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MD Research News

Issue 49

Wednesday Oct 5 , 2011

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Drug treatment

Br J Ophthalmol. 2011 Sep 27. [Epub ahead of print]

Outcomes following three-line vision loss during treatment of neovascular age-related macular degeneration: subgroup analyses from MARINA and ANCHOR.

Wolf S, Holz FG, Korobelnik JF, Lanzetta P, Mitchell P, Prünte C, Schmidt-Erfurth U, Weichselberger A, Hashad Y.

Inselspital, University of Bern, Bern, Switzerland.

Aim: This study aims to assess the impact of continued ranibizumab treatment for neovascular age-related macular degeneration on patients from the MARINA and ANCHOR randomised clinical studies who lost ≥3 lines of best-corrected visual acuity (BCVA) at any time during the first year of treatment.

Methods: Baseline characteristics, mean BCVA over time and ocular adverse events (AEs) were evaluated both for patients whose BCVA loss occurred at any post-baseline visit and for patients whose BCVA loss was acute. The visit when the ≥3-line BCVA loss was detected was defined as the new baseline.

Results: Continued monthly ranibizumab treatment led to an improvement in mean BCVA from the new baseline. On average, patients with acute BCVA loss gained 11.9 letters at 3 months after the new baseline, compared with 0.3 letters gained with sham. No strong signals were detected in patient demographics and baseline characteristics for prognostic markers of BCVA loss. Furthermore, there was no pattern in the AE profile of patients with acute BCVA loss to suggest that BCVA recovery could be attributed to spontaneously resolving AEs.

Conclusion: Continued ranibizumab treatment appears to be beneficial for patients with neovascular age-related macular degeneration who experience a ≥3-line BCVA loss during the first year of treatment.

PMID: 21951567 [PubMed - as supplied by publisher]

Clin Exp Optom. 2011 Sep 28. doi: 10.1111/j.1444-0938.2011.00662.x. [Epub ahead of print]

Short-term effects of a single intravitreal bevacizumab injection on retinal vessel calibre.

Tatlipinar S, Dinç UA, Yenerel NM, Görgün E.

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Purpose: The aim was to investigate the short-term effects of a single intravitreal bevacizumab injection on the retinal vessel calibre in patients with neovascular age-related macular degeneration and in patients with diabetic macular oedema.

Methods: Twelve patients with neovascular age-related macular degeneration and eight patients with diabetic macular oedema were included in the study. All patients received an intravitreal injection of 1.25 mg bevacizumab. Red-free fundus photographs (35°) were acquired with a fundus camera at baseline and one day, one week and one month after the intravitreal injection. Measurements of retinal vessel diameter were made of the supero-temporal retinal venule and arteriole using the software available on the IMAGEnet program.

Results: Although there appeared to be a trend towards vasoconstriction for the measurements in the diabetic macular oedema group (both for arterioles and venules at day 7) and the age-related macular degeneration group (for venules at day 1 and for arterioles at day 7), it did not reach statistical significance ($p > 0.05$). Optical coherence tomography revealed a significant decrease in foveal thickness measurements in both groups at the one month visit compared with baseline.

Conclusion: The results suggest that intravitreal injection of bevacizumab might induce retinal vasoconstriction; however, low numbers of subjects might have prevented the difference from reaching statistical significance. Further studies with a larger number of subjects would reveal the effect of intravitreal anti-vascular endothelial growth factor treatment on retinal vessel diameters more clearly.

PMID: 21954975 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2011 Sep 22. doi: 10.1111/j.1755-3768.2011.02264.x. [Epub ahead of print]

Efficacy and safety of recombinant tissue plasminogen activator and gas versus bevacizumab and gas for subretinal haemorrhage.

Mayer WJ, Hakim I, Haritoglou C, Gandorfer A, Ulbig M, Kampik A, Wolf A.

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Purpose: To report the 12 months efficacy of initial intravitreal bevacizumab or intravitreal recombinant tissue plasminogen activator (rtPA) combined with expansile gas in patients with subretinal haemorrhage caused by neovascular age-related macular degeneration (AMD).

Methods: Forty-five eyes of 45 patients with subretinal haemorrhage (1-5 disc diameters) involving the fovea secondary to neovascular AMD were evaluated retrospectively consecutively. Thirty-two eyes underwent treatment with rtPA (50 µg/0.05 ml) combined with intravitreal sulphur hexafluoride (SF6). The other 13 eyes were treated with bevacizumab (1.25 mg/0.05 ml) and SF6. Thereafter, all patients received Vascular Endothelial Growth Factor (anti-VEGF) treatment according to modified PrONTO criteria. Main outcome was change of best-corrected visual acuity (VA) at 12 months as determined by Early Treatment Diabetic Retinopathy (ETDRS).

Results: There was more improvement in patients initially treated with rtPA and gas (14 letters; bevacizumab and gas eight letters) and not suffering from adverse events. The incidence of vitreous haemorrhages was significantly higher in the rtPA group (nine of 32 versus one of 13, $p < 0.01$). In both groups, an average of 3.5 anti-VEGF injections were performed per patient during 12 months (no difference between both groups).

Conclusion: Both initial treatment regimen lead to improved functional results after 1 year. However, patients, not suffering from adverse events, who underwent initial treatment with rtPA and gas showed better results. To maintain VA, controlling neovascular AMD by anti-VEGF treatment regime after initial treatment with rtPA+gas is important for all cases.

PMID: 21952010 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2011 Sep 22. doi: 10.1111/j.1755-3768.2011.02265.x. [Epub ahead of print]

Intravitreal bevacizumab versus ranibizumab for the treatment of retinal angiomatous proliferation.

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Purpose: To evaluate the effects of intravitreal bevacizumab and ranibizumab treatments in retinal angiomatous proliferation (RAP). Methods: Fifty patients affected by RAP were randomly assigned either to intravitreal bevacizumab injection (IVBI) or intravitreal ranibizumab injection (IVRI). After a loading phase including three consecutive monthly injections, the retreatment was administered in cases of persistent RAP. The primary outcome measures were the mean changes in BCVA between the two treatment groups, and the proportion of eyes gaining 1 and 3 lines at the end of the follow-up. Secondary outcomes included central macular thickness (CMT) changes and progression to more advanced stages of RAP. Results: Fifty patients affected by stage 1 and 2 RAP were recruited. Twenty-six and 24 patients received IVBI and IVRI, respectively. At the baseline, mean best corrected visual acuity (BCVA) values were 0.59 ± 0.21 (LogMAR ± SD, approximately corresponding to 20/80 Snellen Equivalent-SE) in IVBI group and 0.66 ± 0.33 (approximately 20/90 SE) in IVRI group with no statistical difference. At 12-month examination, both groups showed a statistically significant improvement in the BCVA, with a final mean value of 0.43 ± 0.24 (approximately 20/54 SE) in IVBI group and 0.50 ± 0.32 (approximately 20/63 SE) in the IVRI group. A BCVA gain of 1 and 3 lines was registered in 20 and 8 eyes, respectively, in the IVBI group. Similarly, 17 and 7 eyes showed an improvement of 1 or 3 lines, respectively, in the IVRI group. The CMT reduced significantly from baseline to 12-month examination in both groups. A lower proportion of eyes with complete pigment epithelium detachment resolution was noted in the IVBI group than in the IVRI group (40% versus 90%). Conclusions: Our study shows that both IVBI and IVRI are equally effective in improving the BCVA over a 1-year follow-up in eyes affected by stage 1 and 2 RAP.

PMID: 21951313 [PubMed - as supplied by publisher]

Curr Eye Res. 2011 Oct;36(10):958-63.

Comparing Treatment of Neovascular Age-related Macular Degeneration with Sequential Intravitreal Avastin and Macugen Versus Intravitreal Mono-therapy-A Pilot Study.

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Purpose: To examine if the sequential treatment of Avastin and Macugen is safe and more efficient than the mono-therapies in a prospective randomized masked pilot study.

Materials and Methods: Subjects with exudative age-related macular degeneration were randomized to receive three intravitreal injections of either 1 mg of Avastin, 0.3 mg Macugen, or first 1 mg Avastin followed by retreatment of 0.3 mg Macugen. Follow-up examinations were performed after 1, 6, 12 weeks, and 6 months.

Results: Forty-eight subjects were included (13:18:17). Avastin resulted in lasting significant changes in visual acuity at 6 weeks, increase in contrast sensitivity at 6 weeks, and a significant decrease in macular thickness after 6 and 12 weeks. Macugen showed a significant decrease in retinal thickness after 6 weeks, but a significant decrease in visual acuity after 6 months, and a significant decrease in contrast sensitivity after 12 weeks and 6 months. The sequential treatment showed a decrease in retinal thickness after 1 and 12 weeks.

Conclusion: Avastin alone is more effective in increasing visual acuity and contrast sensitivity and decreasing retinal thickness, than Macugen or the sequential treatment. We conclude that the sequential treatment of Avastin with Macugen is safe, but the single treatment of Avastin is more efficient.

PMID: 21950702 [PubMed - in process]

Acta Ophthalmol. 2011 Sep 29. doi: 10.1111/j.1755-3768.2011.02240.x. [Epub ahead of print]

Vascular endothelial growth factor plasma levels before and after treatment of neovascular age-related macular degeneration with bevacizumab or ranibizumab.

Carneiro AM, Costa R, Falcão MS, Barthelmes D, Mendonça LS, Fonseca SL, Gonçalves R, Gonçalves C, Falcão-Reis FM, Soares R.

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Purpose: To evaluate the changes of vascular endothelial growth factor (VEGF) plasma levels after intravitreal injections of ranibizumab or bevacizumab in patients with exudative age-related macular degeneration (AMD).

Methods: Forty-three patients with exudative AMD and 19 age- and sex-matched control patients without chorioretinal diseases were studied. Nineteen patients were treated with intravitreal ranibizumab 0.5 mg, 24 with intravitreal bevacizumab 1.25 mg. Blood samples were collected just before the first injection, and 28 days after three initial consecutive injections performed in 4-weekly intervals (loading dose). Concentration of VEGF in the plasma was measured by ELISA.

Results: At baseline, the median VEGF concentrations in controls were 180.97 pg/ml, in the bevacizumab group 189.72 pg/ml and in the ranibizumab group 191.36 pg/ml. VEGF plasma concentrations in patients with wet AMD were comparable to controls ($p = 0.225$). Twenty-eight days after the third injection, a significant reduction of 42% in the median VEGF plasma levels was found in bevacizumab-treated patients (109.97 pg/ml; $p = 0.0002$) but not in ranibizumab-treated patients (189.97 pg/ml; $p = 0.198$) where a reduction of 0.7% in the median value was found.

Conclusions: Intravitreal bevacizumab significantly reduced VEGF plasma levels until 28 days after intravitreal injection in patients with exudative AMD. Ranibizumab did not achieve a significant plasma VEGF reduction at the same time-point. These findings alert to the potential systemic safety differences between the two drugs after intravitreal administration.

PMID: 21958440 [PubMed - as supplied by publisher]

J Clin Pharmacol. 2011 Sep 23. [Epub ahead of print]

Population Pharmacokinetics of Pegaptanib in Patients With Neovascular, Age-Related Macular Degeneration.

Basile AS, Hutmacher M, Nickens D, Nielsen J, Kowalski K, Whitfield L, Masayo O, Nakane M.

Pfizer Global Research and Development.

Abstract

The anti-vascular endothelial growth factor (VEGF) aptamer pegaptanib is eliminated primarily by renal

clearance. Because renal function declines with age, pegaptanib exposure in patients with age-related macular degeneration (AMD) may increase. Therefore, a population pharmacokinetic (PK) analysis of pegaptanib was undertaken in Western and Asian AMD patients to determine the influence of renal function on apparent pegaptanib clearance (CL). Pegaptanib (0.3-3 mg per eye) was administered every 4 to 6 weeks to 262 AMD patients in 4 studies. Pegaptanib exposures (area under the concentration-time curve [AUC] and maximum plasma concentration) after 8 doses were similar to exposures following the first dose, consistent with the absence of plasma accumulation. A 1-compartment model parameterized in terms of the absorption rate constant, apparent volume of distribution, and CL was used to describe the pegaptanib plasma concentration data. Creatinine clearance (CLCR), body weight (WT), and age influenced pegaptanib PK. Decreasing CLCR from 70 to 30 mL/min doubled AUC. After adjustment for CLCR, WT, and age, the model predicted no race differences in CL or AUC. Given that the therapeutic 0.3 mg per eye dose of pegaptanib results in exposures one-tenth of those observed following the well-tolerated 3-mg dose, these results suggest that no dose adjustment is warranted for AMD patients with moderate renal insufficiency (CLCR >30 mL/min).

PMID: 21947371 [PubMed - as supplied by publisher]

Other treatment & diagnosis

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

Ocular Manifestations of Trichothiodystrophy.

Brooks BP, Thompson AH, Clayton JA, Chan CC, Tamura D, Zein WM, Blain D, Hadsall C, Rowan J, Bowles KE, Khan SG, Ueda T, Boyle J, Oh KS, Digiovanna JJ, Kraemer KH.

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OBJECTIVE: Trichothiodystrophy (TTD) is a rare, autosomal recessive disorder characterized by sulfur-deficient brittle hair and multisystem abnormalities. Many TTD patients have a defect in known DNA repair genes. This report systematically evaluates the ocular manifestations of the largest-to-date cohort of TTD patients and xeroderma pigmentosum (XP)/TTD patients.

DESIGN: Case series.

PARTICIPANTS: Thirty-two participants, ages 1 to 30 years, referred to the National Eye Institute for examination from 2001 to 2010; 25 had TTD and 7 had XP/TTD.

METHODS: Complete, age- and developmental stage-appropriate ophthalmic examination.

MAIN OUTCOME MEASURES: Visual acuity (VA), best-corrected VA, ocular motility, state of the ocular surface and corneal endothelial cell density, corneal diameter, and lens assessment.

RESULTS: Developmental abnormalities included microcornea (44% TTD), microphthalmia (8% TTD, 14% XP/TTD), nystagmus (40% TTD), and infantile cataracts (56% TTD, 86% XP/TTD). Corrective lenses were required by 65% of the participants, and decreased best-corrected VA was present in 28% of TTD patients and 71% of XP/TTD patients. Degenerative changes included dry eye (32% TTD, 57% XP/TTD) and ocular surface disease identified by ocular surface staining with fluorescein (32% TTD) that usually are exhibited by much older patients in the general population. The 2 oldest TTD patients exhibited clinical signs of retinal/macular degeneration. Four XP/TTD patients presented with corneal neovascularization.

CONCLUSIONS: These TTD and XP/TTD study participants had a wide variety of ocular findings including refractive error, infantile cataracts, microcornea, nystagmus, and dry eye/ocular surface disease. Although many of these can be ascribed to abnormal development-likely owing to abnormalities in basal transcription of critical genes-patients may also have a degenerative course.

PMID: 21959366 [PubMed - as supplied by publisher]

Ultrasonics. 2011 Aug 27. [Epub ahead of print]

Noninvasive estimation of the ocular elastic modulus for age-related macular degeneration in the human eye using sequential ultrasound imaging.

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INTRODUCTION: Elastic modulus estimation may be an important clinical criterion, as it seems to affect such eye parameters as intraocular pressure, ocular pulsation, blood flow, effect of topical medications, and post-refractive surgery complications. The purpose of this study was to examine the differences in elasticity in the ocular axial length, posterior wall thickness (posterior pole), and retina-choroid thickness under normal and aged-related macular degeneration (AMD) conditions in the human eye by directly estimating the elastic modulus with sequential and noninvasive ultrasound image processing.

MATERIALS AND METHODS: In this study, 25 healthy subjects and 20 patients with non-neovascular AMD participated in the experiment. The deformation of the ocular axial length, posterior wall thickness and retina-choroid complex thickness was captured using high-resolution ultrasonography before and after loading. The B-mode (20MHz) and A-mode (8MHz) frames were obtained and processed with an echo tracking technique. The elastic modulus was estimated using changes in ocular axial length, posterior wall thickness and retina-choroid complex thickness and with applied stress measurements.

RESULTS: There was a significant difference ($p<0.05$) in the ocular axial length elastic modulus between the AMD and healthy subjects (AMD patients: 95.165±26.431kPa, vs. healthy subjects: 49.539±25.867kPa). Moreover, there was a statistically significant difference ($p<0.05$) in the posterior wall thickness elastic modulus between AMD patients and healthy subjects (AMD patients: 50.519±12.295kPa, vs. healthy subjects: 20.519±11.827kPa). However, no statistically significant difference (p-value>0.05) was found in the retina-choroid complex elastic modulus between the two groups (AMD patients: 20.134±3.898kPa, vs. healthy subjects: 15.630±4.250kPa).

CONCLUSION: Although the results were obtained examining a relatively low number of patients, it would appear that noninvasive ultrasound estimation of the local elastic moduli of ocular axial length and posterior wall thickness is suited to aid in detection of the non-exudative AMD thus manifesting its potential as a screening tool in symptom-free individuals.

PMID: 21944993 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2011 Jul;26(4-5):304-11.

Autoimmunity and Age-related Macular Degeneration: A Review of the Literature.

Fazelat A, Bahrani H, Buzney S, Lashkari K, Weiter JJ.

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PMID: 21958179 [PubMed - in process]

Pathogenesis

Adv Exp Med Biol. 2012;946:161-83.

Complement involvement in neovascular ocular diseases.

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Abstract

Pathological neovascularization (NV) is a hallmark of late stage neovascular age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinopathy of prematurity (ROP). There is accumulating evidence that alterations in inflammatory and immune system pathways that arise from genetic differences, injury, and disease can predispose individuals to retinal neovascular eye diseases. Yet the mechanism of disease progression with respect to the complement system in these maladies is not fully understood. Recent studies have implicated the complement system as an emerging player in the etiology of several retinal diseases. We will summarize herein several of the complement system pathways known to be involved in ocular neovascular pathologies. Current treatment for many neovascular eye diseases focuses on suppression of NV with laser ablation, photodynamic therapy, or anti-VEGF angiogenic inhibitors. However, these treatments do not address the underlying cause of many of these diseases. A clear understanding of the cellular and molecular mechanisms could bring a major shift in our approach to disease treatment and prevention.

PMID: 21948368 [PubMed - in process]

PLoS One. 2011;6(9):e24245. Epub 2011 Sep 22.

Tauroursodeoxycholic Acid (TUDCA) Protects Photoreceptors from Cell Death after Experimental Retinal Detachment.

Mantopoulos D, Murakami Y, Comander J, Thanos A, Roh M, Miller JW, Vavvas DG.

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BACKGROUND: Detachment of photoreceptors from the underlying retinal pigment epithelium is seen in various retinal disorders such as retinal detachment and age-related macular degeneration and leads to loss of photoreceptors and vision. Pharmacologic inhibition of photoreceptor cell death may prevent this outcome. This study tests whether systemic administration of tauroursodeoxycholic acid (TUDCA) can protect photoreceptors from cell death after experimental retinal detachment in rodents.

METHODOLOGY/PRINCIPAL FINDINGS: Retinal detachment was created in rats by subretinal injection of hyaluronic acid. The animals were treated daily with vehicle or TUDCA (500 mg/kg). TUNEL staining was used to evaluate cell death. Photoreceptor loss was evaluated by measuring the relative thickness of the outer nuclear layer (ONL). Macrophage recruitment, oxidative stress, cytokine levels, and caspase levels were also quantified. Three days after detachment, TUDCA decreased the number of TUNEL-positive cells compared to vehicle (651±68/mm(2) vs. 1314±68/mm(2), P=0.001) and prevented the reduction of ONL thickness ratio (0.84±0.03 vs. 0.65±0.03, P=0.002). Similar results were obtained after 5 days of retinal detachment. Macrophage recruitment and expression levels of TNF-a and MCP-1 after retinal detachment were not affected by TUDCA treatment, whereas increases in activity of caspases 3 and 9 as well as carbonyl-protein adducts were almost completely inhibited by TUDCA treatment.

CONCLUSIONS/SIGNIFICANCE: Systemic administration of TUDCA preserved photoreceptors after retinal detachment, and was associated with decreased oxidative stress and caspase activity. TUDCA may be used as a novel therapeutic agent for preventing vision loss in diseases that are characterized by photoreceptor detachment.

PMID: 21961034 [PubMed - in process]

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

HYPOXIA-REGULATED RETINAL GLIAL CELL-SPECIFIC PROMOTER FOR POTENTIAL GENE THERAPY IN DISEASE.

Prentice HM, Biswal MR, Dorey CK, Blanks JC.

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Purpose: Retinal Műller cells span the retina and secrete several trophic factors and represent the functional link between blood vessels and neurons, making them attractive targets for gene therapy. Therefore, a hypoxia-regulated, retinal glial cell-specific vector was constructed and tested for its response to hypoxia.Methods:A hybrid promoter containing domains of human GFAP and several hypoxia-responsive and aerobically silenced elements (HRSE) was incorporated separately into plasmid vectors for generation of self complementary AAV. Műller cells trasfected with plasmids or virus were compared to other cell lines using standard

Methods: The mouse model of oxygen induced retinopathy (OIR) was used to analyze retinas from mice exposed to high oxygen or room air to evaluate the induction of regulated promoter.

Results:The regulated promoter was silenced under aerobic conditions in comparison to unregulated promoter in Műller cells. Hypoxia induced a 12-fold and 16-fold increase in promoter activity in primary Műller cells and human Műller cell lines, respectively. In the OIR model, intravitreal injection of the regulated promoter at P7 resulted in high levels of GFP expression only in retinal Műller cells at P17. GFP expression was absent in retinas of mice only exposed to room air. In vivo studies confirm normoxia silencing, hypoxic induction and cell specificity of the regulated promoter in the mouse retina.

Conclusions:Our hypoxia-regulated, retinal glial cell-specific AAV vector provides a platform for gene therapy within regions of retinal hypoxia which are found in diabetic retinopathy and age related macular degeneration.

PMID: 21960554 [PubMed - as supplied by publisher]

Naunyn Schmiedebergs Arch Pharmacol. 2011 Sep 25. [Epub ahead of print]

Bp5250 inhibits vascular endothelial growth factor-induced angiogenesis and HIF-1α expression on endothelial cells.

Lin KT, Lien JC, Chung CH, Kuo SC, Huang TF.

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Abstract

Angiogenesis plays a critical role in many physiological and pathological phenomena. A number of anti-angiogenesis drugs have been used in the clinical treatment of diseases such as malignant tumors and macular degeneration. Vascular endothelial growth factor (VEGF), the major pro-angiogenesis factor, is known to stimulate various steps of endothelial angiogenic activity, such as proliferation, migration, and differentiation into vessel-like tubes. In this study, we tested the effects of bp5250 on the angiogenesis of human umbilical endothelial cells (HUVECs). Bp5250 suppressed VEGF-induced endothelial cell proliferation by triggering apoptosis, and reduced endothelial cell migration toward VEGF. Bp5250 also decreased VEGF-stimulated tube formation and rat aortic ring sprouting on Matrigel in a concentration-dependent manner. In the VEGF-activated signaling pathways, bp5250 decreased the phosphorylation of ERK, p38, PI3K-AKT, Src, and FAK and also reduced the activation of the cytoskeleton-associated Rho family, all in a concentration-dependent manner. Bp5250 also attenuated the hypoxia-inducible factor-1α (HIF-1α) and

VEGF-stimulated mRNA expression of HUVECs under the hypoxic condition. In vivo, angiogenesis was restrained by a daily intraperitoneal administration of bp5250 in a dose-dependent manner (1-3 mg/kg/d) in the Matrigel plug implantation assay. These results indicate that bp5250 is a potential candidate for developing anti-angiogenic agents.

PMID: 21947252 [PubMed - as supplied by publisher]

Aging (Albany NY). 2011 Sep 21. [Epub ahead of print]

Oxidation as "The Stress of Life"

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Abstract

Multiple biological consequences of oxidative stress are known to contribute to aging and aging-related pathologies. It was recently shown that (carboxyalkyl)pyrroles (CAPs), the end products of phospholipid oxidation serve as a novel class of endogenous ligands for Toll-like receptors (TLRs) and promote the process of angiogenesis. In this review, we discuss implications of these findings in the context of age-related pathologies, including tumorigenesis. Accumulation of oxidation products in tissues of aging organisms might create conditions for uncontrolled pathological angiogenesis as seen in patients with age related macular degeneration. CAPs and their receptors, TLRs might also promote the progression of atherosclerotic lesions. Importantly, besides their role in a number of pathologies, oxidative products of phospholipids contribute to tissue repair processes thereby antagonizing the destructive effects of oxidation.

PMID: 21946568 [PubMed - as supplied by publisher]

Epidemiology

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

Risk Models for Progression to Advanced Age-Related Macular Degeneration Using Demographic, Environmental, Genetic, and Ocular Factors.

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PURPOSE: To expand our predictive models for progression to advanced stages of age-related macular degeneration (AMD) based on demographic, environmental, genetic, and ocular factors, using longer follow-up, time varying analyses, calculation of absolute risks, adjustment for competing risks, and detailed baseline AMD and drusen status.

DESIGN: Prospective, longitudinal study.

PARTICIPANTS: We included 2937 individuals in the Age-Related Eye Disease Study, of which 819 subjects progressed to advanced AMD during 12 years of follow-up.

METHODS: Cox proportional hazards regression analyses were performed to calculate hazard ratios for progression. Covariates included demographic and environmental factors, 6 variants in 5 genes, baseline macular drusen size, and presence and type of advanced AMD in 1 eye at baseline. To assess the ability of

risk scores based on all covariates to discriminate between progressors and nonprogressors, an algorithm was developed and the area under the receiver operating characteristic curve (AUC) was calculated. To validate the overall model, the total sample was randomly subdivided into derivation and test samples. Another model was built based on the derivation sample and assessed for calibration and discrimination in the test sample. Sample sizes needed for testing new treatments in clinical trials were estimated based on models with and without genetic variables.

MAIN OUTCOME MEASURES: Progression to advanced AMD, including geographic atrophy and neovascular disease.

RESULTS: In multivariate models, age, smoking, body mass index, single nucleotide polymorphisms in the CFH, ARMS2/HTRA1, C3, C2, and CFB genes, as well as presence of advanced AMD in 1 eye and drusen size in both eyes were all independently associated with progression. The AUC for progression at 10 years in the model with genetic factors, drusen size, and environmental covariates was 0.915 in the total sample. In the test sample, based on a model estimated from the derivation sample, the AUC was 0.908. The sample sizes needed for clinical trials were estimated to be lower when genetic susceptibility was considered.

CONCLUSIONS: Factors reflective of nature and nurture were incorporated into an expanded algorithm for risk prediction, which performed very well in both derivation and test samples. Risk scores and predicted progression rates will be useful for AMD surveillance and for designing clinical trials.

PMID: 21959373 [PubMed - as supplied by publisher]

Genetics

Biometrics. 2011 Sep 28. doi: 10.1111/j.1541-0420.2011.01680.x. [Epub ahead of print]

Logistic Bayesian LASSO for Identifying Association with Rare Haplotypes and Application to Age-Related Macular Degeneration.

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Summary: Rare variants have been heralded as key to uncovering "missing heritability" in complex diseases. These variants can now be genotyped using next-generation sequencing technologies; nonetheless, rare haplotypes may also result from combination of common single nucleotide polymorphisms available from genome-wide association studies (GWAS). The National Eye Institute's data on age-related macular degeneration (AMD) is such an example. Studies on AMD had identified potential rare variants; however, due to lack of appropriate statistical tools, effects of individual rare haplotypes were never studied. Here we develop a method for identifying association with rare haplotypes for case-control design. A logistic regression based retrospective likelihood is formulated and is regularized using logistic Bayesian LASSO (LBL). In particular, we penalize the regression coefficients using appropriate priors to weed out unassociated haplotypes, making it possible for the rare associated ones to stand out. We applied LBL to the AMD data and identified common and rare haplotypes in the complement factor H gene, gaining insights into rare variants' contributions to AMD beyond the current literature. This analysis also demonstrates the richness of GWAS data for mapping rare haplotypes-a potential largely unexplored. Additionally, we conducted simulations to investigate the performance of LBL and compare it with Hapassoc. Our results show that LBL is much more powerful in identifying rare associated haplotypes when the false positive rates for both approaches are kept the same.

PMID: 21955118 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2011 Sep 21:0. doi: 10.5301/ejo.5000053. [Epub ahead of print]

Susceptibility to exudative age-related macular degeneration and three genetic polymorphisms of glutathione S-transferase Z1 (GSTZ1).

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Purpose: To investigate whether genetic polymorphisms of GSTZ1 contribute to the development of exudative age-related macular degeneration (AMD).

Methods: The present case-control study consisted of 112 patients (44 female, 68 male) with exudative AMD and 112 sex frequency-matched healthy controls were randomly selected from unrelated volunteers in the same clinic. Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism-based method.

Results: There was no significant association between study polymorphisms and susceptibility to exudative AMD. Considering the significant difference in age distribution between cases and controls, age was used as a covariate in further analysis. After odds ratio adjustment for age, the same results were observed. The study polymorphisms showed linkage disequilibrium. Analysis revealed that there was no difference between cases and controls for the prevalence of the haplotypes of GSTZ1.

Conclusions: Our study did not support any association between susceptibility to exudative AMD and polymorphisms of GSTZ1.

PMID: 21948024 [PubMed - as supplied by publisher]