthalmology, Tung Wah Eastern Hospital, Sheung Wan, Hong Kong.

OBJECTIVES: To report the incidence of endophthalmitis after intravitreal injection of anti-vascular endothelial growth factor and the safety profile of multiple doses of bevacizumab from the same vial reused for multiple patients.

DESIGN: Case series.

SETTING: A private hospital in Hong Kong.

PATIENTS: A systematic retrospective review of consecutive intravitreal anti-vascular endothelial growth factor injections between 5 June 2006 and 17 December 2010 at a single institute was conducted. Patients were identified from prospectively designed audit forms, and each patient's medical record was reviewed for any documented complications. Bevacizumab 1.25 mg/0.05 mL to 2.50 mg/0.1 mL was aspirated from the designated vial, with a maximum of 10 consecutive injections being aspirated from the same vial. The opened vial was then discarded without overnight storage. Ranibizumab was aspirated from the commercially available 1 mg/0.1 mL single-use vial.

RESULTS: A total of 1655 intravitreal anti-vascular endothelial growth factor injections into 392 eyes of 383 patients were evaluated during the study period. There were 1184 bevacizumab injections and 471 ranibizumab injections. There was one case of suspected endophthalmitis after ranibizumab injection, though culture of the vitreous tap was negative. The point prevalence of endophthalmitis was 0.06%

(1/1655) for the total number of injections: 0.21% (1/471) after ranibizumab, and 0% after bevacizumab.

CONCLUSION: Although many centres aliquot multiple syringes from a single vial to be kept in a refrigerator for use, the current study shows that so long as proper sterile techniques are implemented, there were no cases of endophthalmitis from using the same vial, which was reused for a maximum of 10 consecutive injections. For intravitreal injection, bevacizumab costs approximately US$50 to US$100 per dose, as opposed to US$2000 per dose for ranibizumab. Sharing multiple doses of bevacizumab from a single vial can substantially reduce the cost of treatment.

PMID: 23223649 [PubMed - in process]

Klin Monbl Augenheilkd. 2012 Dec 10. [Epub ahead of print]

[Improvement of Fixation in Diabetic Macular Oedema Patients under Intravitreal Ranibizumab Treatment.] [Article in German]

Seidensticker F, Reznicek L, Cserhati S, Liegl RG, Langer J, Wolf A, Kampik A, Ulbig M, Haritoglou C, Kernt M.

Augenklinik, Ludwig-Maximilians-Universität München.

Background: The aim of this study was to evaluate the fixation and other functional and morphological alterations in patients with diabetic macular oedema (DMO) under intravitreal ranibizumab therapy.

Patients and Methods: Thirty patients (39 eyes) with DMO with central involvement were included in this prospective study. Morphological (fluorescein angiography, OCT) as well as functional (visual acuity, microperimetry including fixation) parameters were analysed before and after three monthly intravitreal applications of ranibizumab.

Results: Best-corrected mean visual acuity (BCVA) increased significantly by 6.85 + 6.45 letters from 26.15 ± 13.83 to 33.03 ± 13.31 letters. Mean central retinal thickness and mean central retinal volume decreased significantly from 503.72 ± 143.78 µm, respectively ($p < 0.001$) before treatment to 387.05 ± 122.02 µm after the third intravitreal injection with ranibizumab. Mean retinal sensitivity obtained with microperimetry did not change significantly over the course of treatment. Mean fixation within 2° (4°) improved from 64.15% (85.7 %) before treatment significantly to 70.15% (91.5%) after three intravitreal injections with ranibizumab. Mean fixation stability within 2° improved from 43.9% before treatment significantly to 58.5% after three intravitreal injections.

Conclusion: DMO improved both morphologically with a significant reduction of central retinal thickness and volume and a significantly improved BCVA as well as fixation and fixation stability over the course of three monthly intravitreal injections with ranibizumab. Retinal sensitivity obtained in microperimetry did not change significantly over the course. Based on our observations we interpret and suggest fixation and fixation stability as an early functional parameter and prior to microperimetrically detectable changes of retinal sensitivity additional to BCVA during treatment of diabetic macular edema.

PMID: 23229224 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Dec 6. pii: S0002-9394(12)00705-2. doi: 10.1016/j.ajo.2012.10.003. [Epub ahead of print]

Diffusion of Technologies for the Care of Older Adults with Exudative Age-Related Macular Degeneration.

Stein JD, Hanrahan BW, Comer GM, Sloan FA.

Department of Ophthalmology and Visual Sciences, University of Michigan Medical School, Ann Arbor, Michigan.

PURPOSE: To determine patterns of diffusion of diagnostic tests and therapeutic interventions in the United States through 2010 for patients with newly diagnosed exudative macular degeneration (AMD).

DESIGN: Retrospective longitudinal cohort analysis.

METHODS: setting and patient population: A total of 23 941 Medicare beneficiaries with exudative AMD newly diagnosed during 1992-2009. observation procedures: Current Procedural Technology (CPT-4) billing codes were used to identify use of diagnostic tests (optical coherence tomography, fluorescein angiography, and fundus photography) and therapeutic interventions (argon laser photocoagulation, photodynamic therapy, intravitreal corticosteroids, and anti-vascular endothelial growth factor [VEGF] agents) used by these beneficiaries during the first year following diagnosis. main outcome measures: Rates of use of study diagnostic and therapeutic procedures.

RESULTS: Diffusion was rapid for each successive new diagnostic and treatment modality, with use of newer procedures quickly replacing existing ones. The number of beneficiaries treated with anti-VEGF agents for exudative AMD was considerably greater than for prior innovations, rising from use in 4.0% of beneficiaries in 2004-05 to 62.7% in 2009-10. In each year from first diagnosis years 2006-2009 and in different practice settings, use of bevacizumab exceeded that of ranibizumab (60%-78% vs 33%-47%, respectively). Rates of diffusion of the various therapies were relatively similar in communities throughout the United States irrespective of presence of a major teaching hospital in the vicinity.

CONCLUSIONS: Newer, more effective therapeutic interventions for exudative AMD diffused rapidly throughout the United States, quickly replacing older, less effective interventions. Although improving patient outcomes, rapid diffusion raises important public policy issues for Medicare and other payers to consider.

PMID: 23219066 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Dec 3. pii: S0002-9394(12)00688-5. doi: 10.1016/j.ajo.2012.09.032. [Epub ahead of print]

Treatment of Diabetic Macular Edema With a Designed Ankyrin Repeat Protein That Binds Vascular Endothelial Growth Factor: A Phase 1/2 Study.

Campochiaro PA, Channa R, Berger BB, Heier JS, Brown DM, Fiedler U, Hepp J, Stumpp MT.

The Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland. Electronic address: pcampo@jhmi.edu.

PURPOSE: To evaluate the safety and bioactivity of MP0112, a Designed Ankyrin Repeat Protein (DARPin) that specifically binds vascular endothelial growth factor (VEGF) in patients with diabetic macular edema (DME). DARPins are a novel class of proteins selected for specific, high-affinity binding to a target protein.

DESIGN: Phase I/II, open-label, multicenter dose-escalation trial.

METHODS: After a single intravitreal injection of MP0112, the main outcomes were safety assessments, aqueous MP0112 levels, change in best-corrected visual acuity (BCVA), and foveal thickness measured by optical coherence tomography. Six cohorts were planned, but only 3 were enrolled (0.04, 0.15, 0.4 mg), because a maximally tolerated dose of 1.0 mg was identified in a parallel age-related macular degeneration trial.

RESULTS: Median aqueous concentration of MP0112 was 555 nM 1 week and >10 nM in 3 of 4 patients

12 weeks post injection of 0.4 mg. Median BCVA improvement at week 12 was 4, 6, and 10 letters in cohorts 1, 2, and 3. Ocular inflammation was observed in 11 patients (61%) and was severe in 1. High-resolution chromatography separated proinflammatory impurities from MP0112, resulting in a new formulation.

CONCLUSIONS: A single intraocular injection of 0.4 mg MP0112 resulted in levels above the half-maximal inhibitory concentration and neutralization of VEGF in aqueous humor for 8-12 weeks. Despite inflammation in several patients, there was prolonged edema reduction and improvement in vision in several patients. The source of the inflammation was eliminated from a new preparation that is being tested in an ongoing clinical trial.

PMID: 23218689 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Ophthalmologica. 2012 Dec 8. [Epub ahead of print]

Monitoring of Drusen and Geographic Atrophy Area Size after Cataract Surgery Using the MD3RI Tool for Computer-Aided Contour Drawing.

Brunner S, Mora A, Fonseca J, Weber T, Falkner-Radler CI, Oeser R, Binder S.

Department for Ophthalmology at the Rudolfstiftung Hospital and the Ludwig-Boltzmann Institute for Retinology and Biomicroscopic Laser Surgery, Vienna, Austria.

Background/Aims: To monitor possible changes in the cumulated drusen or geographic atrophy area size (CDGAS) of nonexudative age-related macular degeneration (AMD) in patients before and after cataract surgery, using a new tool for computer-aided image quantification.

Methods: Randomized, prospective, clinical trial. 54 patients with cataract and nonexudative AMD were randomly assigned into an early surgery group (ES = 28) and a control group (CO = 26) with a 6-month delay of surgery. CDGAS was determined with the MD3RI tool for contour drawing in a central region of digitized fundus photographs, measuring 3,000 µm in diameter. To evaluate CDGAS progression, differences in pixels and square millimeters were calculated by equivalent tests.

Results: Forty-nine patients completed the visits over the 12-month period (ES = 27 and CO = 22). Mean pixel values increased from 201.5 (11.33 × 10(-3) mm(2)) to 202.7 (11.39 × 10(-3) mm(2)) in the ES group and from 191.6 (10.77 × 10(-3) mm(2)) to 194.6 (10.94 × 10(-3) mm(2)) in the CO group. Finally, equivalence of CDGAS differences between ES and CO could be demonstrated. No exudative AMD was recorded during the study period.

Conclusion: In our cohorts, no significant changes were found in CDGAS 12 months after cataract surgery. The MD3RI software could serve as an efficient, precise and objective tool for AMD quantification and monitoring in future trials.

PMID: 23235439 [PubMed - as supplied by publisher]

Doc Ophthalmol. 2012 Dec 13. [Epub ahead of print]

Dichoptic multifocal visual evoked potentials identify local retinal dysfunction in age-related macular degeneration.

Sabeti F, James AC, Essex RW, Maddess T.

ARC Centre of Excellence in Vision Science, John Curtin School of Medical Research, The Australian

National University (ANU), Canberra, ACT, 0200, Australia, faran.sabeti@anu.edu.au.

PURPOSE: To evaluate the ability of multifocal visual evoked potentials (mfVEPs) to identify functional loss in patients with early and exudative age-related macular degeneration (AMD). A dichoptic multifocal stimulus presentation was employed to investigate the regional effects of AMD and the potential diagnostic utility in macular disease.

METHODS: MfVEP responses were recorded from 19 unilateral exudative AMD patients with non-exudative (n = 15) or normal (n = 4) presentations in the fellow eye and 28 age-matched controls. Root mean square (RMS) waveforms were pooled across selected EEG channels to produce global field RMS (gfRMS) waveforms. GfRMS amplitudes and response delays were analysed by multivariate linear models, and diagnostic capacity was measured using areas under the curve (AUC) of receiver operator characteristic plots.

RESULTS: The mean gfRMS amplitude of the exudative eye of AMD patients was significantly reduced compared with the controls (-2.03 ± 0.08 dB, t = -12.9). Fellow non-exudative AMD eyes were less effected but still significantly reduced (-0.84 ± 0.07 dB, t = -11.5). No significant difference in mean gfRMS delay of AMD eyes across the central 46° was observed. AUC values of 100 ± 0.0 % (mean ± SE) for exudative and 79.7 ± 6.5 % for non-exudative eyes were obtained for response amplitudes.

CONCLUSION: The study demonstrated that mfVEP identified retinal dysfunction in both exudative AMD and fellow non-exudative AMD eyes, but mostly affecting the macular field. The reduced testing duration and good diagnostic accuracy suggest that dichoptic mfVEPs may be a sensitive tool for monitoring progression in AMD.

PMID: 23238587 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Dec 12. [Epub ahead of print]

Abnormal Fixation in Individuals With Age-Related Macular Degeneration When Viewing an Image of a Face.

Seiple W, Rosen RB, Garcia PM.

*PhD †MD New York University School of Medicine, New York, New York (WS); New York Eye and Ear Infirmary, New York, New York (WS, RBR, PMTG); Jesse Brown VAMC, Chicago, Illinois (WS); Lighthouse International, New York, New York (WS).

PURPOSE: It has been reported that patients with macular disease have difficulties with face perception. Some of this difficulty may be caused by the sensory and perceptual consequences of using peripheral retina. However, strong correlations have not always been found between performance on face tasks and clinical measure of function. Based on the evidence of abnormal eye movements by patients with age-related macular degeneration (AMD), we explored whether abnormal fixation patterns occur when these patients view an image of a face.

METHODS: An OPKO OCT/SLO was used to collect structural and functional data. For each subject, the structural location of disease was determined, and the locus and stability of fixation were quantified. A SLO movie of fundus movements was recorded while the subject viewed an image of a face.

RESULTS: The number of fixations on internal (eyes, nose, and mouth) and external features were measured. A two-way repeated-measures analysis of variance found significant differences between the control and patient groups and among locations. A significant interaction between group and location was also found. Post hoc comparisons found a significantly greater proportion of fixations on external features for the AMD group than that in the control group.

CONCLUSIONS: The observed patterns of fixations of our subjects with AMD were similar to those

observed in other groups of patients who have difficulties with face perception. For example, individuals with social phobias, Williams syndrome, autism, schizophrenia, or prosopagnosia have altered face perceptions and also have a significantly greater proportion of fixations on external features of faces. Abnormal eye movement patterns and fixations may contribute to deficits in face perception in AMD patients.

PMID: 23238260 [PubMed - as supplied by publisher]

Optom Vis Sci. 2012 Dec 8. [Epub ahead of print]

Clinicopathologic Correlation of Disc and Peripapillary Region Using Spectral Domain Optical Coherence Tomography.

Sigler EJ, Mascarenhas KG, Tsai JC, Loewen NA.

*MD † MD, PhD Division of Vitreoretinal Surgery, Charles Retina Institute, Memphis, Tennessee (EJS); Yale University School of Medicine, Department of Ophthalmology and Visual Science, New Haven, Connecticut (KGM, JCT); and Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (NAL).

PURPOSE: To describe a technique for evaluating peripapillary and optic nerve head (ONH) anatomy using spectral domain optical coherence tomography (SD-OCT) raster scanning in humans and compare quantifiable parameters between diagnosis categories.

METHODS: Ninety-five eyes of 51 consecutive patients were evaluated in this retrospective cross-sectional pilot study. Cirrus 5-line raster SD-OCTs with a resolution of 5 to 15 μm obtained through the ONH were included. A single observer manually measured neural canal opening (NCO), prelaminar canal depth (PLCD), peripapillary choroidal thickness (PPCT), and canal nerve fiber layer (CNFL) in normals, ocular hypertension, primary open-angle glaucoma (POAG), low-pressure glaucoma (LPG), secondary glaucoma, and early atrophic age-related macular degeneration. Clinical information, including central corneal thickness (CCT), was obtained via medical record review. Mean anatomical values within diagnosis categories were compared using one-way analysis of variance and multivariate analysis. Bivariate analysis was used to investigate relationships between continuous variables, and significant ($p < 0.05$) relationships were incorporated into the final statistical model.

RESULTS: Horizontal NCO was significantly greater in eyes with LPG than that in normals ($p = 0.021$). The PPCT was thinner in age-related macular degeneration ($p = 0.001$) and glaucoma ($p = 0.004$) compared with that in controls (normals). Mean CNFL was thinner in POAG ($p < 0.001$) and LPG ($p = 0.053$) compared with that in normals. Vertical NCO was inversely correlated to CCT ($p = 0.013$). Multivariate analysis indicated a positive correlation between PLCD and PPCT ($p = 0.008$) and an inverse correlation between CNFL and PLCD ($p < 0.001$). Controlling for PPCT, PLCD and CCT were inversely correlated ($p < 0.001$).

CONCLUSIONS: The SD-OCT raster scanning may be used to quantify ONH anatomy in humans. The NCO differences between POAG and LPG may indicate a distinct structural vulnerability in LPG. In addition, CNFL, PPCT, and PLCD may be important parameters to consider in glaucoma. The PLCD correlates with PPCT and should be considered in new models of glaucoma pathogenesis.

PMID: 23232801 [PubMed - as supplied by publisher]

Ophthalmologe. 2012 Dec 9. [Epub ahead of print]

[Cytokine determination from vitreous samples in retinal vascular diseases.] [Article in German]

Pfister M, Koch FH, Cinatl J, Rothweiler F, Schubert R, Singh P, Ackermann H, Koss MJ.

Universitätsaugenklinik, Goethe Universität, Theodor Stern Kai 7, 60590, Frankfurt am Main, Deutschland, marcel.pfister@kgu.de.

PURPOSE: The aim of this study was to determine cytokine levels from vitreous samples of treatment-naive patients with diabetic retinopathy (DRP), retinal vein occlusion (RVO) and exudative age-related macular degeneration (ARMD).

METHODS: In this study 187 patients (median age 67 years, 101 males) were treated with a combined drug therapy including a 23-gauge core vitrectomy. Interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and intravitreal vascular endothelial growth factor (VEGF-A) levels were determined a using cytometric bead assay (CBA) and compared to those of the control group.

RESULTS: Compared to the control group all diseases had significantly elevated cytokine levels, except VEGF in ARMD. In DRP samples of patients with diffuse diabetic macula edema (DME) higher VEGF-A and MCP-1 levels were found than in patients with focal DME. Ischemic DRP had higher VEGF levels than non-ischemic DRP. All measured cytokines were significantly higher in central retinal vein occlusion (CRVO) than in branch retinal vein occlusion (BRVO).

CONCLUSIONS: Differences in intravitreal cytokine levels in DRP, RVO and ARMD could be demonstrated. The knowledge of depicted specific characteristic dysregulation of cytokines could allow more targeted future therapies.

PMID: 23224211 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Dec 3. pii: S0002-9394(12)00640-X. doi: 10.1016/j.ajo.2012.09.010. [Epub ahead of print]

Morphologic Features and Viability Analysis of Human Detached Retinal Pigment Epithelium in Age-Related Macular Degeneration.

Han L, Ma Z, Wang C, Hu Y, Jin Y.

Department of Ophthalmology, Peking University Third Hospital, Key Laboratory of Vision Loss and Restoration, Ministry of Education, Beijing, People's Republic of China.

PURPOSE: To evaluate the morphologic features and viability of human retinal pigment epithelium (RPE) cells captured from the pigment epithelium detachment (PED) region outside the choroidal neovascular membrane lesion in eyes with hemorrhagic age-related macular degeneration.

DESIGN: Prospective, observational case series.

METHODS: Five specimens of the RPE sheet were obtained from the PED region after choroidal neovascular membrane excision in 5 eyes of 5 patients during RPE transplantation for hemorrhagic age-related macular degeneration. The specimens were stained with hematoxylin and eosin and with periodic acid-Schiff. Immunohistochemistry analysis for RPE-65 and zonula occludens-1 also was performed. RPE cells from the PED region were cultured and passaged 5 times. Scanning and transmission electron microscopy were performed to analyze the specimens.

RESULTS: The RPE cells of the specimens contained brownish pigment and were autofluorescent in vitro. Periodic acid-Schiff staining revealed that the Bruch membrane below the RPE monolayer was not intact. The specimens demonstrated positive results for both zonula occludens-1 and RPE-65 staining. The RPE basement membrane in the specimen was observed by both scanning and transmission electron microscopy. Intercellular tight junctions among RPE cells of the specimen also were observed. RPE cells captured from the PED region were cultured successfully and were passaged 5 times.

CONCLUSIONS: The RPE sheet developed from the PED region outside the choroidal neovascular membrane lesion had tight intercellular junctions, a simple RPE basement membrane, and active cellular viability. This monolayer RPE sheet may be considered as a substitution for subfoveal RPE loss in eyes with hemorrhagic age-related macular degeneration.

PMID: 23218698 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Dec 10:1-8. doi: 10.1001/jamaophthalmol.2013.1165. [Epub ahead of print]

Vision Insurance, Eye Care Visits, and Vision Impairment Among Working-Age Adults in the United States.

Li YJ, Xirasagar S, Pumkam C, Krishnaswamy M, Bennett CL.

OBJECTIVES: To compare rates of eye care visits and vision impairment among working-age adults with vision insurance vs without, among the total sample of Behavioral Risk Factor Surveillance Survey respondents and among a subsample of respondents who had diagnoses of glaucoma, age-related macular degeneration (ARMD), and/or cataract.

DESIGN: Using the Behavioral Risk Factor Surveillance Survey 2008 vision module data, we examined the likelihood of an eye care visit within the past year and of self-reported visual impairment among 27 152 adults aged 40 to 65 years and among a subset of 3158 persons (11.6%) with glaucoma, ARMD, and/or cataract. Multivariate logistic regression models were used.

RESULTS: About 40% of both the study population and the subsample with glaucoma, ARMD, and/or cataract had no vision insurance. Respondents with vision insurance were more likely than those without to have had eye care visits (general population adjusted odds ratio [AOR], 1.90 [95% CI, 1.89-1.90]; glaucoma -ARMD-cataract subsample AOR, 2.15 [95% CI, 2.13-2.17]), to have no difficulty recognizing friends across the street (general population AOR, 1.24 [95% CI, 1.22-1.26]; eye-disease subsample AOR, 1.45 [95% CI, 1.42-1.49]), and to have no difficulty reading printed matter (general population AOR, 1.34 [95% CI, 1.33-1.35]; eye-disease subsample AOR, 1.37 [95% CI, 1.34-1.39]). Respondents from the total sample who had an eye care visit were better able to recognize friends across the street (AOR, 1.07) and had no difficulty reading printed matter (AOR, 1.70), and respondents from the eye-disease subsample who had an eye care visit also were better able to recognize friends across the street (AOR, 1.71) and had no difficulty reading printed matter (AOR, 1.45).

CONCLUSIONS: Lack of vision insurance impedes eye care utilization, which, in turn, may irrevocably affect vision. Vision insurance for preventive eye care should cease to be a separate insurance benefit and should be mandatory in all health plans.

PMID: 23229123 [PubMed - as supplied by publisher]

J Neurochem. 2012 Dec 5. doi: 10.1111/jnc.12116. [Epub ahead of print]

Role of endoplasmic reticulum stress in light-induced photoreceptor degeneration in mice.

Nakanishi T, Shimazawa M, Sugitani S, Kudo T, Imai S, Inokuchi Y, Tsuruma K, Hara H.

Molecular Pharmacology, Department of Biofunctional Evaluation, Gifu Pharmaceutical University, 1-25-4 Daigaku-nishi, Gifu, Japan.

Abstract: Exposure to excessive levels of light induces photoreceptor apoptosis and can be a causative factor in age-related macular degeneration (AMD). However, the cellular events that mediate this apoptotic response are poorly understood. Here, we investigated the roles of endoplasmic reticulum (ER) stress in light-induced cell death in the murine retina and murine photoreceptor cells (661W). Excessive light

exposure induced retinal dysfunction, photoreceptor degeneration, and apoptosis. Furthermore, the accumulation of polyubiquitinated proteins and the transcriptional expression of ER stress-related factors, including 78-kDa glucose-regulated protein (GRP78)/immunoglobulin binding protein (BiP) and C/EBP-homologous protein (CHOP), were increased in light-exposed retinas. Light exposure also induced both cell death and up-regulation of polyubiquitinated proteins, S-opsin aggregation, bip and chop mRNAs in 661W cells in vitro. Knockdown of chop mRNA inhibited photoreceptor cell death induced by light exposure. Furthermore, treatment with BiP inducer X (BIX), an ER stress inhibitor, induced bip mRNA and reduced both chop expression and light-induced photoreceptor cell death. These data indicate that excessive ER stress may induce photoreceptor cell death in light-exposed retinas via activation of the CHOP-dependent apoptotic pathway, suggesting that the ER stress may play a pivotal role in light exposure-induced retinal damage. © 2012 International Society for Neurochemistry, J. Neurochem. (2012) 10.1111/jnc.12116.

PMID: 23216380 [PubMed - as supplied by publisher]

Expert Opin Ther Pat. 2012 Dec 10. [Epub ahead of print]

Pharmaceutical composition for treating macular degeneration (WO2012079419).

Wang S, Cunnusamy K.

Tulane University, Department of Cell and Molecular Biology , LA , USA swang1@tulane.edu.

Abstract: A pharmaceutical composition composed of several traditional Chinese medicines is claimed to treat age-related macular degeneration (AMD). This represents a novel and alternative therapeutic solution for wet AMD, with the potential advantage of treating both the symptoms and the underlying causes of this devastating degenerative retinal disease.

PMID: 23215532 [PubMed - as supplied by publisher]

Pathogenesis

Exp Eye Res. 2012 Dec 8. pii: S0014-4835(12)00342-9. doi: 10.1016/j.exer.2012.11.015. [Epub ahead of print]

Ccl2, Cx3cr1 and Ccl2/Cx3cr1 chemokine deficiencies are not sufficient to cause age-related retinal degeneration.

Luhmann UF, Carvalho LS, Robbie SJ, Cowing JA, Duran Y, Munro PM, Bainbridge JW, Ali RR.

Department of Genetics, 1 UCL Institute of Ophthalmology, London, United Kingdom. Electronic address: u.luhmann@ucl.ac.uk.

Abstract: Monocytes, macrophages, dendritic cells and microglia play critical roles in the local immune response to acute and chronic tissue injury and have been implicated in the pathogenesis of age-related macular degeneration. Defects in Ccl2-Ccr2 and Cx3cl1-Cx3cr1 chemokine signalling cause enhanced accumulation of bloated subretinal microglia/macrophages in senescent mice and this phenomenon is reported to result in the acceleration of age-related retinal degeneration. The purpose of this study was to determine whether defects in CCL2-CCR2 and CX3CL1-CX3CR1 signalling pathways, alone or in combination, cause age-dependent retinal degeneration. We tested whether three chemokine knockout mouse lines, Ccl2(-/-), Cx3cr1(-/-) and Ccl2(-/-)/Cx3cr1(-/-), in comparison to age-matched C57Bl/6 control mice show differences in subretinal macrophage accumulation and loss of adjacent photoreceptor cells at 12-14 months of age. All mouse lines are derived from common parental strains and do not carry the homozygous rd8 mutation in the Crb1 gene that has been a major confounding factor in previous reports. We quantified subretinal macrophages by counting autofluorescent lesions in fundus images obtained by

scanning laser ophthalmoscopy (AF-SLO) and by immunohistochemistry for Iba1-positive cells. The accumulation of subretinal macrophages was enhanced in Ccl2(-/-), but not in Cx3cr1(-/-) or Ccl2(-/-)/ Cx3cr1(-/-) mice. We identified no evidence of retinal degeneration in any of these mouse lines by TUNEL-staining or semithin histology. In conclusion, CCL2-CCR2 and/or CX3CL1-CX3CR1 signalling defects may differentially affect the trafficking of microglia and macrophages in the retina during ageing, but do not appear to cause age-related retinal degeneration in mice.

PMID: 23232206 [PubMed - as supplied by publisher]

Front Immunol. 2012;3:338. doi: 10.3389/fimmu.2012.00338. Epub 2012 Nov 27.

Good news-bad news: the Yin and Yang of immune privilege in the eye.

Forrester JV, Xu H.

Laboratory of Immunology, Lion's Eye Institute, University of Western Australia Perth, WA, Australia ; Ocular Immunology Laboratory, Section of Immunology and Infection, Institute of Medical Sciences, University of Aberdeen Aberdeen, UK.

Abstract: The eye and the brain are prototypical tissues manifesting immune privilege (IP) in which immune responses to foreign antigens, particularly alloantigens are suppressed, and even completely inhibited. Explanations for this phenomenon are numerous and mostly reflect our evolving understanding of the molecular and cellular processes underpinning immunological responses generally. IP is now viewed as a property of many tissues and the level of expression of IP varies not only with the tissue but with the nature of the foreign antigen and changes in the limited conditions under which privilege can operate as a mechanism of immunological tolerance. As a result, IP functions normally as a homeostatic mechanism preserving normal function in tissues, particularly those with highly specialized function and limited capacity for renewal such as the eye and brain. However, IP is relatively easily bypassed in the face of a sufficiently strong immunological response, and the privileged tissues may be at greater risk of collateral damage because its natural defenses are more easily breached than in a fully immunocompetent tissue which rapidly rejects foreign antigen and restores integrity. This two-edged sword cuts its swathe through the eye: under most circumstances, IP mechanisms such as blood-ocular barriers, intraocular immune modulators, induction of T regulatory cells, lack of lymphatics, and other properties maintain tissue integrity; however, when these are breached, various degrees of tissue damage occur from severe tissue destruction in retinal viral infections and other forms of uveoretinal inflammation, to less severe inflammatory responses in conditions such as macular degeneration. Conversely, ocular IP and tumor-related IP can combine to permit extensive tumor growth and increased risk of metastasis thus threatening the survival of the host.

PMID: 23230433 [PubMed]

Invest Ophthalmol Vis Sci. 2012 Dec 6. pii: iovs.12-10655v1. doi: 10.1167/iovs.12-10655. [Epub ahead of print]

NLRP3 Inflammasome Activation in Retinal Pigment Epithelial Cells by Lysosomal Destabilization: Implications for Age-Related Macular Degeneration.

Tseng WA, Thein T, Kinnunen K, Lashkari K, Gregory MS, D'Amore PA, Ksander BR.

Department of Pathology, Harvard Medical School, Schepens Eye Research Institute/Massachusetts Eye and Ear, Boston, MA, United States.

PURPOSE: To evaluate the effect of lysosomal destabilization on NLRP3 inflammasome activation in RPE cells and to investigate the mechanisms by which inflammasome activation may contribute to the pathogenesis of age-related macular degeneration (AMD).

METHODS: Human ocular tissue sections from patients with geographic atrophy or neovascular AMD were stained for NLRP3 and compared to tissues from age-matched controls. Expression of the IL-1β precursor, pro-IL-1β, was induced in ARPE-19 cells by IL-1α treatment. Immunoblotting was performed to assess expression of NLRP3 inflammasome components (NLRP3, ASC, and procaspase-1) and pro-IL-1β in ARPE-19 cells. Lysosomes were destabilized using the lysosomotropic agent Leu-Leu-OMe. Active caspase-1 was detected using FAM-YVAD-FMK, a fluorescent-labeled inhibitor of caspases (FLICA) specific for caspase-1. IL-1β was detected by immunoblotting and ELISA, and cytotoxicity was evaluated by LDH quantification.

RESULTS: RPE of eyes affected by geographic atrophy or neovascular AMD exhibited NLRP3 staining at lesion sites. ARPE-19 cells were found to express NLRP3, ASC, and procaspase-1. IL-1α dose-dependently induced pro-IL-1β expression in ARPE-19 cells. Lysosomal destabilization induced by Leu-Leu-OMe triggered caspase-1 activation, IL-1β release, and ARPE-19 cell death. Blocking Leu-Leu-OMe-induced lysosomal disruption with the compound Gly-Phe-CHN2 or inhibiting caspase-1 with Z-YVAD-FMK abrogated IL-1β secretion and ARPE-19 cytotoxicity.

CONCLUSIONS: NLRP3 upregulation occurs in the RPE during the pathogenesis of advanced AMD, in both geographic atrophy and neovascular AMD. Destabilization of RPE lysosomes induces NLRP3 inflammasome activation, which may contribute to AMD pathology through the release of the proinflammatory cytokine IL-1β and through caspase-1-mediated cell death, known as "pyroptosis."

PMID: 23221073 [PubMed - as supplied by publisher]

Adv Clin Exp Med. 2012 Jan-Feb;21(1):105-14.

Deficiencies and excessive human complement system activation in disorders of multifarious etiology.

Tichaczek-Goska D.

Department of Biology and Medical Parasitology, Wroclaw Medical University, Wroclaw, Poland. dgoska@biolog.am.wroc.pl

Abstract: Complement is an integral part of the immune system protecting the host organism against invasion and proliferation of various microorganisms. It is also involved in the removal of the body's own damaged and altered cells. Activation of the complement system is a very precise process and it is strictly controlled by regulatory proteins present in both plasma and at host cells' surfaces. C3 protein plays a major role in the complement activation and generation of immune responses. Deficiencies of the C3 and other complement components, so-called early and late complement proteins, contribute to the emergence of recurrent bacterial, viral and fungal infections. The low level of mannose-binding lectin is also important. This protein plays a protective role in the early stages of infection and in the control of inflammation. Its deficit is one of the most common reasons for human immunodeficiency, observed in microbial infections as well as in autoimmune diseases such as rheumatoid arthritis. On the other hand, the excessive activation of complement proteins is often discovered to be the reason for many diseases. These include e.g. autoimmune diseases, Alzheimer's syndrome, schizophrenia, atypical hemolytic-uremic syndrome, angioedema, macular degeneration, and Crohn's disease.

PMID: 23214307 [PubMed - in process]

Biochim Biophys Acta. 2012 Dec 5. pii: S0167-4889(12)00350-3. doi: 10.1016/j.bbamcr.2012.11.018. [Epub ahead of print]

Maturation of autophagosomes and endosomes: A key role for Rab7.

Hyttinen JM, Niittykoski M, Salminen A, Kaarniranta K.

Department of Ophthalmology, Institute of Clinical Medicine, University of Eastern Finland, P.O.Box 1627, FI-70211 Kuopio, Finland. Electronic address: Juha.Hyttinen@uef.fi.

Abstract: Macroautophagy is an important route in cellular maintenance, in the breakdown and reuse intracellular of materials. It is closely related to endocytosis, the means by which the cell can absorb extracellular material, as both macroautophagy and endocytosis have converging steps and common participating molecules. The point where autophagosomes and endosomes fuse with lysosomes to permit for the final degradation of their contents is important. One of the most substantial molecules in the maturation of autophagosomes/endosomes is Rab7, a member of small GTPases. Rab7 designates the maturation of endosomes and also autophagosomes, directing the trafficking of cargos along microtubules, and finally, participating in the fusion step with lysosomes. Rab7 is an effective multifunctional regulator of autophagy and endocytosis. Since many aggregation-based diseases, e.g. age-related macular degeneration of the eye (AMD) and Alzheimer's disease are due of malfunctioning in the autophagic process, the management of Rab7 activity might hold potential as a therapeutic target against these diseases.

PMID: 23220125 [PubMed - as supplied by publisher]

J Biomol Screen. 2012 Dec 10. [Epub ahead of print]

A High-Throughput Cell-Based Gaussia Luciferase Reporter Assay for Identifying Modulators of Fibulin-3 Secretion.

Hulleman JD, Brown SJ, Rosen H, Kelly JW.

Department of Chemistry and the Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, USA.

Abstract: An R345W mutation in fibulin-3 causes its inefficient secretion, increased intracellular steady-state levels, and the macular dystrophy, Malattia Leventinese (ML), a disease similar to age-related macular degeneration. It is unknown whether R345W causes ML through increased intracellular levels, by the secretion of a potentially aggregation-prone protein, or both. To identify small molecules that alter the secretion of fibulin-3, we developed ARPE19 retinal cell lines that inducibly express wild-type (WT) or R345W fibulin-3 fused to an enhanced Gaussia luciferase (eGLuc2). Screening of the Library of Pharmacologically Active Compounds demonstrated that these cell lines and the GLuc assay are suitable for high-throughput chemical screening. Two estrogen-related compounds enhanced fibulin-3 secretion, whereas a diverse series of small molecules reduced fibulin-3 secretion. A counterscreen identified compounds that did not substantially alter the secretion of unfused eGLuc2, demonstrating at least partial selectivity for fibulin-3. A secondary assay using untagged fibulin-3 confirmed that the top three inhibitory compounds reduced R345W fibulin-3 secretion. Interestingly, in untagged fibulin-3 studies, one compound, phorbol 12-myristate 13-acetate, reduced R345W fibulin-3 secretion while minimally enhancing WT fibulin-3 secretion, the desired activity and selectivity we sought for ML. The identified compounds could serve as tools for probing the etiology of fibulin-3-related diseases.

PMID: 23230284 [PubMed - as supplied by publisher]

Genetics

Invest Ophthalmol Vis Sci. 2012 Dec 11. pii: iovs.12-10453v1. doi: 10.1167/iovs.12-10453. [Epub ahead of print]

Association between polymorphisms of complement pathway genes and age-related macular

degeneration in a Chinese population.

Wu L, Tao Q, Chen W, Wang Z, Song Y, Sheng S, Li P, Zhou J.

Department of Ophthalmology, Huazhong University of Science and Technology, Tongji Medical College, Union Hospital, Wuhan, China.

Purpose: To assess the association between complement pathway genes and AMD in a Chinese population.

Methods: In a case-control study, 165 AMD patients and 216 unrelated controls were recruited from two hospitals in central China. We selected and genotyped six single nucleotide polymorphisms (SNPs) of four complement pathway genes, including rs800292 and rs1410996 of complement H (CFH), rs9332739 of complement 2 (C2), rs4151667 of complement factor b (CFB), rs2241394 and rs2230199 of complement 3 (C3). The associations between SNPs and AMD, adjusted by age and gender, were assessed by using both logistic regression models and haplotype association analysis.

Results: In our study, two SNPs of CFH and their haplotypes were significantly associated with AMD and the adjusted odd ratios (ORs) were 2.45 (95%CI: 1.25 to 4.79) for rs800292 (genotype: GG versus AA), 2.49 (95%CI: 1.24 to 5.00) for rs1410996 (genotype: TT versus CC), and 4.45 (95%CI: 2.32 to 8.55) for haplotype block of rs800292-rs1410996 (haplotype: G-C versus A-C), respectively. The haplotype of C2/CFB was also significantly associated with AMD, and the adjusted OR was 8.86 (95%CI: 1.88 to 41.69) for the haplotype block of rs9332739-rs4151667 (haplotype: G-A versus G-T), though no relationship was found in genotype association analysis of the two SNPs of C2/CFB. With the sample size of this study, no relationship was found for AMD and the two SNPs of C3. CONCLUSIONS. Gene variants in CFH and C2/CFB contribute to AMD in the Chinese population.

PMID: 23233260 [PubMed - as supplied by publisher]

Diet

Ophthalmology. 2012 Dec 5. pii: S0161-6420(12)00850-0. doi: 10.1016/j.ophtha.2012.08.040. [Epub ahead of print]

Secondary Outcomes in a Clinical Trial of Carotenoids with Coantioxidants versus Placebo in Early Age-Related Macular Degeneration.

Beatty S, Chakravarthy U, Nolan JM, Muldrew KA, Woodside JV, Denny F, Stevenson MR.

Macular Pigment Research Group, Waterford Institute of Technology, Waterford City, Waterford, Republic of Ireland.

PURPOSE: To report the secondary outcomes in the Carotenoids with Coantioxidants in Age-Related Maculopathy trial.

DESIGN: Randomized double-masked placebo-controlled clinical trial (registered as ISRCTN 94557601).

PARTICIPANTS: Participants included 433 adults 55 years of age or older with early age-related macular degeneration (AMD) in 1 eye and late-stage disease in the fellow eye (group 1) or early AMD in both eyes (group 2).

INTERVENTION: An oral preparation containing lutein (L), zeaxanthin (Z), vitamin C, vitamin E, copper, and zinc or placebo. Best-corrected visual acuity (BCVA), contrast sensitivity (CS), Raman spectroscopy, stereoscopic colour fundus photography, and serum sampling were performed every 6 months with a minimum follow-up time of 12 months.

MAIN OUTCOME MEASURES: Secondary outcomes included differences in BCVA (at 24 and 36 months),

CS, Raman counts, serum antioxidant levels, and progression along the AMD severity scale (at 12, 24, and 36 months).

RESULTS: The differential between active and placebo groups increased steadily, with average BCVA in the former being approximately 4.8 letters better than the latter for those who had 36 months of follow-up, and this difference was statistically significant (P = 0.04). In the longitudinal analysis, for a 1-log-unit increase in serum L, visual acuity was better by 1.4 letters (95% confidence interval, 0.3-2.5; P = 0.01), and a slower progression along a morphologic severity scale (P = 0.014) was observed.

CONCLUSIONS: Functional and morphologic benefits were observed in key secondary outcomes after supplementation with L, Z, and coantioxidants in persons with early AMD.

PMID: 23218821 [PubMed - as supplied by publisher]