

Issue 2

Monday November 8, 2010

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".

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Drug Management

1. Arch Pharm Res. 2010 Oct;33(10):1557-65. Epub 2010 Oct 30.

How to overcome retinal neuropathy: The fight against angiogenesis related blindness.

Jo DH, Kim JH, Kim JH.

Department of Ophthalmology, College of Medicine, Seoul National University, Seoul, 151-742, Korea.

Abstract

The retina consists of neuronal cells of high metabolic activity that are supplied by an abundant vasculature. It is a main theme of ophthalmologic research, because retinopathies are common causes of blindness in all age groups: age-related macular degeneration in the elderly, diabetic retinopathy in the middle aged, and retinopathy of prematurity and retinoblastoma in children. Interestingly, angiogenesis underlies the pathogenesis of all these diseases, and breakdown of the blood-retinal barrier is also thought to play an important role before and throughout the process of new vessel formation. However, so far, most treatments have targeted angiogenesis only, especially vascular endothelial growth factor. Consideration of the restoration of the blood-retinal barrier should be required. In this review, we discuss the clinical manifestation, pathogenesis, and current treatment options for angiogenesis-related blindness. In addition, because of the recent introduction of novel strategies, we describe pathogenesis-based treatment options to treat angiogenesis-related blindness.

PMID: 21052933 [PubMed - in process]

2. Invest Ophthalmol Vis Sci. 2010 Nov 4. [Epub ahead of print]

Quantification of the therapeutic response of intraretinal, subretinal and subpigmentepithelial compartments in exudative AMD during anti-VEGF therapy.

Golbaz I, Ahlers C, Stock G, Schuetze C, Schriebl S, Schlanitz FG, Simader C, Prunte C, Schmidt-Erfurth U.

Ophthalmology, University of Vienna, Vienna, Austria.

Abstract

Purpose: To analyze functional and morphological effects of different ranibizumab treatment regimen on retinal and subretinal as well as sub RPE compartments in neovascular age-related macular degeneration

(nAMD), using spectral-domain optical coherence tomography (SD-OCT) and manual segmentation software. Methods: 27 eyes of 27 patients with nAMD were examined over a 12-month period. Two treatment arms received either monthly or quarterly administered intravitreal ranibizumab. Intraretinal, subretinal and sub-RPE volume equivalents were delineated using manual segmentation software over a defined series of B-scans obtained by SD-OCT. The mean area in pixels was calculated for each compartment at each time interval. Results: SD-OCT and manual segmentation allowed for exact identification of intraretinal, subretinal and sub-RPE compartments and their response to different treatment regimen. The loading dose demonstrated a corresponding treatment effect on all anatomic parameters. In contrast to the sub-RPE compartment, intraretinal (IRFA)- and subretinal fluid accumulation (SRFA) demonstrated an immediate response to ranibizumab therapy. The overall plasticity of the morphologic response declined over time. In general SRFA demonstrated the greatest sensitivity for therapeutic effects and was most frequently associated with recurrent disease. Conclusions: An exact quantification of fluid in different anatomical compartments based on SD-OCT imaging, using appropriate segmentation software systems, may be useful to determine optimal treatment and retreatment parameters and explains the lack of correlation of BCVA and conventional OCT values.

PMID: 21051733 [PubMed - as supplied by publisher]

3. Invest Ophthalmol Vis Sci. 2010 Nov 4. [Epub ahead of print]

Response of retinal vessels and retrobulbar hemodynamics to intravitreal anti VEGF treatment in eyes with branch retinal vein occlusion.

Sacu S, Pemp B, Weigert G, Matt G, Garhofer G, Prunte C, Schmetterer L, Schmidt-Erfurth U.

Department of Ophthalmology, Medical University of Vienna, Vienna, Austria.

Abstract

Purpose: To investigate whether intravitreal ranibizumab (0.05ml) treatment affects retinal vessel diameters and retrobulbar blood velocities in patients with acute branch retinal vein occlusion (BRVO). Methods: 30 patients with clinically significant macular edema secondary to BRVO were included. The duration of the study was 3 months. Subjects were studied before, 1 week, 1 month, 2 and 3 months after the first ranibizumab injection. Depending on the clinical requirements up to 3 ranibizumab injections were administered. Retinal vessel diameters were measured using a Retinal Vessel Analyzer. Flow velocities in the retrobulbar central retinal artery were measured using Color Doppler Imaging. Best-corrected visual acuity was assessed using ETDRS charts. Measurements were done in the affected as well as in the contralateral eye. Results: Three patients were lost for follow up. In the remaining 27 patients, we observed a significant vasoconstriction in retinal veins ($p < 0.001$ versus baseline) and in retinal arteries ($p = 0.001$ versus baseline) of the affected eyes. In addition, we observed a significant reduction in flow velocities in the BRVO eyes over time (peak systolic velocity: $p = 0.003$, end diastolic velocity: $p = 0.003$). The reduction in retinal vessel diameters and flow velocities did not correlate with changes in visual acuity or number of retreatments. In the contralateral eyes no change in retinal blood flow parameters was seen. Discussion: BRVO is an ischemic retinal disease. Given that ranibizumab treatment reduces retinal perfusion in these eyes the potential long-term effects of this vasoconstriction needs to be considered.

PMID: 21051706 [PubMed - as supplied by publisher]

4. Invest Ophthalmol Vis Sci. 2010 Nov 4. [Epub ahead of print]

Silicone Oil Microdroplets and Protein Aggregates in Repackaged Bevacizumab and Ranibizumab: Effects of Long-term Storage and Product Mishandling.

Liu L, Ammar DA, Ross L, Mandava N, Kahook M, Carpenter J.

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Abstract

Purpose: To quantify levels of subvisible particles and protein aggregates in repackaged bevacizumab obtained from compounding pharmacies as well as in samples of bevacizumab and ranibizumab tested in controlled laboratory experiments. **Methods:** Repackaged bevacizumab was purchased from four external compounding pharmacies. For controlled laboratory studies, bevacizumab and placebo were drawn into plastic syringes and incubated at -20°C, 4°C and room temperature (with and without exposure to light) for 12 weeks. Additionally, mechanical shock occurring during shipping was mimicked with syringes containing bevacizumab. Particle counts and size distributions were quantified by Micro-Flow Imaging. Levels of monomer and soluble aggregates of bevacizumab were determined with size exclusion high performance liquid chromatography (SE-HPLC). **Results:** Repackaged bevacizumab from the compounding pharmacies had a wide range of particle counts ($89,006 \pm 56,406$ to $602,062 \pm 18,349$ /mL). Bevacizumab sampled directly from original glass vial had particle counts of $63,839 \pm 349$ /mL. There was up to 10% monomer loss for repackaged bevacizumab. Laboratory samples of repackaged bevacizumab and placebo had initial particle counts, respectively, of $283,675 \pm 60,494$ /mL and $492,314 \pm 389,361$ /mL. Freeze-thawing of both bevacizumab and placebo samples led to >1.2 million particles/mL. In all repackaged samples, the majority of particles were due to silicone oil. SE-HPLC showed no significant differences for repackaged samples incubated in the laboratory under various conditions compared with bevacizumab directly from vial. However, repeated freeze-thawing caused over 10% monomer loss. **Conclusion:** Bevacizumab repackaged in plastic syringes could contain protein aggregates and was contaminated by silicone oil microdroplets. Freeze-thawing or other mishandling can further increase levels of particle contaminants.

PMID: 21051703 [PubMed - as supplied by publisher]

5. J Fr Ophtalmol. 2010 Nov 1. [Epub ahead of print]

[Intravitreal ranibizumab injections for the treatment of choroidal neovascularization complicating high myopia.]

[Article in French]

Ouhadj O, Bouarfa A, Akel S, Mendil L, Nebab A, Nouri MT.

Service d'ophtalmologie, CHU Béni-Messous, Alger, Algérie.

Abstract

INTRODUCTION: Macular choroidal neovascularization (CNV) is a serious complication of high myopia, compromising the visual prognosis in young patients. The purpose of this study was to evaluate the safety and efficacy of first-line intravitreal ranibizumab in the treatment of myopic CNV.

PATIENTS AND METHODS: We conducted a single-center prospective, consecutive, interventional study of patients with subfoveal or juxtafoveal CNV secondary to pathologic myopia (PM) treated with intravitreal injection of ranibizumab in the Beni-Messous University Hospital from January 2009 to April 2010. Best-corrected visual acuity (BCVA), fundus examination, optical coherence tomography (OCT), and fluorescein angiography (FA) were performed at baseline and monthly for all patients. Indications for retreatment were persistence or recurrence of the neovascular activity.

RESULTS: The study included 40 eyes of 40 patients, 33 of whom were females (82.5%), with a mean age of 40.22 ± 10.81 years (range, 20-55 years), with visual acuity between 1/100 and 1/10. The mean spherical equivalent refractive error was -14.13 ± 4.65 diopters (range, -7 D to -23 D). The mean follow-up time was 8 months (range, 3-15 months). The mean number of intravitreal injections administered for each patient was 2.2 (range: 1-4). Follow-up ranged from 3 to 15 months (mean, 8 months). All patients maintained or

improved their vision; the average gain in visual acuity was three lines (range: 1-9 lines). No injection complications or drug-related side effects were noted during the follow-up period.

DISCUSSION: Intravitreal ranibizumab to treat CNV complicated by high myopia seems to be associated with an improvement in VA and good tolerance. This study confirms the efficacy of first-line anti-VEGF, in particular, ranibizumab in this indication.

CONCLUSION: In this series of eyes with limited follow-up, intravitreal ranibizumab was a safe and effective treatment for CNV secondary to PM, resulting in functional and anatomic improvement.

PMID: 21047702 [PubMed - as supplied by publisher]

6. Acta Ophthalmol. 2010 Nov 2. doi: 10.1111/j.1755-3768.2010.02010.x. [Epub ahead of print]

Treatment of diabetic retinopathy with anti-VEGF drugs.

Waisbourd M, Goldstein M, Loewenstein A.

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Abstract

The aim of this review is to summarize the latest developments in the treatment of diabetic retinopathy (DR) with anti-vascular endothelial growth factor (VEGF) drugs. We reviewed recent studies that evaluated the role of the anti-VEGF agents bevacizumab, ranibizumab and pegaptanib in the treatment of DR. There was only one large randomized controlled trial that evaluated the role of ranibizumab in diabetic macular oedema (DME). Other prospective and retrospective studies provided important insight into the role of anti-VEGF drugs in DR, but most of them were not conducted in large scales. The growing evidence indicates that anti-VEGF drugs are beneficial in DR, especially in DME. Further studies are needed to fully evaluate the role of these agents, especially in proliferative DR and in DR candidates for vitrectomy surgery.

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PMID: 21044274 [PubMed - as supplied by publisher]

7. Clin Experiment Ophthalmol. 2010 Oct 8. doi: 10.1111/j.1442-9071.2010.02424.x. [Epub ahead of print]

Visual acuity outcomes in ranibizumab-treated neovascular age-related macular degeneration; stratified by baseline vision.

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Abstract

Background: Ranibizumab (Lucentis ®) is currently indicated for use in neovascular age-related macular degeneration (NV-AMD). This study assessed the real-life outcomes based on baseline visual acuity when treated with intravitreal ranibizumab on a three + PRN dosing schedule for NV-AMD. **Design:** This retrospective chart-review was conducted at King's College Hospital. The patients were stratified into three groups based on baseline VA: poor visual acuity (24 - 34 ETDRS letters), intermediate VA (35-54 ETDRS letters) and good VA (≥55 ETDRS letters). **Participants:** Eighty-seven patients with treatment-naïve NV-AMD were included in this study with 27 each in both poor and good vision group respectively and 33 patients in the intermediate vision group. **Methods:** All patients underwent best corrected visual acuity assessment with ETDRS charts at 2 metres, fluorescein angiography and central macular thickness

assessment by OCT. All patients received a three + PRN dosing schedule of ranibizumab injections (0.5mg/0.05ml) and all patients completed 12 month follow up. Main Outcome Measures: The mean change in VA at 12months in the 3 groups. Results: Mean gain in ETDRS letters at 12 months was +14.00 ($p < 0.0001$), +7.10 ($p = 0.012$) and +2.85 ($p = 0.19$) and mean number of injections was 5.30, 6.12 and 5.70 in the poor, intermediate and good baseline vision group respectively over the 12 month follow up period. Conclusions: Poor baseline visual acuity (24-34 ETDRS letters) is a predictor of maximum gain in visual acuity. However, eyes with better baseline visual acuity (≥ 55 letters) had a better final visual acuity.

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PMID: 21040311 [PubMed - as supplied by publisher]

8. J AAPOS. 2010 Oct;14(5):457-9.

Delayed-onset retinal detachment after an intravitreal injection of ranibizumab for zone 1 plus retinopathy of prematurity.

Jang SY, Choi KS, Lee SJ.

Department of Ophthalmology, College of Medicine, Soonchunhyang University, Seoul, Korea.

Abstract

Intravitreal injection of bevacizumab has been shown to satisfactorily treat retinopathy of prematurity; nevertheless, the safety of antivascular endothelial growth factor therapy in children remains uncertain. We report a patient with bilateral, zone 1, stage 3 plus retinopathy of prematurity who was treated with combined laser photocoagulation and intravitreal ranibizumab injection and demonstrated full regression at 3 months after injection but then developed bilateral retinal detachments 1 month later.

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PMID: 21035077 [PubMed - in process]

Genetics

9. Mol Interv. 2010 Oct;10(5):271-81.

Age-related Macular Degeneration: Genetic and Environmental Factors of Disease.

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Abstract

Age-related macular degeneration (AMD) is the most common cause of visual impairment among the elderly in developed countries, and its prevalence is thus increasing as the population ages; however, treatment options remain limited because the etiology and pathogenesis of AMD are incompletely defined. Recently, much progress has been made in gene discovery and mechanistic studies, which clearly indicate that AMD involves the interaction of multiple genetic and environmental factors. The identification of genes that have a substantial impact on the risk for AMD is not only facilitating the diagnosis and screening of populations at risk but is also elucidating key molecular pathways of pathogenesis. Pharmacogenetic studies of treatment responsiveness among patients with the "wet" form of AMD are increasingly proving to

be clinically relevant; pharmacogenetic approaches hold great promise for both identifying patients with the best chance for vision recovery as well as tailoring individualized therapies.

PMID: 21045241 [PubMed - in process]

Other Management & Epidemiology

10. Ophthalmology. 2010 Oct 28. [Epub ahead of print]

Prevalence and Predictors of Ocular Complications Associated with Cataract Surgery in United States Veterans.

Greenberg PB, Tseng VL, Wu WC, Liu J, Jiang L, Chen CK, Scott IU, Friedmann PD.

Section of Ophthalmology, VA Medical Center, Providence, Rhode Island; Division of Ophthalmology, Warren Alpert Medical School of Brown University, Providence, Rhode Island; Research Enhancement Award Program, VA Medical Center, Providence, Rhode Island.

Abstract

PURPOSE: To investigate the prevalence and predictors of intraoperative and 90-day postoperative ocular complications associated with cataract surgery performed in the United States Veterans Health Administration (VHA) system.

DESIGN: Retrospective cohort study.

PARTICIPANTS: Forty-five thousand eighty-two veterans who underwent cataract surgery in the VHA.

METHODS: The National Patient Care Database was used to identify all VHA patients who underwent outpatient extracapsular cataract surgery and who underwent only 1 cataract surgery within 90 days of the index surgery between October 1, 2005, and September 30, 2007. Data collected include demographics, preoperative systemic and ocular comorbidities, intraoperative complications, and 90-day postoperative complications. Adjusted odds ratios (ORs) of factors predictive of complications were calculated using logistic regression modeling.

MAIN OUTCOME MEASURES: Intraoperative and postoperative ocular complications within 90 days of cataract surgery.

RESULTS: During the study period, 53786 veterans underwent cataract surgery; 45082 met inclusion criteria. Common preoperative systemic and ocular comorbidities included diabetes mellitus (40.6%), chronic pulmonary disease (21.2%), age-related macular degeneration (14.4%), and diabetes with ophthalmic manifestations (14.0%). The most common ocular complications were posterior capsular tear, anterior vitrectomy, or both during surgery (3.5%) and posterior capsular opacification after surgery (4.2%). Predictors of complications included: black race (OR, 1.38; 95% confidence interval [CI], 1.28-1.50), divorced status (OR, 1.10; 95% CI, 1.03-1.18), never married (OR, 1.26; 95% CI, 1.14-1.38), diabetes with ophthalmic manifestations (OR, 1.33; 95% CI, 1.23-1.43), traumatic cataract (OR, 1.80; 95% CI, 1.40-2.31), previous ocular surgery (OR, 1.29; 95% CI, 1.02-1.63), and older age.

CONCLUSIONS: In a cohort of United States veterans with a high preoperative disease burden, selected demographic factors and ocular comorbidities were associated with greater risks of cataract surgery complications. Further large-scale studies are warranted to investigate cataract surgery outcomes for non-VHA United States patient populations.

FINANCIAL DISCLOSURE(S): The author(s) have no proprietary or commercial interest in any materials discussed in this article.

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PMID: 21035868 [PubMed - as supplied by publisher]

11. Ophthalmology. 2010 Oct 28. [Epub ahead of print]

Progression of Geographic Atrophy in Age-Related Macular Degeneration Imaged with Spectral Domain Optical Coherence Tomography.

Yehoshua Z, Rosenfeld PJ, Gregori G, Feuer WJ, Falcão M, Lujan BJ, Puliafito C.

Abstract

PURPOSE: To determine the area and enlargement rate (ER) of geographic atrophy (GA) in patients with age-related macular degeneration (AMD) using the spectral domain optical coherence tomography (SD-OCT) fundus image.

DESIGN: Prospective, longitudinal, natural history study.

PARTICIPANTS: Eighty-six eyes of 64 patients with ≥ 6 months of follow-up.

METHODS: Patients with GA secondary to AMD were enrolled in this study. Macular scans were performed using the Cirrus SD-OCT (Carl Zeiss Meditec, Dublin, CA). The areas of GA identified on the SD-OCT fundus images were quantified using a digitizing tablet. Reproducibility of these measurements was assessed and the ER of GA was calculated. The usefulness of performing square root transformations of the lesion area measurements was explored.

MAIN OUTCOME MEASURES: Enlargement rate of GA.

RESULTS: At baseline, 27% of eyes had a single area of GA. The mean total area at baseline was 4.59 mm² (1.8 disc areas [DA]). The mean follow-up time was 1.24 years. Reproducibility, as assessed with the intraclass correlation coefficient (ICC), was excellent on both the original area scale (ICC = 0.995) and the square root scale (ICC = 0.996). Intergrader differences were not an important source of variability in lesion size measurement (ICC = 0.999, 0.997). On average, the ER of GA per year was 1.2 mm² (0.47 DA; range, 0.01-3.62 mm²/year). The ER correlated with the initial area of GA ($r = 0.45$; $P < 0.001$), but there were variable growth rates for any given baseline area. When the square root transformation of the lesion area measurements was used as a measure of lesion size, the ER (0.28 mm/yr) was not correlated with baseline size ($r = -0.09$; $P = 0.40$). In this cohort of lesions, no correlation was found between ER and length of follow-up. Square root transformation of the data helped to facilitate sample size estimates for controlled clinical trials involving GA.

CONCLUSIONS: The SD-OCT fundus image can be used to visualize and quantify GA. Advantages of this approach include the convenience and assurance of using a single imaging technique that permits simultaneous visualization of GA along with the loss of photoreceptors and the retinal pigment epithelium that should correlate with the loss of visual function.

FINANCIAL DISCLOSURE(S): Proprietary or commercial disclosure may be found after the references.

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PMID: 21035861 [PubMed - as supplied by publisher]

12. Nig Q J Hosp Med. 2010 Jul-Sep;20(3):125-8.

Causes of blindness and low vision in Bayelsa State, Nigeria: a clinic based study.

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Abstract

BACKGROUND: No data are yet available on the causes of blindness and low vision in Bayelsa State of Nigeria.

OBJECTIVE: The study is to provide baseline data on the causes of blindness and low vision in Yenagoa, Bayelsa State, Nigeria.

METHODS: A prospective study was conducted among new consecutive patients presenting at the eye clinic of Niger Delta University Teaching Hospital. Patients with visual acuity of less than 6/18 in the better eye after optical correction or with pin hole as necessary were studied. Their visual acuity was determined using a snellen chart followed by anterior and posterior segment examination using a Haagstreet slit lamp biomicroscope and direct or indirect ophthalmoscope respectively (Keeler). Other information obtained from patients included their age, sex and occupation. Main outcome measure: Visual acuity < 3/60 in the better eye and visual acuity < 6/18 in the better eye. Statistical analysis: Statistical analysis was done using a scientific calculator.

RESULTS: Over a period of one year, 230 patients presented with visual impairment consisting of 124 blind cases and 106 cases of low vision. Their ages ranged from 3 to 90 years with a mean of 48 years. There were 118 males and 112 females giving a male:female ratio of 1:1.1. Cataract and glaucoma were the leading causes of blindness and low vision. Cataract was responsible for 63% of blindness and 49.8% of low vision while glaucoma accounted for 22% of blindness and 17.9% of low vision. The other causes of blindness in decreasing order includes maculopathy (4.3%), retinitis pigmentosa (3.4%), optic atrophy, phthisis bulbi, keratopathy (each 2.6%) and age related macular degeneration (0.9%). The other causes of low vision in decreasing order includes refractive error (15%), maculopathy (5.6), optic atrophy (3.8%), retinitis pigmentosa, retinopathy (each 2.8%) and age related macular degeneration (1.9%). Majority of blindness is avoidable (93.5%), and found in the fifth and sixth decades of life.

CONCLUSION: Cataract and glaucoma are the predominant causes of blindness and low vision in the study population and majority of the blindness (93.5%) is avoidable. A more aggressive approach to clear cataract backlog and improvement of early diagnosis and treatment of glaucoma are needed to combat blindness in this community.

PMID: 21033320 [PubMed - in process]

Pre-Clinical

13. Invest Ophthalmol Vis Sci. 2010 Nov 4. [Epub ahead of print]

Establishment of a new animal model of focal subretinal fibrosis that resembles disciform lesion in advanced age-related macular degeneration.

Jo YJ, Sonoda KH, Oshima Y, Takeda A, Kohno R, Yamada J, Hamuro J, Yang Y, Notomi S, Hisatomi T, Ishibashi T.

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Abstract

Purpose: Subretinal fibrosis causes damage to visual acuity, especially if the lesion is in the macula, which is frequently observed in advanced age-related macular degeneration. Exudated leukocytes form abnormal vessels that initiate regional inflammation accompanied with local glial proliferation and matrix production. The purpose of this study was to establish an animal model of focal subretinal fibrosis. **Methods:** Macrophage-rich peritoneal exudative cells (PECs) were inoculated into the subretinal space of C57BL/6 or MCP-1 knockout (KO) mice. Seven days later, the size of subretinal fibrotic issue was evaluated by the adhered area of glial fibrillary acidic protein (GFAP) positive retinal glial cells on choroidal flat mounts. Myofibroblastic changes and collagen synthesis were detected by alpha-smooth muscle actin (α -SMA) and

Masson-trichrome staining of the histological section, respectively. We also examined α -SMA expression on retinal pigment epithelium (RPE) cells during the co-culture with activated macrophages. Results: Subretinal fibrous tissue was observed by fundus scope in PEC-inoculated mice after seven days. The tissue was consisted of monotonous and low cell-density area, which expressed α -SMA with collagen synthesis. Both steroid and anti-oxidant treatment can reduce the glial residual. Because PEC-inoculated MCP-1 KO mice showed less amount of glial residual, not only exogenous macrophages, but also intrinsic macrophages are critical. Activated macrophages directly induced myofibrotic changes in RPE cells in vitro. Conclusions: Activated macrophages formed subretinal fibrosis when they were placed in the subretinal space and induce myofibrotic changes in RPE cells.

PMID: 21051730 [PubMed - as supplied by publisher]

14. Invest Ophthalmol Vis Sci. 2010 Nov 4. [Epub ahead of print]

Oral iron chelator deferiprone protects against iron overload induced retinal degeneration.

Hadziahmetovic M, Song Y, Wolkow N, Iacovelli J, Grieco S, Lee J, Lyubarsky A, Pratico D, Connelly J, Spino M, Harris ZL, Dunaief J.

F.M. Kirby Center for Molecular Ophthalmology, Scheie Eye Institute, University of Pennsylvania, Philadelphia, United States.

Abstract

PURPOSE: Iron-induced oxidative stress may exacerbate age-related macular degeneration (AMD). Herein, we use Ceruloplasmin/Hephaestin double knockout (DKO) mice with age-dependent retinal iron accumulation and some features of AMD to test retinal protection by the oral iron chelator deferiprone (DFP).

METHODS: Cultured retinal pigment epithelial cells (ARPE-19) and mice were treated with DFP. Transferrin receptor mRNA (Tfrc), an indicator of iron levels, was quantified by qPCR. In mice, retinal oxidative stress was assessed by mass spectrometry, and degeneration by histology and electroretinography.

RESULTS: DFP at 60 μ M decreased labile iron in ARPE-19 cells, increasing Tfrc and protecting 70% of cells against a lethal dose of H₂O₂. DFP 1mg/ml in drinking water increased retinal Tfrc mRNA 2.7-fold after 11days and also increased transferrin receptor protein. In DKO mice, DFP over 8mo decreased retinal iron levels to 72% of untreated mice, diminished retinal oxidative stress to 70% of untreated, and markedly ameliorated retinal degeneration. DFP was not retina-toxic in wild-type (w.t.) or DKO mice as assessed by histology and electroretinography.

CONCLUSION: Oral DFP was not toxic to the mouse retina. It diminished retinal iron levels and oxidative stress, and protected DKO mice against iron overload-induced retinal degeneration. Further testing of DFP for retinal disease involving oxidative stress is warranted.

PMID: 21051716 [PubMed - as supplied by publisher]

15. Toxicol In Vitro. 2010 Oct 30. [Epub ahead of print]

Diarylheptanoid 7-(3,4 dihydroxyphenyl)-5-hydroxy-1-phenyl-(1E)-1-heptene from *Curcuma comosa* roxb. protects retinal pigment epithelial cells against oxidative stress-induced cell death.

Jitsanong T, Khanobdee K, Piyachaturawat P, Wongprasert K.

Toxicology Graduate Program, Faculty of Science, Mahidol University, Bangkok, Thailand.

Abstract

Chronic exposure to oxidative stress causes damage to retinal pigment epithelial cells which may lead to the development of age-related macular degeneration, the major cause of vision loss in humans. Anti-oxidants provide a natural defense against retinal cell damage. The present study was designed to evaluate the potential antioxidant activity and protective effect of two diarylheptanoids isolated from a medicinal herb *Curcuma comosa*; 7-(3,4 dihydroxyphenyl)-5-hydroxy-1-phenyl-(1E)-1-heptene, (compound A) and 1,7-diphenyl-4(E), 6(E)-heptadien-3-ol, (compound B) against oxidative stress (H₂O₂) induced human retinal pigment epithelial (ARPE-19) cell death. The 2, 2-Diphenyl-1-picrylhydrazyl (DPPH) assay indicated that the antioxidant activity (IC₅₀) of compound A was similar to that of vitamin C. Pretreatment of ARPE-19 cells with 20 μM compound A for 4 hours afforded greater protection against the insult from 500 μM H₂O₂, compared to a similar protection period for compound B. Compound A lowered H₂O₂-induced lipid peroxidation, malondialdehyde formation and intracellular reactive oxygen species. Furthermore, compound A ameliorated the H₂O₂-induced decrease in antioxidant enzyme activities and subsequent apoptotic cell death in ARPE-19 cells in a dose and time-dependent manner. These results suggest that compound A protects ARPE-19 cells against oxidative stress, in part, by enhancing several antioxidant defense mechanisms. Therefore, compound A may have therapeutic potential for diseases associated with oxidative stress, particularly degenerative retinal diseases.

PMID: 21044678 [PubMed - as supplied by publisher]

16. Lab Invest. 2010 Nov 1. [Epub ahead of print]

Evidence for enhanced tissue factor expression in age-related macular degeneration.

Cho Y, Cao X, Shen D, Tuo J, Parver LM, Rickles FR, Chan CC.

Immunopathology Section, Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD, USA.

Abstract

Tissue factor (TF) is the primary initiator of blood coagulation. In addition to hemostasis, TF can initiate intracellular signaling and promote inflammation and angiogenesis, the key processes underlying the pathogenesis of age-related macular degeneration (AMD). AMD, the leading cause of irreversible blindness among the elderly, involves many genetic and environmental risk factors, including oxidative stress and inflammation. In this study, TF expression was examined in human AMD tissue and in the eyes of a model of AMD, the Ccl2(-/-)/Cx3cr1(-/-) (DKO) mouse, as well as in the ARPE-19 cell line after lipopolysaccharide (LPS) and H₂O₂ stimulation. Total RNA was extracted from tissue samples and further analyzed by real-time RT-PCR. Immunohistochemistry was performed to evaluate TF protein expression. In the human retina, a 32-fold increase of TF mRNA expression was detected in AMD macular lesions compared with normal maculae. TF protein expression was also enhanced in human AMD maculae. Similarly, TF transcript and protein expression were moderately increased in retinal lesions, neuroretinal tissue, and cultured RPE cells of DKO mice compared with age-matched wild-type mice. TF expression level correlated with age in both wild-type and DKO mice. In order to better understand how AMD might lead to enhanced TF expression, 1, 5, and 10 μg/ml LPS as well as 100 and 200 μM H₂O₂ were used to stimulate ARPE-19 cells for 24 and 2 h, respectively. LPS treatment consistently increased TF transcript and protein expression. H₂O₂ alone or in combination with LPS also moderately enhanced TF expression. These results indicate that upregulated TF expression may be associated with AMD, and inflammatory and oxidative stress may contribute to TF expression in AMD eyes. Laboratory Investigation advance online publication, 1 November 2010; doi:10.1038/labinvest.2010.184.

PMID: 21042291 [PubMed - as supplied by publisher]

17. J Chromatogr A. 2010 Oct 14. [Epub ahead of print]

Identification and quantification of phosphatidylcholines containing very-long-chain polyunsaturated fatty acid in bovine and human retina using liquid chromatography/tandem mass spectrometry.

Berdeaux O, Juaneda P, Martine L, Cabaret S, Bretillon L, Acar N.

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Abstract

The retina is one of the vertebrate tissues with the highest content in polyunsaturated fatty acids (PUFA). A large proportion of retinal phospholipids, especially those found in photoreceptor membranes, are dipolyunsaturated molecular species. Among them, dipolyunsaturated phosphatidylcholine (PC) molecular species are known to contain very-long-chain polyunsaturated fatty acids (VLC-PUFA) from the n-3 and n-6 series having 24-36 carbon atoms (C24-C36) and four to six double bonds. Recent interest in the role played by VLC-PUFA arose from the findings that a protein called elongation of very-long-chain fatty acids 4 (ELOVL4) is involved in their biosynthesis and that mutations in the ELOVL4 gene are associated with Stargardt-like macular dystrophy (STD3), a dominantly inherited juvenile macular degeneration leading to vision loss. The aim of the present study was to develop an HPLC-ESI-MS/MS method for the structural characterisation and the quantification of dipolyunsaturated PC molecular species containing VLC-PUFA and validate this methodology on retinas from bovines and human donors. Successful separation of phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidylserine (PS), PC, lyso-phosphatidylcholine (LPC) and sphingomyelin (SM) was achieved using a silica gel column and a gradient of hexane/isopropanol/water containing ammonium formate as a mobile phase. A complete structural characterisation of intact phosphatidylcholine species was obtained by collision-induced dissociation (CID) in the negative mode. Fatty acid composition and distribution can be clearly assigned based on the intensity of sn-2/sn-1 fragment ions. The PC species were characterised on bovine retina, 28 of which were dipolyunsaturated PC species containing one VLC-PUFA (C24-C36) with three to six double bonds. VLC-PUFA was always in the sn-1 position while PUFA at the sn-2 position was exclusively docosahexaenoic acid (DHA, C22:6n-3). Most of these VLC-PUFA-containing dipolyunsaturated PCs were detected and quantified in human retinas. The quantitative analysis of the different PC molecular species was performed in the positive mode using precursor ion scanning of m/z 184 and 14:0/14:0-PC and 24:0/24:0-PC as internal standards. The relationship between the MS peak intensities of different PC species and their carbon chain length was included for calibration. The main compounds represented were those having VLC-PUFA with 32 carbon atoms (C32:3, C32:4, C32:5 and C32:6) and 34 carbon atoms (C34:3, C34:4, C34:5 and C34:6). Dipolyunsaturated PCs with 36:5 and 36:6 were detected but in smaller quantities. In conclusion, this new HPLC-ESI-MS/MS method is sensitive and specific enough to structurally characterise and quantify all molecular PC species, including those esterified with VLC-PUFA. This technique is valuable for a precise characterisation of PC molecular species containing VLC-PUFA in retina and may be useful for a better understanding of the pathogenesis of STD3.

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