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MD Research News

Issue 35

Monday July 4 , 2011

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Drug treatment

Ophthalmology. 2011 Jun 25. [Epub ahead of print]

Outcomes and Risk Factors Associated with Endophthalmitis after Intravitreal Injection of Anti-Vascular Endothelial Growth Factor Agents.

Shah CP, Garg SJ, Vander JF, Brown GC, Kaiser RS, Haller JA; Post-Injection Endophthalmitis (PIE) Study Team(□).

Ophthalmic Consultants of Boston, Boston, Massachusetts; MidAtlantic Retina, The Retina Service of Wills Eye Institute, Thomas Jefferson University, Philadelphia, Pennsylvania.

OBJECTIVE: To describe outcomes of and risk factors for endophthalmitis after intravitreal anti-vascular endothelial growth factor (VEGF) injection.

DESIGN: Single-center, consecutive, case series and retrospective case-control study.

PARTICIPANTS: Between January 1, 2009, and May 31, 2010, 16 vitreoretinal surgeons administered a total of 27 736 injections. During this period, 23 cases of presumed infectious endophthalmitis occurred. Each surgeon used his own preferred injection technique.

INTERVENTION: Vitreous or aqueous tap, or both, with intravitreal antibiotic injection and subsequent topical antibiotic and steroid drops.

MAIN OUTCOME MEASURES: Visual acuity, bladed lid speculum use, conjunctival displacement, hemisphere of injection, bevacizumab versus ranibizumab, and infectious organism.

RESULTS: Seven of 23 cases had positive culture results; 3 grew coagulase-negative Staphylococcus. All cases had pain and vitritis on average 3.4 days (range, 1-6 days) after injection, with no difference between culture-positive and culture-negative groups. Eighteen (78%) of 23 cases had a hypopyon. Fifteen of 23 cases returned to baseline vision (±2 lines) within 3 months. Neither lid speculum use (0.10% vs. 0.066% in the no-use group; P = 0.27), conjunctival displacement (0.11% vs. 0.076% in the no-displacement group; P = 0.43), hemisphere of injection (0.11% superior vs. 0.079% inferior; P = 0.56), or bevacizumab versus ranibizumab (0.11% vs. 0.066%; P = 0.21) affected risk. Analysis of only culture-positive results yielded similar results. There was no statistically significant difference between the proportion of culture-negative cases after bevacizumab injection (83%) versus ranibizumab injection (55%; P = 0.13).

CONCLUSIONS: Most patients in whom presumed infectious endophthalmitis develop after anti-VEGF injection regained baseline vision after treatment. Bladed lid speculum use, conjunctival displacement, hemisphere of injection, and type of anti-VEGF agent did not affect risk. No difference in culture-negative

endophthalmitis rates was detected after bevacizumab versus ranibizumab injection. Neither the presence of pain, vitritis, decreased vision, hypopyon, nor the interval between injection and development of symptoms differentiate culture-positive from culture-negative cases. Because a subgroup of patients had poor outcomes, a low threshold for vitreous tap with intravitreal antibiotic injection may be warranted.

PMID: 21705087 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2011 Jun 24. [Epub ahead of print]

Monthly Ranibizumab for Choroidal Neovascularizations Secondary to Angioid Streaks in Pseudoxanthoma Elasticum: A One-Year Prospective Study.

Finger RP, Charbel Issa P, Hendig D, Scholl HP, Holz FG.

Department of Ophthalmology, University of Bonn, Bonn, Germany.

PURPOSE: To evaluate the efficacy and safety of monthly intravitreal ranibizumab for the treatment of choroidal neovascularizations (CNV) secondary to angioid streaks (AS) in pseudoxanthoma elasticum (PXE).

DESIGN: Twelve-month prospective, open-label, uncontrolled, nonrandomized interventional clinical trial.

METHODS: In 7 patients, 1 eye with an active CNV was injected with 0.5 mg ranibizumab monthly over 1 year. Distance and reading visual acuity, reading speed, angiographic findings, and central retinal thickness (CRT) on optical coherence tomography were assessed at each visit. Central retinal light increment sensitivity (LIS) was assessed by microperimetry at baseline, at 6 months, and 3 to 4 months after the last injection.

RESULTS: Best-corrected visual acuity increased significantly from baseline to month 12 (20/63 or 61 ETDRS letters to 20/32 or 73 ETDRS letters; P = .012). The effect was maintained 3 months later (61 ETDRS letters to 72 ETDRS letters; P = .055). Reading acuity and speed could be maintained throughout the study. Central LIS improved (6.6 dB, SD ± 5.9 at baseline to 7.4 dB, SD ± 6.2 at last follow-up; P < .001). Leakage from active CNVs subsided. Mean change in CRT from baseline to month 12 and 15 was -86 μm (P = .074) and -65 μm (P = .182), respectively. No serious adverse events occurred.

CONCLUSIONS: Efficacy outcomes indicate a beneficial therapeutic effect of intravitreal ranibizumab on central visual function including retinal LIS. Both the functional and morphologic response based on angiographic and OCT findings to ranibizumab treatment implicate an important pathophysiological role of vascular endothelial growth factor in CNVs secondary to AS in PXE. Intravitreal ranibizumab appears to be a safe and efficacious treatment in these patients.

PMID: 21704964 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2011 Apr;46(2):182-5.

Efficacy of intravitreal bevacizumab after unresponsive treatment with intravitreal ranibizumab.

Almony A, Mansouri A, Shah GK, Blinder KJ.

Department of Ophthalmology, University of Missouri-Columbia, Columbia, Mo., USA. Presented in part at the 26th Annual Meeting of the American Society of Retina Specialists, Maui, October 2008. gkshah1@gmail.com.

Objective: To evaluate visual outcomes of eyes with choroidal neovascular membrane secondary to age-related macular degeneration that were initially treated with intravitreal ranibizumab then switched to in-

travitreal bevacizumab due to treatment failure.

Design: Retrospective chart review.

Participants: Fifty eyes of 50 patients presenting to the Barnes Retina Institute.

Methods: Patients unresponsive to treatment with intravitreal ranibizumab were switched to intravitreal bevacizumab. Main outcome measures included number of intravitreal injections, visual acuity (VA), and resolution of leakage. Mean follow-up was 6 months after the final intravitreal bevacizumab injection. On average, each patient received 3.5 ranibizumab injections and 2.5 bevacizumab injections. Each patient received an average of 6 injections.

Results: Resolution of leakage on fluorescein angiography and optical coherence tomography was achieved in 44 eyes (88%). Initial VA ranged from 20/30 to counting fingers (CF) (median VA 20/125). Final VA ranged from 20/20 to CF (median VA 20/100). Change in VA varied from loss of 2 lines to gain of 4 lines, but overall, remained stable (average gain 0.3 lines). Eighteen eyes (36%) had a final VA of ≥ 20/50 and 18 eyes (36%) had a final VA of ≤20/200.

Conclusions: Treatment with intravitreal bevacizumab may be effective, as measured by visual and anatomic criteria, in patients who are unresponsive to treatment with intravitreal ranibizumab.

PMID: 21708088 [PubMed - in process]

Eye (Lond). 2011 Jun 24. doi: 10.1038/eye.2011.146. [Epub ahead of print]

Long-term visual outcome of pigment epithelial tears in association with anti-VEGF therapy of pigment epithelial detachment in AMD.

Gutfleisch M, Heimes B, Schumacher M, Dietzel M, Lommatzsch A, Bird A, Pauleikhoff D.

Department of Ophthalmology, St Franziskus Hospital, Muenster, Germany.

Purpose: Retinal pigment epithelium (RPE) tears may develop as a complication after anti-VEGF (vascular endothelial growth factor) treatment for pigment epithelial detachments (PEDs) in exudative age-related macular degeneration (AMD). This retrospective study analyses best-corrected visual acuity (BCVA) and foveal involvement after RPE tears that are associated with anti-VEGF therapy due to PED in exudative AMD.

Methods: A total of 37 patients with RPE tears during anti-VEGF therapy (bevacizumab 12, ranibizumab 21 and pegaptanib 4 eyes) for progressive PED in AMD (PED with occult choroidal neovascularization 25 eyes and PED with retinal angiomatous proliferation 12 eyes) were included in this study. We analyzed BCVA and different morphologic aspects by means of appearance on fluorescein angiography and optical coherence tomography. Mean follow-up was 88 weeks.

Results: RPE tears were diagnosed a mean of 56 days after the first injection. BCVA deteriorated after RPE tear and during follow-up significantly (P<0.001), with 53.2% of eyes being legally blind (WHO, world health organization) at 12 months. RPE-free foveal area, foveal wrinkling of the RPE, and fibrotic scar development were significantly associated with worse visual acuity.

Discussion: RPE tears can be observed in 12-15% of treated eyes during anti-VEGF therapy for PED in exudative AMD. Owing to the close time relationship with the therapy, this complication must be taken into consideration. Visual prognosis is associated with a decrease in vision in the long term, often resulting in a severe visual disability. Relevant factors for a negative visual prognosis were the potential foveal involvement of the central RPE and morphologic fibrovascular transformation of the RPE tear.Eye advance online publication, 24 June 2011; doi:10.1038/eye.2011.146.

PMID: 21701525 [PubMed - as supplied by publisher]

Optom Vis Sci. 2011 Jun 23. [Epub ahead of print]

Objective Visual Assessment of Antiangiogenic Treatment for Wet Age-Related Macular Degeneration.

Baseler HA, Gouws A, Crossland MD, Leung C, Tufail A, Rubin GS, Morland AB.

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PURPOSE: To assess cortical responses in patients undergoing antiangiogenic treatment for wet age-related macular degeneration (AMD) using functional magnetic resonance imaging (fMRI) as an objective, fixation-independent measure of topographic visual function.

METHODS: A patient with bilateral neovascular AMD was scanned using fMRI before and at regular intervals while undergoing treatment with intravitreal antiangiogenic injections (ranibizumab). Blood oxygenation level-dependent signals were measured in the brain while the patient viewed a stimulus consisting of a full-field flickering (6 Hz) white light alternating with a uniform gray background (18 s on and 18 s off). Topographic distribution and magnitude of activation in visual cortex were compared longitudinally throughout the treatment period (<1 year) and with control patients not currently undergoing treatment. Clinical behavioral tests were also administered, including visual acuity, microperimetry, and reading skills.

RESULTS: The area of visual cortex activated increased significantly after the first treatment to include more posterior cortex that normally receives inputs from lesioned parts of the retina. Subsequent treatments yielded no significant further increase in activation area. Behavioral measures all generally showed an improvement with treatment but did not always parallel one another. The untreated control patient showed a consistent lack of significant response in the cortex representing retinal lesions.

CONCLUSIONS: Retinal treatments may not only improve vision but also result in a concomitant improvement in fixation stability. Current clinical behavioral measures (e.g., acuity and perimetry) are largely dependent on fixation stability and therefore cannot separate improvements of visual function from fixation improvements. fMRI, which provides an objective and sensitive measure of visual function independent of fixation, reveals a significant increase in visual cortical responses in patients with wet AMD after treatment with antiangiogenic injections. Despite recent evidence that visual cortex degenerates subsequent to retinal lesions, our results indicate that it can remain responsive as its inputs are restored.

PMID: 21705938 [PubMed - as supplied by publisher]

Retina. 2011 Jun 28. [Epub ahead of print]

BILATERAL EFFECT OF UNILATERAL RANIBIZUMAB IN PATIENTS WITH UVEITIS-RELATED MACULAR EDEMA.

Acharya NR, Sittavarakul W, Qian Y, Hong KC, Lee SM.

From the *F.I. Proctor Foundation, and †Department of Ophthalmology, University of California, San Francisco, San Francisco, California.

PURPOSE: To describe an observed therapeutic effect of ranibizumab in untreated contralateral eyes of patients with bilateral uveitis-related cystoid macular edema.

METHODS: The authors conducted an open-label, prospective, nonrandomized, interventional study to evaluate the effect of intravitreal ranibizumab injections for the off-label treatment of persistent uveitic cys-

toid macular edema. Patients were given 3 monthly injections of 0.5 mg intravitreal ranibizumab in the eye with worse vision. Subsequent monthly ranibizumab injections were administered based on macular thickness measurements. Best-spectacle corrected visual acuity measurements and optical coherence tomography scans were performed on both eyes at baseline and at monthly follow-up visits.

RESULTS: Three of the seven patients in our nonrandomized consecutive case series presented with controlled uveitis and cystoid macular edema bilaterally. Two of the three patients demonstrated a significant improvement in visual acuity and a reduction in macular edema in both eyes after three monthly injections to the study eye. One patient experienced limited effect bilaterally possibly because of the presence of epiretinal membranes in both eyes.

CONCLUSION: The authors observed a beneficial effect of ranibizumab in both eyes of patients who were treated unilaterally for uveitis-related cystoid macular edema. This warrants further investigation of the pharmacokinetics and systemic availability of ranibizumab, particularly in patients with uveitis.

PMID: 21716165 [PubMed - as supplied by publisher]

Ophthalmic Res. 2011 Jun 29;47(2):57-60. [Epub ahead of print]

Treatment of Neovascular Glaucoma after Proton Therapy for Uveal Melanomas with Ranibizumab Injection: Preliminary Results.

Caujolle JP, Maschi C, Freton A, Pages G, Gastaud P.

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Abstract

A last-chance intravitreal injection of ranibizumab was administered alone or in combination with cryotherapy before enucleation for 14 melanomas with neovascular glaucoma (NVG) after proton therapy. These patients were uncontrolled despite medical treatment and experienced pain. All of our patients had a minimum of 4 months of follow-up (ranging from 4 to 22 months). In all of the cases, the neovessels disappeared, and the intra-ocular pressure was normal for 11 out of the 14 patients with or without antiglaucoma drops. No patient experienced pain after the first injection. Tumour regression increased in some patients. However, thus far, the number of cases has been too small to perform any statistical analyses. Although very promising, our results are only preliminary.

PMID: 21720186 [PubMed - as supplied by publisher]

Ophthalmology. 2011 Jun 27. [Epub ahead of print]

Sustained Benefits from Ranibizumab for Macular Edema following Central Retinal Vein Occlusion: Twelve-Month Outcomes of a Phase III Study.

Campochiaro PA, Brown DM, Awh CC, Lee SY, Gray S, Saroj N, Murahashi WY, Rubio RG.

Departments of Ophthalmology and Neuroscience, The Johns Hopkins School of Medicine, Baltimore, Maryland.

PURPOSE: Assess the 12-month efficacy and safety of intraocular injections of 0.3 mg or 0.5 mg ranibizumab in patients with macular edema after central retinal vein occlusion (CRVO).

DESIGN: Prospective, randomized, sham injection-controlled, double-masked, multicenter clinical trial.

PARTICIPANTS: We included 392 patients with macular edema after CRVO.

METHODS: Eligible patients were randomized 1:1:1 to receive 6 monthly intraocular injections of 0.3 mg or 0.5 mg of ranibizumab or sham injections. After 6 months, all patients with BCVA ≤20/40 or central subfield thickness ≥250 μm could receive ranibizumab.

MAIN OUTCOME MEASURES: Mean change from baseline best-corrected visual acuity (BCVA) letter score at month 12, additional parameters of visual function, central foveal thickness (CFT), and other anatomic changes were assessed.

RESULTS: Mean (95% confidence interval) change from baseline BCVA letter score at month 12 was 13.9 (11.2-16.5) and 13.9 (11.5-16.4) in the 0.3 mg and 0.5 mg groups, respectively, and 7.3 (4.5-10.0) in the sham/0.5 mg group (P<0.001 for each ranibizumab group vs. sham/0.5 mg). The percentage of patients who gained ≥15 letters from baseline BCVA at month 12 was 47.0% and 50.8% in the 0.3 mg and 0.5 mg groups, respectively, and 33.1% in the sham/0.5 mg group. On average, there was a marked reduction in CFT after the first as-needed injection of 0.5 mg ranibizumab in the sham/0.5 mg group to the level of the ranibizumab groups, which was sustained through month 12. No new ocular or nonocular safety events were identified.

CONCLUSIONS: On average, treatment with ranibizumab as needed during months 6 through 11 maintained the visual and anatomic benefits achieved by 6 monthly ranibizumab injections in patients with macular edema after CRVO, with low rates of ocular and nonocular safety events. After sham injections for 6 months, treatment with ranibizumab as needed for 6 months resulted in rapid reduction in CFT in the sham/0.5 mg group to a level similar to that in the 2 ranibizumab treatment groups and an improvement in BCVA, but not to the same level as that in the 2 ranibizumab groups. Intraocular injections of ranibizumab provide an effective treatment for macular edema after CRVO.

PMID: 21715011 [PubMed - as supplied by publisher]

Ophthalmologica. 2011 Jun 30. [Epub ahead of print]

Intravitreal Ranibizumab for Choroidal Neovascularization Secondary to Pathological Myopia: 12-Month Follow-Up.

Lorenzo D, Arias L, Alcubierre R, Pujol O, Caminal JM, Rubio M, Català J, Garcia-Bru P, Arruga J.

Department of Ophthalmology, Bellvitge University Hospital, L'Hospitalet de Llobregat, Spain.

Purpose: To evaluate the efficacy and safety of intravitreal ranibizumab in the treatment of choroidal neovascularization (CNV) due to pathological myopia (PM). Methods: This retrospective case series studied outcomes in patients with CNV secondary to PM who were treated with intravitreal ranibizumab. Patients underwent complete ophthalmic evaluation, which included best-corrected visual acuity testing measured with Early Treatment Diabetic Retinopathy Study charts, optical coherence tomography (OCT) and baseline fluorescein angiography (FA). Indications for retreatment included the persistence of subretinal fluid on OCT as well as hemorrhages and new CNV on FA. Patients were followed for a minimum of 12 months. Results: We treated 29 eyes in 29 patients; the mean age was 56.8 years. Thirteen eyes were naïve, while 16 had been previously treated with photodynamic therapy or intravitreal bevacizumab. The mean initial visual acuity was 44.8 letters; at the 12-month follow-up, it was 53.7 letters. The mean OCT foveal thickness decreased by 35.3 μm. Patients received an average of 1.38 injections. Statistically significant differences were observed both in visual acuity and in central foveal thickness. All subgroups had favorable outcomes. None of the patients developed injection-induced complications or drug-related side effects. Conclusion: Intravitreal injection of ranibizumab appears to be safe and efficacious in patients with CNV secondary to PM followed over a 12-month period.

PMID: 21720153 [PubMed - as supplied by publisher]

Eye (Lond). 2011 Jun 24. doi: 10.1038/eye.2011.130. [Epub ahead of print]

Short-term changes of visual hallucinations after intravitreal injection of ranibizumab in age related macular degeneration.

Mitrut I, Chua P, Aslam T, Vani A, Armbrecht AM, Dhillon B.

The Princess Alexandra Eye Pavilion, Edinburgh, UK.

PMID: 21701530 [PubMed - as supplied by publisher]

Eye (Lond). 2011 Jun 24. doi: 10.1038/eye.2011.129. [Epub ahead of print]

Visual hallucinations after intravitreal injection of ranibizumab in neovascular age-related macular degeneration.

Tan CS.

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PMID: 21701527 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Am J Ophthalmol. 2011 Jun 25. [Epub ahead of print]

Analysis of Choroidal Thickness in Age-Related Macular Degeneration Using Spectral-Domain Optical Coherence Tomography.

Manjunath V, Goren J, Fujimoto JG, Duker JS.

New England Eye Center, Tufts Medical Center, Boston, Massachusetts.

PURPOSE: To understand the relationship between choroidal thickness and various disease factors in patients with age-related macular degeneration (AMD) using spectral-domain optical coherence tomography.

DESIGN: Cross-sectional, retrospective analysis.

METHODS: Fifty-seven eyes of 47 patients with wet and dry AMD seen between November 2009 and January 2010 at the New England Eye Center, Boston, Massachusetts, were analyzed. Choroidal thickness was measured by 2 independent observers at 11 sites with high-definition horizontal 1-line raster scans through the foveal center. A retrospective chart review was performed to obtain data concerning duration of disease, number of intravitreal anti-vascular endothelial growth factor injections, visual acuity, lens status, and concomitant retinal pathologic features. The Pearson correlation and Student t test were used for statistical analysis for assessment of choroidal thickness changes in wet and dry AMD.

RESULTS: The choroid in eyes with wet and dry AMD demonstrated a wide range of thicknesses above and below the normal mean (range, 77.5 to 399.5 μm; standard deviation [SD], 90.2). Nearly one third (33.3%) of the eyes with AMD measured less than 1 SD below the mean. Eyes with wet AMD demonstrated a mean subfoveal choroidal thickness of 194.6 μm (SD, 88.4; n = 40) compared with 213.4 μm (SD, 92.2; n = 17) in the dry AMD group. The choroidal thickness in eyes with dry AMD was correlated inversely with age (r = -0.703; P = .002); however, analysis of the number of intravitreal anti-vascular endothelial growth factor injections, number of years of disease, and visual acuity failed to demonstrate any significant correlations with choroidal thickness.

CONCLUSIONS: This study demonstrated that choroidal thickness can be measured by spectral-domain optical coherence tomography and that variable choroidal thickness exists among patients with the clinical diagnosis of wet and dry AMD. However, it is unclear at this time why in some eyes, choroidal thickness either increases or decreases with the disease. Further studies need to be carried out to understand the significance of choroidal thickness with respect to visual function and disease progression over time.

PMID: 21708378 [PubMed - as supplied by publisher]

Ophthalmologe. 2011 Jul 1. [Epub ahead of print]

[Use of nanoparticles in ophthalomology.]

[Article in German]

Hahn I, Heiduschka P, Endl E, Eter N.

Institut für Molekulare Medizin, Universität Bonn, Bonn, Deutschland.

Abstract

Nanotechnology, the manufacture and use of structures and implements of around a few 100 nm in size, is becoming a key technology of the twenty-first century. An important element for the manufacture of nanoparticles is gold. Gold nanoparticles can be custom made and chemically modified in their size and form. Initial investigations have shown that they are physiologically non-hazardous. A potential application is in neovascular age-related macular degeneration. Gold nanoparticles of suitable dimensions introduced into newly forming blood vessels can be targeted and heated which selectively destroys these blood vessels. This principle has already been demonstrated in cultivated endothelial cells.

PMID: 21717225 [PubMed - as supplied by publisher]

Duke Med Health News. 2011 Jun;17(6):8.

I've been seeing tiny, random black specks in front of my eyes. Could this be some kind of eye disease, like macular degeneration?

[No authors listed]

PMID: 21714174 [PubMed - in process]

Postgrad Med J. 2011 Jul;87(1029):487-95.

Republished review: Gene therapy for ocular diseases.

Liu MM, Tuo J, Chan CC.

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Abstract

The eye is an easily accessible, highly compartmentalised and immune-privileged organ that offers unique advantages as a gene therapy target. Significant advancements have been made in understanding the genetic pathogenesis of ocular diseases, and gene replacement and gene silencing have been implicated as potentially efficacious therapies. Recent improvements have been made in the safety and specificity of vector-based ocular gene transfer methods. Proof-of-concept for vector-based gene therapies has also been established in several experimental models of human ocular diseases. After nearly two decades of ocular

gene therapy research, preliminary successes are now being reported in phase 1 clinical trials for the treatment of Leber congenital amaurosis. This review describes current developments and future prospects for ocular gene therapy. Novel methods are being developed to enhance the performance and regulation of recombinant adeno-associated virus- and lentivirus-mediated ocular gene transfer. Gene therapy prospects have advanced for a variety of retinal disorders, including retinitis pigmentosa, retinoschisis, Stargardt disease and age-related macular degeneration. Advances have also been made using experimental models for non-retinal diseases, such as uveitis and glaucoma. These methodological advancements are critical for the implementation of additional gene-based therapies for human ocular diseases in the near future.

PMID: 21705775 [PubMed - in process]

Epidemiology & pathogenesis

Cell Biosci. 2011 Mar 8;1(1):10.

Chloroquine treatment of ARPE-19 cells leads to lysosome dilation and intracellular lipid accumulation: possible implications of lysosomal dysfunction in macular degeneration.

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BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of vision loss in elderly people over 60. The pathogenesis is still unclear. It has been suggested that lysosomal stress may lead to drusen formation, a biomarker of AMD. In this study, ARPE-19 cells were treated with chloroquine to inhibit lysosomal function.

RESULTS: Chloroquine-treated ARPE-19 cells demonstrate a marked increase in vacuolation and dense intracellular debris. These are identified as chloroquine-dilated lysosomes and lipid bodies with LAMP-2 and LipidTOX co-localization, respectively. Dilation is an indicator of lysosomal dysfunction. Chloroquine disrupts uptake of exogenously applied rhodamine-labeled dextran by these cells. This suggests a disruption in the phagocytic pathway. The increase in LAMP protein levels, as assessed by Western blots, suggests the possible involvement in autophagy. Oxidative stress with H2O2 does not induce vacuolation or lipid accumulation.

CONCLUSION: These findings suggest a possible role for lysosomes in AMD. Chloroquine treatment of RPE cells may provide insights into the cellular mechanisms underlying AMD.

PMID: 21711726 [PubMed - in process]

PMCID: PMC3125200

Invest Ophthalmol Vis Sci. 2011 Jun 29. [Epub ahead of print]

Inhibition of TLR3-mediated proinflammatory effects by alkylphosphocholines in human retinal pigment epithelial cells.

Wörnle M, Merkle M, Wolf A, Ribeiro A, Himmelein S, Kernt M, Kampik A, Eibl-Lindner KH.

Ludwig-Maximilians-University, Medical Policlinic, Department of Internal Medicine, Klinikum der Universität München, Campus Innenstadt, Munich, Germany.

Purpose: To elucidate the role of Toll-like receptor 3 (TLR3) in the pathogenesis of age-related macular degeneration (AMD) and to investigate the effect of alkylphosphocholines (APC) on the TLR3-mediated

expression of cytokines and growth factors in human retinal pigment epithelial (RPE) cells.

Methods: Confluent cultures of human retinal pigment epithelial cells (ARPE-19) were stimulated with poly (I:C) RNA as a well established ligand for TLR3. Cytokine profiles were determined by RT-PCR upon activation of TLR3. RPE cells were transfected with siRNA specific for TLR3 and RIG-1 to determine the receptors involved. The effect of pre-incubation of RPE cells with APC on the expression level of target genes was assessed.

Results: Poly (I:C) RNA stimulation led to a dose dependent increase in expression of TLR3 and RIG-I. A significant increase in expression levels of IL-6, TNF-α, IL-8, MCP-1, ICAM-1 and b-FGF was observed after poly (I:C) RNA stimulation ($p<0.05$). This effect was time and dose dependent. No effect on PEDG and VEGF expression was seen. Transfection of RPE cells with siRNA specific for TLR3 reduced poly (I:C) RNA induced mRNA expression of the genes ($p<0.05$). Pre-incubation of RPE cells with APC significantly reduced the poly (I:C) RNA induced expression of the target genes ($p<0.05$).

Conclusions: We demonstrate that expression of proinflammatory cytokines and chemokines in RPE cells depends on activation of TLR3. The induction of downstream gene expression is blocked by siRNA specific for TLR3 and alkylphosphocholines. Therefore, TLR3 should be considered as a novel target in AMD therapy.

PMID: 21715345 [PubMed - as supplied by publisher]

Adv Drug Deliv Rev. 2011 Jun 16. [Epub ahead of print]

Complement in health and disease.

Carroll MV, Sim RB.

Abstract

The complement system consists of about 35-40 proteins and glycoproteins present in blood plasma or on cell surfaces. Its main biological function is to recognise "foreign" particles and macromolecules, and to promote their elimination either by opsonisation or lysis. Although historically complement has been studied as a system for immune defence against bacteria, it has an important homeostatic role in which it recognises damaged or altered "self" components. Thus complement has major roles in both immune defence against microorganisms, and in clearance of damaged or "used" host components. Since complement proteins opsonise or lyse cells, complement can damage healthy host cells and tissues. The system is regulated by many endogenous regulatory proteins. Regulation is sometimes imperfect and both too much and too little complement activation is associated with many diseases. Excessive or inappropriate activation can cause tissue damage in diseases such as rheumatoid arthritis, age-related macular degeneration (AMD), multiple sclerosis, ischemia-reperfusion injury (e.g. ischemic stroke). Insufficient complement activity is associated with susceptibility to infection (mainly bacterial) and development of autoimmune disease, like SLE (systemic lupus erythematosus).

PMID: 21704094 [PubMed - as supplied by publisher]

Am J Pathol. 2011 Jul;179(1):335-48. Epub 2011 May 3.

Bmp6 regulates retinal iron homeostasis and has altered expression in age-related macular degeneration.

Hadziahmetovic M, Song Y, Wolkow N, Iacovelli J, Kautz L, Roth MP, Dunaief JL.

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Abstract

Iron-induced oxidative stress causes hereditary macular degeneration in patients with aceruloplasminemia. Similarly, retinal iron accumulation in age-related macular degeneration (AMD) may exacerbate the disease. The cause of retinal iron accumulation in AMD is poorly understood. Given that bone morphogenetic protein 6 (Bmp6) is a major regulator of systemic iron, we examined the role of Bmp6 in retinal iron regulation and in AMD pathogenesis. Bmp6 was detected in the retinal pigment epithelium (RPE), a major site of pathology in AMD. In cultured RPE cells, Bmp6 was down-regulated by oxidative stress and up-regulated by iron. Intraocular Bmp6 protein injection in mice up-regulated retinal hepcidin, an iron regulatory hormone, and altered retinal labile iron levels. Bmp6(-/-) mice had age-dependent retinal iron accumulation and degeneration. Postmortem RPE from patients with early AMD exhibited decreased Bmp6 levels. Because oxidative stress is associated with AMD pathogenesis and down-regulates Bmp6 in cultured RPE cells, the diminished Bmp6 levels observed in RPE cells in early AMD may contribute to iron build-up in AMD. This may in turn propagate a vicious cycle of oxidative stress and iron accumulation, exacerbating AMD and other diseases with hereditary or acquired iron excess.

PMID: 21703414 [PubMed - in process]

PMCID: PMC3123855 [Available on 2012/7/1]

PLoS One. 2011;6(6):e21621. Epub 2011 Jun 24.

Soluble CD59 Expressed from an Adenovirus In Vivo Is a Potent Inhibitor of Complement Deposition on Murine Liver Vascular Endothelium.

Gandhi J, Cashman SM, Kumar-Singh R.

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Abstract

Inappropriate activation of complement on the vascular endothelium of specific organs, or systemically, underlies the etiology of a number of diseases. These disorders include atypical hemolytic uremic syndrome, membranoproliferative glomerulonephritis, atherosclerosis, age-related macular degeneration, diabetic retinopathy, and transplant rejection. Inhibition of the terminal step of complement activation, i.e. formation of the membrane attack complex, using CD59 has the advantage of retaining the upstream processes of the complement cascade necessary for fighting pathogens and retaining complement's crucial role in tissue homeostasis. Previous studies have shown the necessity of membrane targeting of soluble CD59 in order for it to prove an effective inhibitor of complement deposition both in vitro and in vivo. In this study we have generated an in vivo model of human complement activation on murine liver vascular endothelium. This model should prove useful for the development of anti-complement therapies for complement-induced pathologies of vascular endothelium. Using this model, we have demonstrated the viability of a non membrane-targeted soluble CD59 to significantly inhibit complement deposition on the endothelium of murine liver vasculature when expressed in vivo from an adenovirus. This result, unanticipated based on prior studies, suggests that the use of non membrane-targeted sCD59 as an anti-complement therapy be re-visited.

PMID: 21720565 [PubMed - in process]

Genetics

Mol Biol Rep. 2011 Jun 24. [Epub ahead of print]

Age-related macular degeneration and genetic polymorphisms of glutathione S-transferases M1 (GSTM1) and T1 (GSTT1).

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Abstract

The aim of this study is to understand the multifactorial causes of age-related macular degeneration (ARMD), and, therefore, it is reasonable to investigate whether genetic polymorphisms of antioxidant enzymes (GSTM1 and GSTT1) contribute to the development of ARMD. This study consisted of 112 subjects (44 females, 68 males) with exudative ARMD, who were recruited from Khalili Hospital ophthalmic clinic in Shiraz (southern Iran), referred by vitreoretinal surgeon. Also 112 sex-matched controls (44 females, 68 males) were randomly selected from unrelated volunteers in the same clinic. We excluded patients and controls with cataract or past history of cataract surgery, asthma, past history of malignancy, cardiovascular disease that on medication and known cases of glaucoma, because these traits were associated with GSTM1 and/or GSTT1 polymorphisms. There was no association between polymorphisms of neither GSTM1 nor GSTT1 and risk of ARMD. The combination genotypes of GSTM1 and GSTT1 were not associated with the risk of ARMD. We considered the time of deterioration of vision as the time of onset of exudative ARMD. The Kaplan-Meier analysis revealed that there was significant difference between genotypes of GSTM1 (log rank statistic = 7.03, df = 1, P = 0.008). The age at onset among GSTM1 null genotype was lower than the active genotype of GSTM1. Our results support the hypothesis that the protein encoded by the GSTM1 gene might have a protective function against oxidative stress in retina. Since the age at onset is influenced by the GSTM1 polymorphism, this implies that GSTM1 is a modifier gene.

PMID: 21701824 [PubMed - as supplied by publisher]

FASEB J. 2011 Jun 28. [Epub ahead of print]

Toll-like receptor 3 C1234T may protect against geographic atrophy through decreased dsRNA binding capacity.

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Abstract

The genetic association between a variant in the Toll-like receptor 3 (TLR3) gene (C1234T in mRNA, L412F in protein, Reference SNP Cluster Report rs3775291) and geographic atrophy (GA; also called advanced "dry" age-related macular degeneration) was controversial in previous studies. We performed a meta-analysis by pooling the current evidence in literature and found that the T allele of the TLR3 C1234T variant showed a summary odds ratio of 0.753 (95% confidence interval: 0.612-0.927; P=0.007). Further experiments were performed to analyze how this mutant influences the function of TLR3. We found that this SNP did not affect mRNA, protein, or surface expression of TLR3. However, the binding capacity of L412F mutation of TLR3 for double-stranded RNA in the TLR3 protein was only 51.12 ± 3.96% (P<0.001) of the wild-type level. There was a consistently reduced TLR3-mediated NF-κB activation. Therefore, TLR3 C1234T (L412F in the protein) may protect against GA by reduced binding capacity of TLR3 to dsRNA. This study may provide a better understanding of the genetic architecture underlying disease susceptibility and may advance the potential for preclinical prediction in future genetic testing.-Zhou, P., Fan, L., Yu, K. -D., Zhao, M. -W., Li, X. -X. Toll-like receptor 3 C1234T may protect against geographic atrophy through

decreased dsRNA binding capacity.

PMID: 21712495 [PubMed - as supplied by publisher]

Diet

Nutrition. 2011 Jun 22. [Epub ahead of print]

26th Hohenheim Consensus Conference, September 11, 2010 Scientific substantiation of health claims: Evidence-based nutrition.

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OBJECTIVE: The objective was to define the term evidence based nutrition on the basis of expert discussions and scientific evidence.

METHODS AND PROCEDURES: The method used is the established Hohenheim Consensus Conference. The term "Hohenheim Consensus Conference" defines conferences dealing with nutrition-related topics. The major aim of the conference is to review the state of the art of a given topic with experts from different areas (basic science, clinicians, epidemiologists, etc.). Based on eight to 12 questions, the experts discuss short answers and try to come to a consensus. A scientifically based text is formulated that justifies the consensus answer. To discuss the requirements for the scientific substantiation of claims, the 26th Hohenheim Consensus Conference gathered the views of many academic experts in the field of nutritional research and asked these experts to address the various aspects of a claims substantiation process and the possibilities and limitations of the different approaches.

RESULTS: The experts spent a day presenting and discussing their views and arrived at several consensus statements that can serve as guidance for bodies performing claims assessments in the framework of regulatory systems.

CONCLUSION: The 26th Hohenheim Consensus Conference addresses some general aspects and describes the current scientific status from the point of view of six case studies to illustrate specific areas of scientific interest: carotenoids and vitamin A in relation to age-related macular degeneration, the quality of carbohydrates (as expressed by the glycemic index) in relation to health and well-being, probiotics in relation to intestinal and immune functions, micronutrient intake and maintenance of normal body functions, and food components with antioxidative properties and health benefits.

PMID: 21700425 [PubMed - as supplied by publisher]