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MD Research News

Issue 90

Monday July 23 , 2012

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

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Drug treatment

Am J Ophthalmol. 2012 Aug;154(2):222-6.

Aflibercept for age-related macular degeneration: a game-changer or quiet addition?

Browning DJ, Kaiser PK, Rosenfeld PJ, Stewart MW.

Charlotte Eye, Ear, Nose and Throat Associates, Charlotte, North Carolina.

PURPOSE: To describe the pharmacokinetics, preclinical studies, and clinical trials of the newly approved anti-vascular endothelial growth factor (VEGF) drug aflibercept (Eylea (VEGF Trap-Eye); Regeneron; and Bayer).

DESIGN: Review with editorial commentary.

METHODS: A review of the medical literature and pertinent Internet postings combined with analysis of key studies with expert opinion regarding the use of aflibercept for the treatment of exudative age-related macular degeneration.

RESULTS: Aflibercept, a fusion protein with binding domains from native VEGF receptors, binds VEGF-A, VEGF-B, and placental growth factors 1 and 2 with high affinity. Preclinical ophthalmologic studies demonstrated that aflibercept suppresses choroidal neovascularization in several animal models. The results of phase 1 and 2 trials showed excellent short-term suppression of choroidal neovascularization in patients with exudative age-related macular degeneration and suggested a longer durability of aflibercept compared with other anti-VEGF drugs. The pivotal phase 3 Vascular Endothelial Growth Factor (VEGF) Trap-Eye: Investigation of Efficacy and Safety in Wet Age-Related Macular Degeneration 1 and 2 trials showed that monthly and bimonthly aflibercept were noninferior to monthly ranibizumab at preventing vision loss (< 15-letter loss) with comparable vision gains and safety. Year 2 treatment involved monthly pro re nata injections with required injections every 3 months and maintained vision gains from the first year, with an average of 4.2 injections of aflibercept and 4.7 injections of ranibizumab.

CONCLUSIONS: Aflibercept promises to deliver excellent visual outcomes for exudative age-related macular degeneration patients while undergoing fewer injections compared with ranibizumab. With a wholesale cost of $1850 per dose, the cost per patient with aflibercept treatment promises to be lower than with ranibizumab.

PMID: 22813448 [PubMed - in process]

Case Report Ophthalmol. 2012 May;3(2):221-225. Epub 2012 Jun 26.

Tear of Retinal Pigment Epithelium following YAG Laser Posterior Capsulotomy in a Patient on Anti-VEGF Treatment for AMD: Six Months' Follow-Up.

Vardarinos A, Empeslidis T, Periysamy K, Menassa N, Shahid F, Uppal S, Deane J.

Medical Retina Department, Leicester Royal Infirmary, University Hospitals of Leicester, Leicester, UK.

PURPOSE: To present a rare case of retinal pigment epithelium (RPE) rupture following YAG laser posterior capsulotomy (YAG PC) in a patient with exudative age-related macular degeneration (AMD).

MATERIALS AND METHODS: An 85-year-old pseudophakic male patient on ranibizumab 0.5 mg/0.05 ml treatment due to exudative AMD received YAG PC for dense posterior capsule opacification (PCO) in his right eye. The patient had received his last intravitreal ranibizumab injection 3 months before YAG PC; his macula appeared stable on fundoscopy and optical coherence tomography scans at repeated visits, but his vision deteriorated to counting fingers due to PCO.

RESULTS: Following left eye posterior YAG PC, his best-corrected visual acuity (BCVA) improved to 6/12 (Snellen chart). Despite satisfactory visual results, the patient developed a parafoveal inferotemporal RPE rupture. A decision for further treatment with ranibizumab (0.5 mg/0.05 ml) intravitreal injections was made. After a total of 7 injections, the patient was clinically stable and his BCVA was 6/18 (Snellen chart).

CONCLUSIONS: RPE rupture is a well-known, serious complication in patients with exudative AMD, which often has devastating results on patients' vision. Offering YAG PC to those patients could lead to a rupture of the RPE even in cases which appear to be stable and well controlled. Clinicians should be aware of this complication and inform the patients accordingly.

PMID: 22807911 [PubMed - as supplied by publisher] PMCID: PMC3398079

Arch Soc Esp Oftalmol. 2012 Aug;87(8):237-246. Epub 2012 May 26.

Long-term visual acuity in patients with age-related macular degeneration and persistence of subretinal fluid after treatment with ranibizumab.

[Article in English, Spanish]

Torrón C, Fernández-Pérez S, Ruiz O, Leciñena J, Pablo L.

Servicio de Oftalmología, Hospital Universitario Miguel Servet, Zaragoza, España.

OBJECTIVE: To analyse the long-term visual acuity (VA) in patients with age-related macular degeneration (ARMD) treated with ranibizumab, and who had persistent subretinal fluid after the induction therapy and/or in the successive controls.

MATERIALS AND METHODS: We reviewed the medical records, optical coherence tomography (OCT) and fluorescein angiograms of 216 patients treated with ranibizumab between January 2008 and April 2010, selecting those who had persistent subretinal fluid or recurrent fluid for at least one year of follow-up.

RESULTS: A total of 36 eyes from 34 patients were included, with 19 eyes (52.7%) having persistent, and 17 (47.2%) recurrent subretinal fluid throughout the follow- up (mean 29.06±9.28 months). The average number of injections was 7.89±3.2. The central macular thickness (CMT) at the start of follow-up was 330±84µm, at 3 months 265.2±62µm, and 294.5±37µm at the end of the follow-up. The initial mean VA was 0.3±0.2, at 3 months 0.43±0.2 (P<.05) and at the final review, 0.41±0.22 (P<.05). Haemorrhages in recurrences were associated with a worse final VA (P=.004). At the end of follow-up, 18 eyes (50%) continued with ranibizumab treatment, 16 eyes (44%) were kept under observation, and 2 patients died. There were no differences between VA and CMT between the groups.

CONCLUSIONS: The persistence or recurrence of macular subretinal fluid in patients treated with ranibizumab does not significantly reduce the visual gain obtained after induction therapy, despite discontinuation of treatment during follow-up. Haemorrhages in the recurrences were associated with a worse final VA.

PMID: 22794170 [PubMed - as supplied by publisher]

Mcgill J Med. 2011 Jun;13(1):38.

Quantifying the increasing use of anti-vascular endothelial growth factor therapy in ophthalmology.

Micieli JA, Micieli M.

Introduction: Bevacizumab (Avastin; Genetech Inc., South San Francisco, CA) and ranibizumab (Lucentis, Genetech Inc.) are two anti-Vascular Endothelial Growth Factor (VEGF) agents used in increasing amounts off-label to treat ocular conditions. To date, no study has quantified how far reaching these therapies have been in treating eye disease and compared their off-label use to the number of clinical trials performed.

Method: A systematic search of Ovid MEDLINE using the keywords bevacizumab and ranibizumab limited to "Case Reports" was used as an index of the number of diseases treated. Each keyword was also limited to "Clinical Trials, All" and "Phase III Clinical Trials" to discern the quality of evidence for these uses.

Results: Bevacizumab has been utilized for the treatment of 58 different ocular conditions, but only 14 conditions were studied in a trial, and none were part of a phase III clinical trial. Ranibizumab has been used for 17 different eye conditions, with only 6 studied in a trial and only 1 disease, "wet" age-related macular degeneration reported in 4 phase III trials. In the case reports, there were 21 different adverse events ascribed to bevacizumab and 2 to ranibizumab with retinal pigment epithelial tears being the most common.

Conclusion: Bevacizumab is one of the most far reaching drugs in ophthalmology and even medicine, but it is not yet supported by high quality evidence. The much higher cost of ranibizumab may be responsible for bevacizumab's popularity among eye specialists. Patients should be fully informed about the off-label use of bevacizumab and the associated risks with its use.

PMID: 22815647 [PubMed - as supplied by publisher]

Open Ophthalmol J. 2012;6:54-58. Epub 2012 Jun 25.

Controlled Release of Bevacizumab Through Nanospheres for Extended Treatment of Age-Related Macular Degeneration.

Li F, Hurley B, Liu Y, Leonard B, Griffith M.

Ottawa Hospital Research Institute, 501 Smyth Road, Ottawa, Ontario K1H8L6, Canada.

Abstract

Bevacizumab (Avastin(®)) has been used by ophthalmologists in many countries as an off-label drug for the treatment of wet age-related macular degeneration (AMD). Due to its short half-life necessitating frequent intravitreal injection, a method for sustained delivery is in need. We demonstrated that bevacizumab could be released in a sustained fashion over 90 days from nano- and microspheres fabricated from poly(DL-lactide-co-glycolide) and poly(ethylene glycol)-b-poly(D,L-lactic acid), respectively. The drug release rate could be adjusted by alteration of the drug/polymer ratio. The use of such nano- and microspheres as bevacizumab delivery vehicles may improve the treatment of wet AMD.

PMID: 22798970 [PubMed - as supplied by publisher] PMCID: PMC3394187

Mol Med Report. 2012 Jul 11. doi: 10.3892/mmr.2012.986. [Epub ahead of print]

Cell cycle regulation by bevacizumab in ARPE-19 human retinal pigment epithelial cells.

Kuo CN, Chen CY, Lai CH, Lai LJ, Wu PC, Hung CH, Chen CH.

Department of Ophthalmology, Chang Gung Memorial Hospital, Chiayi, Taiwan R.O.C.

Abstract

Bevacizumab, a recombinant humanized monoclonal antibody, binds vascular endothelial growth factor (VEGF) and inhibits its interaction with receptors found on endothelial cells. Bevacizumab has been increasingly used as an off-label treatment for exudative age-related macular degeneration (AMD). Whether or not bevacizumab is capable of arresting the growth of human retinal pigment epithelial cells remains to be clarified. In this study, flow cytometry was used to evaluate whether bevacizumab markedly induced the G1/S phase arrest. The G1/S phase cycle-related protein analysis demonstrated that the expression of cyclin-dependent kinase (CDK)2, 4 and 6 and of cyclin D and E, as well as the phosphorylation of retinoblastoma tumor suppressor protein (ppRB) production were found to be markedly reduced by bevacizumab. By contrast, the protein levels of p53, p16, p21 and p27 were increased in bevacizumab-treated ARPE-19 cells (a human retinal pigment epithelial cell line). These events of G1/S arrest induced by bevacizumab in ARPE-19 cells suggest that a preventive effect of bevacizumab exists in AMD.

PMID: 22798045 [PubMed - as supplied by publisher]

Aging (Albany NY). 2012 Jul 14. [Epub ahead of print]

Chemoprevention of age-related macular regeneration (AMD) with rapamycin.

Zheng XF.

Department of Pharmacology and the Cancer Institute of New Jersey, Robert Wood Johnson Medical School (RWJMS), Piscataway, NJ 08854 USA.

Comment on: Kolosova NG, Muraleva NA, Zhdankina AA, Stefanova NA, Fursova AZ, Blagosklonny MV. Prevention of Age-Related Macular Degeneration-Like Retinopathy by Rapamycin in Rats. Am J Pathol. 2012 Jun 7. Because diseases such as AMD are difficult to cure once they have developed, early chemoprevention is likely the best option. The findings that rapamycin prevents the progression of AMD in a more physiologically model provide a new hope for the high risk AMD population.

PMID: 22796653 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Jun;130(6):806-7.

Systemic and Ocular Risks Associated With Therapies for Macular Degeneration: Clarification vs Confusion.

Friberg TR, Shah V, Bilonick RA.

PMID: 22801854 [PubMed - in process]

Arch Ophthalmol. 2012 Jun;130(6):806-7.

Systemic and Ocular Risks Associated With Therapies for Macular Degeneration: Clarification vs Confusion-Reply.

Curtis LH, Hammill BG, Schulman KA, Cousins SW.

PMID: 22801855 [PubMed - in process]

Arch Ophthalmol. 2012 Jun;130(6):794-5.

Impact of availability of anti-vascular endothelial growth factor therapy on visual impairment and blindness due to neovascular age-related macular degeneration.

Campbell JP, Bressler SB, Bressler NM.

PMID: 22801846 [PubMed - in process]

Other treatment & diagnosis

Am J Public Health. 2012 Jul 19. [Epub ahead of print]

A Layered Approach to Raising Public Awareness of Macular Degeneration in Australia.

Heraghty J, Cummins R.

Australian Macular Degeneration Foundation, Sydney, Australia.

Abstract

Between 2007 and 2011, the Australian Macular Degeneration Foundation conducted a multifaceted campaign to increase public awareness of macular degeneration. Regular national polls conducted by an independent social research company have shown that awareness of macular degeneration increased from 47% to 80% in Australians aged 16 years or older and from 58% to 92% in those aged 50 years or older. The percentage of people aged 50 years or older who reported having had their macula checked in the 2 years prior to the survey increased from 33% to 70% from 2007 to 2011. Other measures, including analysis of Medicare data, have confirmed the success of the campaign. (Am J Public Health. Published online ahead of print July 19, 2012:e1-e5. doi:10.2105/AJPH.2012.300657).

PMID: 22813341 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 Jul 20. [Epub ahead of print]

Multimodal morphological and functional characterization of Malattia Leventinese.

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

Department of Ophthalmology, University Paris Est Creteil, Centre Hospitalier Intercommunal de Creteil, 40 Avenue de Verdun, 94000, Creteil, France, giuseppe.querques@hotmail.it.

BACKGROUND: To analyze the morphological and functional characteristics of malattia leventinese.

METHODS: This was a chart review of patients with Malattia Leventinese. All patients underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA), fundus autofluorescence (FAF), fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT). Microperimetry and Preferential Hyperacuity Perimeter (PHP) were performed in a subset of patients.

RESULTS: Twelve eyes of six patients were included. BCVA ranged from 20/25 to 20/200. The largest drusen were round, not radially distributed, localized in the perimacular area and around the optic disc. The smallest drusen were not round, radially distributed, mostly localized temporally to the macula. FAF revealed an intense autofluorescence of large drusen. On both FA and ICGA, large round drusen turned to hyperfluorescent in the late phase, while small radial drusen progressively decreased their fluorescence. OCT showed the large round drusen as focal or diffuse deposition of hyperreflective material between the RPE and Bruch membrane within the macula, determining focal dome-shaped or diffuse RPE elevation

respectively, and the small radial drusen, which ranged from irregular slight thickening of the RPE/Bruch membrane complex to sawtooth RPE elevation. In three patients (six eyes) that underwent microperimetry and PHP, there was a good correspondence between macular sensitivity and PHP score. Functional impairment correlated topographically to sub-RPE deposition of drusenoid material.

CONCLUSIONS: In this series, large round drusen of Malattia Leventinese appeared similar to drusen in age-related macular degeneration, while small radial drusen of Malattia Leventinese shared similarities with early-onset cuticular drusen.

PMID: 22814526 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Jun;130(6):690-9.

Role of flicker perimetry in predicting onset of late-stage age-related macular degeneration.

Luu CD, Dimitrov PN, Robman L, Varsamidis M, Makeyeva G, Aung KZ, Vingrys AJ, Guymer RH.

OBJECTIVE: To investigate the longitudinal changes in flicker perimetry in patients with age-related macular degeneration (AMD) as the condition progresses from early AMD to geographic atrophy (GA) or choroidal neovascularization (CNV).

METHODS: Patients with AMD and control subjects were recruited from a longitudinal study of retinal function in early AMD consisting of 187 participants. Only those who completed at least 4 consecutive, 6-monthly flicker perimetry tests were selected for this study. Study groups consisted of everyone who went on to develop GA (n = 16) or CNV (n = 5), controls (n = 24), and the high-risk, early- AMD participants whose eyes did not progress to GA or CNV (drusen >125 μm; n = 18). The flicker sensitivity was determined, and its rate of change during the 18 months before the clinical detection of late AMD was calculated.

RESULTS: Eyes that went on to develop GA or CNV had a significantly reduced mean (SD) flicker sensitivity in the months before clinical detection of GA (15.8 [5.6] dB) or CNV (19.1 [3.8] dB) compared with control eyes (22.9 [3.0] dB) (P < .001) and with eyes that did not progress to GA or CNV (21.4 [3.4] dB) (P < .001). The rate of change in flicker sensitivity was significantly increased in GA eyes (-0.07 dB/mo) (P < .001) but not in CNV eyes (0.006 dB/mo) (P = .56) compared with the control eyes (-0.003 dB/mo).

CONCLUSIONS: Flicker sensitivity is reduced in eyes that go on to develop late AMD. The rate of change in flicker sensitivities over time was particularly useful in predicting eyes and areas within the eye that subsequently develop GA.

PMID: 22801825 [PubMed - in process]

Neuron. 2012 Jul 12;75(1):26-39.

Mechanisms of age-related macular degeneration.

Ambati J, Fowler BJ.

Department of Ophthalmology & Visual Sciences, University of Kentucky, Lexington, KY 40506, USA; Department of Physiology, University of Kentucky, Lexington, KY 40506, USA.

Abstract

Age-related macular degeneration (AMD), a progressive condition that is untreatable in up to 90% of patients, is a leading cause of blindness in the elderly worldwide. The two forms of AMD, wet and dry, are

classified based on the presence or absence of blood vessels that have disruptively invaded the retina, respectively. A detailed understanding of the molecular mechanisms underlying wet AMD has led to several robust FDA-approved therapies. In contrast, there are no approved treatments for dry AMD. In this review, we provide insight into the critical effector pathways mediating each form of the disease. A recurring theme that spans most aspects of AMD pathogenesis is defective immune modulation in the classically immune-privileged ocular haven. Interestingly, the latest advances in AMD research also highlight common molecular disease pathways with other neurodegenerative disorders. Finally, the therapeutic potential of intervening at known mechanistic steps of AMD pathogenesis is discussed.

PMID: 22794258 [PubMed - in process]

Arch Soc Esp Oftalmol. 2012 Aug;87(8):247-252. Epub 2012 May 26.

Towards the new spectral-domain optical coherence tomography based classification of age-related macular degeneration.

[Article in English, Spanish]

Gallego-Pinazo R, Dolz-Marco R, Díaz-Llopis M.

Servicio de Oftalmología, Hospital Universitario y Politécnico La Fe, Valencia, España.

INTRODUCTION: Age-related macular degeneration (AMD) is major social and health problem in industrialised societies. The contribution of the new diagnostic techniques, mainly spectral-domain optical coherence tomography (SD-OCT), has led to a better understanding of this disease.

AIM: To review the current clinical classification of AMD, to describe the new tomographic classification of wet AMD, and to review the new topographical findings in dry AMD.

DEVELOPMENT: There are two classically described forms of AMD: dry and wet; there are also three progressive stages of severity: early, intermediate and advanced. This purely clinical stratification does not take into account any criteria based on SD-OCT. On the other hand, a new SD-OCT based classification has been proposed for choroidal neovascularisations secondary to AMD: types 1 (equivalent to occult), 2 (equivalent to classic), and 3 (equivalent to retinal angiomatous proliferation). Finally, SD-OCT offers exclusive and valuable information on the evaluation of dry AMD as regards subretinal drusenoid deposits, drusenoid pigment epithelium detachments, drusen coalescence, or the appearance of subretinal fluid in absence of choroidal neovascularisation.

CONCLUSIONS: Dry AMD exhibits a range of tomographical signs that also have their own relative risk of progression to advance stages of the disease. We need an international consensus in order to follow-up and treat in the best way all those patients with AMD, not only with the wet but also with the dry form.

PMID: 22794171 [PubMed - as supplied by publisher]

Ophthalmologe. 2012 Jul;109(7):665-9.

[Massive subretinal hemorrhage and anticoagulants : An unfortunate combination?].

[Article in German]

Kuhli-Hattenbach C, Miesbach W, Scharrer I, Hattenbach LO.

Klinik für Augenheilkunde, Johann Wolfgang Goethe-Universität, Theodor-Stern-Kai 7, 60590, Frankfurt am Main, Deutschland, kuhli@med.uni-frankfurt.de.

Abstract

Exudative age-related macular degeneration (ARMD) is one of the conditions which has been shown to be associated with a risk of massive subretinal hemorrhage. Patients with thick submacular hemorrhage complicating ARMD typically have a poor visual prognosis. Antiplatelet therapy with aspirin, clopidogrel or ticlopidine has significant benefits in the secondary prevention of fatal and non-fatal coronary and cerebrovascular events. Anticoagulation is frequently used in this elderly age group for a variety of other comorbidities including prosthetic heart valves, atrial fibrillation, ischemic heart disease, cerebrovascular disease and venous thromboembolism. However, it is a well established observation that the longer patients remain on anticoagulant therapy, the higher the cumulative risk of bleeding. Over the past years, there has been a rapidly growing body of literature concerning the risk of hemorrhagic ocular complications with ophthalmic surgery in patients receiving anticoagulant therapy. By contrast, there are still little data on the relationship between anticoagulation or antiplatelet therapy and spontaneous ocular hemorrhages and only few reports have focused on patients with ARMD. Just recently, several authors reported a strong association of anticoagulants and antiplatelet agents with the development of large subretinal hemorrhages in ARMD patients. Moreover, arterial hypertension is a high risk factor for large subretinal hemorrhages in ARMD patients receiving anticoagulants or antiplatelet agents. Physicians should be aware of an increased risk of extensive subretinal hemorrhage in ARMD patients when deciding on the initiation and duration of anticoagulant and antiplatelet therapy.

PMID: 22814925 [PubMed - in process]

Ophthalmologe. 2012 Jul;109(7):657-64.

[Subretinal surgery for massive hemorrhage].

[Article in German]

Szurman P.

Knappschafts-Augenklinik Sulzbach, An der Klinik 10, 66280, Sulzbach/Saar, Deutschland, Peter.Szurman@googlemail.com.

Abstract

Subretinal massive hemorrhage due to exsudative age-related macular degeneration remains a challenging field for submacular surgery. While small hemorrhages can be easily displaced by various pneumatic techniques the correct strategy for massive subretinal bleeding is still under debate. This article reviews the different techniques for these severe cases and assesses the visual prognosis and potential complications. In general, invasive techniques for extraction of the neovascular membrane with or without macular translocation or retinal pigment epithelium (RPE) choroidal patch translocation have the potential to achieve visual improvement. However, the risk of severe visual loss due to subsequent complications has to be considered. Far better visual results with a significantly lower complication rate can be achieved by a 2-step strategy using rTPA-assisted dissolution of the hemorrhage and evacuation of the liquefied clot via a small retinotomy.

PMID: 22814924 [PubMed - in process]

Ophthalmologe. 2012 Jul;109(7):635-43.

[Subretinal hemorrhage : Natural course and staging].

[Article in German]

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Abstract

Subretinal hemorrhages are a complication of various diseases which arise from the choroidal or retinal circulation. Most commonly the underlying pathology is a choroidal neovascular membrane (CNV) especially in patients with age-related macular degeneration (AMD). Less common ocular diseases are those with non-AMD-related CNV and retinal arterial macroaneurysms (RAM). Case studies have demonstrated a poor prognosis, however, a significant portion have favorable outcomes. Therefore, therapeutic decision-making is difficult. As a major difficulty in comparing different treatment modalities for submacular hemorrhages is the lack of a standardized definition of the extent of the hemorrhage. A classification for AMD-related subretinal hemorrhages including size, thickness and intraretinal location is suggested.

PMID: 22814923 [PubMed - in process]

Zhonghua Yan Ke Za Zhi. 2012 Mar;48(3):278-81.

[Study on preferred retinal locus].

[Article in Chinese]

Dai BF, Hu JM, Xu DL.

Department of Ophthalmology, the Second Affiliated Hospital of Fujian Medical University, Quanzhou 362000, China.

Abstract

Preferred retinal locus (PRL) is always found in the age-related macular degeneration and other macular damages in patients with low vision, and it is a very important anatomic position in patients with central vision impairment to achieve the rehabilitation. In recent years, the training of preferred retinal locus (PRL) has become a research hotspot of low vision rehabilitation, it can clearly improve functional vision and quality of life. The authors reviewed relevant literatures, and summarized the definition, position, characteristics, training and clinical implications of the PRL.

PMID: 22800427 [PubMed - in process]

Pathogenesis

Life Sci. 2012 Jul 11. [Epub ahead of print]

Nicotine and Pathological Angiogenesis.

Lee J, Cooke JP.

AIMS: This paper describes the role of endothelial nicotinic acetylcholine receptors (nAChR) in diseases where pathological angiogenesis plays a role.

MAIN METHODS: An extensive review of the literature was performed, focusing on studies that investigated the effect of nicotine upon angiogenesis.

KEY FINDINGS: Nicotine induces pathological angiogenesis at clinically relevant concentrations (i.e. at tissue and plasma concentrations similar to those of a light to moderate smoker). Nicotine promotes endothelial cell migration, proliferation, survival, tube formation and nitric oxide (NO) production in vitro, mimicking the effect of other angiogenic growth factors. These in vitro findings indicate that there may be an angiogenic component to the pathophysiology of major tobacco related diseases such as carcinoma,

atherosclerosis, and age-related macular degeneration. Indeed, nicotine stimulates pathological angiogenesis in pre-clinical models of these disorders. Subsequently, it has been demonstrated that nicotine stimulates nAChRs on the endothelium to induce angiogenic processes; that these nAChRs are largely of the α7 homomeric type; and that there are synergistic interactions between the nAChRs and angiogenic growth factor receptors at the phosphoproteomic and genomic levels.

SIGNIFICANCE: These findings are of potential clinical relevance, and provide mechanistic insights into tobacco-related disease. Furthermore, these findings may lead to novel therapies for diseases characterized by insufficient or inappropriate angiogenesis.

PMID: 22796717 [PubMed - as supplied by publisher]

Biochem Biophys Res Commun. 2012 Jul 13. [Epub ahead of print]

Cholesterol enhances amyloid β deposition in mouse retina by modulating the activities of Aβ - regulating enzymes in retinal pigment epithelial cells.

Wang J, Ohno-Matsui K, Morita I.

Department of Ophthalmology and Visual Science, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8519, Japan.

Abstract

Subretinally-deposited amyloid β (Aβ) is a main contributor of developing age-related macular degeneration (AMD). However, the mechanism causing Aβ deposition in AMD eyes is unknown. Hypercholesterolemia is a significant risk for developing AMD. Thus, we investigated the effects of cholesterol on Aβ production in retinal pigment epithelial (RPE) cells in vitro and in the mouse retina in vivo. RPE cells isolated from senescent (12-month-old) C57BL/6 mice were treated with 10 μg/ml cholesterol for 48 hours. Aβ amounts in culture supernatants were measured by ELISA. Activity and expression of enzymes and proteins that regulate Aβ production were examined by activity assay and real time PCR. The retina of mice fed cholesterol-enriched diet was examined by transmission electron microscopy. Cholesterol significantly increased Aβ production in cultured RPE cells. Activities of Aβ degradation enzyme; neprilysin (NEP) and anti-amyloidogenic secretase; α -secretase were significantly decreased in cell lysates of cholesterol-treated RPE cells compared to non-treated cells, but there was no change in the activities of β- or γ-secretase. mRNA levels of NEP and α -secretase (ADAM10 and ADAM17) were significantly lower in cholesterol-treated RPE cells than non-treated cells. Senescent (12-month-old) mice fed cholesterol-enriched chow developed subRPE deposits containing Aβ, whereas age-matched mice fed standard rodent chow diet did not. Activities and mRNA levels of NEP and α -secretase were significantly lower in native RPE cells freshly isolated from cholesterol-enriched chow fed mice compared to standard rodent chow fed mice. These findings suggest that cholesterol enhances subretinal Aβ accumulation by modulating the activities of enzymes degrading and processing Aβ in RPE cells in senescent subjects.

PMID: 22796523 [PubMed - as supplied by publisher]

PLoS One. 2012;7(7):e39890. Epub 2012 Jul 3.

Low-Dose Lipopolysaccharide Pretreatment Suppresses Choroidal Neovascularization via IL-10 Induction.

Matsumura N, Kamei M, Tsujikawa M, Suzuki M, Xie P, Nishida K.

Department of Ophthalmology, Osaka University Graduate School of Medicine, Osaka, Japan.

Abstract

Recent studies have suggested that some kinds of microbial infection may have a crucial role in the development of many diseases such as autoimmune diseases and certain types of cancer. It has been reported that some chronic infections, such as Chlamydia pneumoniae, and immunological dysfunctions are associated with age-related macular degeneration (AMD), a leading cause of blindness. To evaluate the association between systemic low-level inflammation induced by infection and AMD pathogenesis, we investigated whether intraperitoneal injection of lipopolysaccharide (LPS) can modulate the development of laser-induced choroidal neovascularization (CNV), a key feature of AMD. Contrary to our expectations, the sizes of CNV in mice with LPS pretreatment were approximately 65% smaller than those of the control mice. After LPS pretreatment, serum IL-10 concentration and IL-10 gene expression in peritoneal macrophages and in the posterior part of the eye increased. Peritoneal injection of anti-IL10 antibody reduced CNV suppression by LPS pretreatment. Moreover, adoptive transfer of the resident peritoneal macrophages from LPS-treated mice into control littermates resulted in an approximately 26% reduction in the size of CNV compared with PBS-treated mice. We concluded that CNV formation was suppressed by low-dose LPS pretreatment via IL-10 production by macrophages.

PMID: 22802947 [PubMed - in process] PMCID: PMC3388993

Biochim Biophys Acta. 2012 Jul 13. [Epub ahead of print]

Role of sphingosine 1-phosphate and lysophosphatidic acid in fibrosis.

Pyne NJ, Dubois G, Pyne S.

Cell Biology Group, Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE.

Abstract

This review highlights an emerging role for sphingosine 1-phosphate (S1P) and lysophosphatidic acid (LPA) in many different types of fibrosis. Indeed, both LPA and S1P are involved in the multi-process pathogenesis of fibrosis, being implicated in promoting the well-established process of differentiation of fibroblasts to myofibroblasts and the more controversial epithelial-mesenchymal transition and homing of fibrocytes to fibrotic lesions. Therefore, targeting the production of these bioactive lysolipids or blocking their sites/mechanisms of action has therapeutic potential. Indeed, LPA receptor 1 (LPA(1)) selective antagonists are currently being developed for the treatment of fibrosis of the lung as well as a neutralising anti-S1P antibody that is currently in Phase 1 clinical trials for treatment of age related macular degeneration. Thus, LPA- and S1P-directed therapeutics may not be too far from the clinic.

PMID: 22801038 [PubMed - as supplied by publisher]

Genetics

Am J Ophthalmol. 2012 Jul 16. [Epub ahead of print]

Association of ARMS2 Genotype With Bilateral Involvement of Exudative Age-Related Macular Degeneration.

Tamura H, Tsujikawa A, Yamashiro K, Akagi-Kurashige Y, Nakata I, Nakanishi H, Hayashi H, Ooto S, Otani A, Yoshimura N.

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PURPOSE: To study the association of ARMS2 A69S genotype with the development of exudative age-

related macular degeneration (AMD) in the unaffected fellow eye and to estimate the duration until the development of AMD in the second eye.

DESIGN: Retrospective cohort study.

METHODS: We retrospectively reviewed 326 patients who had exudative AMD in at least 1 eye, genotyping of ARMS2 A69S, and a minimum follow-up of 2 years. Survival analysis and Cox proportional hazard regression analysis were used to examine the association between candidate factors and the duration until the development of AMD in the second eye.

RESULTS: One hundred nineteen patients (36.5%) had bilateral exudative AMD at the initial visit. A risk allele of ARMS2 A69S was more frequently seen in patients with bilateral AMD (P = .0270) than in those with unilateral AMD. Of the 207 unilateral AMD patients, 23 (11.1%) had AMD in the fellow eye after a mean duration of 56.3 ± 40.4 months. Fellow-eye involvement was associated with ARMS2 A69S genotype (hazard ratio [HR], 2.673; P = .0013), age (HR, 1.102; P = .0005), and smoking history (HR, 0.680; P = .3663). As HRs indicate, correlation of genotype (2.673) was as high as that of 10-year aging (1.102(10) = 2.641). Survival analysis revealed that patients with risk homozygous (TT) genotype had second-eye involvement significantly earlier than those with other genotypes (P = .0028). When the observation duration reached 120 months, second-eye involvement had developed in 50%, 6.6%, and 11.2% of the TT, GT, and GG cohorts, respectively.

CONCLUSION: ARMS2 A69S genotype is associated with second-eye involvement of exudative AMD and with the period between first- and second-eye involvements.

PMID: 22809783 [PubMed - as supplied by publisher]

Mol Vis. 2012;18:1787-93. Epub 2012 Jun 30.

COL1A2 polymorphic markers confer an increased risk of neovascular age-related macular degeneration in a Han Chinese population.

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PURPOSE: We have previously documented that neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) have multiple different clinical and genetic characteristics. In this study, we investigated the association of rs42524 in the alpha-2 type I collagen (COL1A2) gene, which has been identified as a risk variant for intracranial aneurysm, with nAMD and PCV in a Han Chinese population.

METHODS: The study prospectively recruited 195 patients with PCV, 136 patients with nAMD, and 181 control individuals. We genotyped the rs42524 polymorphism of COL1A2 using the Multiplex SNaPshot System and direct DNA sequencing. Genotype and allele frequencies were evaluated with PLINK software.

RESULTS: The rs42524 polymorphism was modestly significantly associated with nAMD [minor allele: G, p (allelic)=0.04253, odds ratio=0.5285 (95% confidence interval: 0.2832-0.9866)], but not with PCV [minor allele: G, p(allelic)=0.4164, odds ratio=1.2110 (95% confidence interval: 0.7631-1.9210)]. The pvalues for the additive model were significant for nAMD but not for the dominant or recessive models. None of the models for PCV were statistically significant. The size of our sample cohort resulted in a post hoc power of more than 80% to detect associations of rs42524 with nAMD and PCV.

CONCLUSIONS: The rs42524 polymorphism is a risk allele for nAMD in a Han Chinese population. rs42524 in COL1A2 confers different levels of susceptibility to nAMD and PCV.

PMID: 22815632 [PubMed - in process]

Zhonghua Yan Ke Za Zhi. 2012 Mar;48(3):241-5.

[Interaction of susceptibility genes in patients with exudative age-related macular degeneration].

[Article in Chinese]

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OBJECTIVE: To determine the interaction of susceptibility genes in patients with exudative age-related macular degeneration (AMD) in a Chinese case-control cohort.

METHODS: It was a case-control study. Six single nucleotide polymorphisms (SNPs) previousely genotyped in cases with exudative AMD and control indivisuals, including complement factor H (CFH) non-coding variant rs1410996, CFH rs1061170 (Y402H), LOC387715 rs10490924, C3 rs2230199 (R102G), C3 rs1047286 (P314L), and HTRA1 rs11200638, were selected for analyzing the interactions among susceptibility genes. The numerical data were examined by Student t test. The genotype distributions between cases and controls were compared using the Chi2 test. Genetic interactions were examined using logistic regression model and synergy index (SI) value based on crossover analysis table.

RESULTS: A total of 150 cases with exudative AMD (88 male, 62 female) and 161 control individuals (84 male, 77 female) were included in this study. There was no significant difference in age (t = 0.91, P = 0.37) or gender (Chi2 = 1.32, P = 0.25) between the AMD cases and the controls. SNPs associated with the risk of exudative AMD included CFH non-coding variant rs1410996 (Chi2 = 17.83, P < 0.05), LOC387715 rs10490924 (Chi2 = 17.71, P < 0.05) and HTRA1 rs11200138 (Chi2 = 2.77, P < 0.05). No interaction was observed between CFH rs1410996 and LOC387715 rs10490924 (logistic regression, P = 0.41; SI = 1.04, P = 0.45) or between CFH rs1410996 and HTRA1 rs 11200138 (logistic regression, P = 0.91; SI = 1.42, P = 0.17).

CONCLUSION: The data suggest that LOC387715 rs10490924 / HTRA1 rs11200138 and CFH rs1410996 are independently associated with the risk of exudative AMD in Chinese.

PMID: 22800422 [PubMed - in process]

Epidemiology

Invest Ophthalmol Vis Sci. 2012 Jul 19. [Epub ahead of print]

Genetic, behavioral and sociodemographic risk factors for second eye progression in age-related macular degeneration.

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PURPOSE: This study was conducted to investigate the correlation of genetic, sociodemographic and behavioral risk factors with second eye progression to end-stage age-related macular degeneration (AMD).

METHODS: One hundred-eight patients with end-stage AMD in one or both eyes were included in a retrospective time-to-event analysis of the onset of end-stage AMD in the second eye. Multivariate Cox regression survival analysis was performed for gender, age, smoking, body mass index (BMI), education and sixteen single nucleotide polymorphisms (SNPs) associated with AMD.

RESULTS: Except for education, all analyzed sociodemographic and behavioral risk factors were

significantly associated with a more rapid progression towards second eye involvement. Hazard ratios (HRs) were 2.6 (95% confidence interval [CI], 1.4-5.0) for female gender, 5.0 (95% CI, 2.0-12.5) for age >80, 2.2 (95% CI, 1.1-4.1) for BMI >30, and 4.4 (95% CI, 1.4-14.3) for >40 pack years, compared to the referent groups. Carriers of the Lipoprotein lipase (LPL) (rs12678919) risk alleles were at risk for more rapid progression to end-stage AMD in the second eye compared to the referent wild-type genotype (HR 2.0 ; 95% CI, 1.0-3.6). For Complement factor I (CFI) (rs10033900), homozygous carriers of the risk allele progressed faster than wild-type individuals (HR 2.2 ; 95% CI, 1.1-4.3).

CONCLUSIONS: Sociodemographic, behavioral and genetic risk factors are associated with the rate of second eye progression towards end-stage AMD. The findings of this study underline the importance of lifestyle factors and the complement pathway in AMD progression and suggest a role of the high-density-lipoprotein-metabolism in second eye progression.

PMID: 22815349 [PubMed - as supplied by publisher]

Zhonghua Yan Ke Za Zhi. 2012 Mar;48(3):196-8.

[How to develop molecular epidemiology in conventional epidemiology survey on eye diseases in China].

[Article in Chinese]

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Abstract

Molecular epidemiology is a new branch of eye epidemiology that combines theories and methods in both epidemiology and molecular biology. The definition of molecular epidemiology is to use biological and, in particular, genetic markers (nucleic acid, protein) as measures for detecting the propensity of a disease developing, or as an indicator of a disease or an exposure in the studies of disease distribution. Molecular epidemiology has the same objectives as conventional ophthalmic epidemiology in a defined population. The main designs used in ophthalmic molecular epidemiology include descriptive study, case control study, and nested case control study. Currently, molecular experimental techniques mainly include single nucleotide polymorphism, ELISA, protein and mRNA array, microRNA and the study of epigenetic markers. Gene susceptibility biomarker is one of the most commonly used molecular markers. The findings of ophthalmic molecular epidemiology studies can be used to design personalized therapy. Undoubtedly, ophthalmic molecular epidemiology will evolve and develop in the new era for the prevention and control of complex eye diseases such as age-related macular degeneration, cataract, glaucoma and diabetic retinopathy.

PMID: 22800415 [PubMed - in process]