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MD Research News

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Drug treatment

BioDrugs. 2011 Jun 1;25(3):171-89. doi: 10.2165/11589330-000000000-00000.

Neovascular Age-Related Macular Degeneration: Opportunities for Development of First-in-Class Biopharmaceuticals.

Schiffelers RM, van der Vaart TK, Storm G.

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Abstract

Age-related macular degeneration (AMD) is a condition that may cause blindness. The prevalence of the disease in the Western world is estimated at 1-2% of the population. Over the past decade, treatment of neovascular AMD has been shifting from destruction of newly formed blood vessels towards inhibitors that silence the vascular endothelial growth factor (VEGF) pathway. Such agents are often first-in-class biopharmaceuticals that benefit from the fact that they can be locally administered in an immune-privileged environment with slow clearance. These new VEGF pathway inhibitors have improved therapeutic effects over conventional treatment and have promoted the identification of novel targets for inhibition of AMD angiogenesis. This review describes the rationale behind the shift from conventional to current treatment options and discusses investigational, most notably biopharmaceutical, drugs that are in clinical trials. It also provides possible points for improvement of these treatments, specifically regarding their delivery.

PMID: 21627341 [PubMed - in process]

Curr Med Res Opin. 2011 May 31. [Epub ahead of print]

A systematic review of the efficacy and safety outcomes of anti-VEGF agents used for treating neovascular age-related macular degeneration: comparison of ranibizumab and bevacizumab.

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Objective: To systematically review ocular and systemic events in treatment of wet age-related macular degeneration (AMD) with anti-vascular endothelial growth factor antibodies, ranibizumab and bevacizumab, and to provide a detailed perspective of their differences on clinical use, efficacy and safety.

Research design and methods: This review was based on a 2010 PubMed literature search performed using two separate terms: 'lucentis' OR 'ranibizumab' AND 'age-related macular degeneration' OR 'AMD' or 'avastin' OR 'bevacizumab' AND 'age-related macular degeneration' OR 'AMD'. A clinical diagnosis of wet AMD was defined by the authors of the trial reports. Clinical studies that met Level I or Level II evidence criteria were considered for review.

Findings: Eight large, randomized, controlled trials of ranibizumab (Level I) included 1485 patients (range 162-716) and four open-label studies of ranibizumab (Level II) included 4484 patients (range 32-4300). Six studies (one Level I, five Level II) of bevacizumab included 424 patients (range 28-165). All demonstrated improvements in visual acuity. Only one study (Level II) compared the efficacy of ranibizumab and bevacizumab. Adverse ocular and systemic safety events occurring during the study were prospectively recorded for ranibizumab, irrespective of their suspected relationship to study treatments. Only three of six bevacizumab studies reported details of adverse ocular or systemic events. There was extensive Level I and Level II evidence to support both the efficacy and safety of ranibizumab in wet AMD. Data suggest that bevacizumab provides efficacy in wet AMD, but the safety profile of intravitreal bevacizumab remains to be established.

Conclusion: In contrast to ranibizumab, current safety data for bevacizumab are incomplete and not yet robust. If the medical community remains committed to using intravitreal bevacizumab, it is critical to establish that it has an acceptable safety profile, supported by evidence-based medicine. Considerable further research is warranted to achieve this.

PMID: 21623685 [PubMed - as supplied by publisher]

Expert Opin Drug Metab Toxicol. 2011 Jun 1. [Epub ahead of print]

Toxicological considerations for intravitreal drugs.

Penha FM, Rodrigues EB, Furlani BA, Dib E, Melo GB, Farah ME.

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Introduction: Intravitreal injections are a very common procedure and are the most effective route of drug delivery to the retina. There are currently several drugs available and even more are in development; therefore, safety is a very important concern.

Areas covered: The toxicological considerations of the most common drugs used for intravitreal pharmacotherapy such as anti-VEGFs, corticosteroids and antibiotics. Emerging agents such as anti-TNFs, VEGF-trap and kinase inhibitors are also discussed. An assessment of the efficacy and safety issues of the most relevant drugs including bevacizumab, ranibizumab and triamcinolone is presented.

Expert opinion: The toxicology and safety profiles are available for several drugs that are either in use or will be available for intravitreal injections. Retinal pharmacotherapy is very effective for different retinal diseases; however safety is a very important issue when intravitreal injections are applied and the possibility of retinal toxicity should always be kept in mind. Bevacizumab and ranibizumab are effective for the therapy of wet-age-related macular degeneration and macular edema, while triamcinolone remains an alternative agent to treat secondary macular edema. It is important, as some of these drugs will be used for extended periods of time, that their long-term toxicological effects are better understood.

PMID: 21627546 [PubMed - as supplied by publisher]

J Ocul Pharmacol Ther. 2011 Jun 1. [Epub ahead of print]

Comparison of Intravitreal Bevacizumab and Ranibizumab Treatment for Diabetic Macular Edema.

Ozturk BT, Kerimoglu H, Bozkurt B, Okudan S.

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Aim: The aim of this study was to compare the effects of bevacizumab and ranibizumab on visual function and macular thickness in patients with diabetic macular edema (DME).

Methods: The data of diabetic patients who had been treated with bevacizumab for DME were reviewed. Those patients who received 1 injection of intravitreal bevacizumab and ranibizumab with at least 6-month interval were considered for enrollment. The best-corrected visual acuity (BCVA) assesment with Early Treatment Diabetic Retinopathy Study (ETDRS) chart and central subfield macular thickness (CSMT) measurement using optical coherence tomography-3 before and after the injections were recorded as outcome measures.

Results: The study included 29 eyes of 29 patients with a mean age of 56.18±13.07 years. The median BCVA was 59 ETDRS letters and the median CSMT was 411 µm preceeding the bevacizumab injection. At the 4th-6th week control after the injection, median BCVA increased to 61.50 ETDRS letters and the median CSMT decreased to 373 µm. This change in BCVA and CSMT was found to be statistically significant (P=0.029 and P=0.011, respectively). The mean interval between bevacizumab and ranibizumab treatment was 9.54±2.64 months. Ranibizumab treatment increased the median BCVA from 53 to 66 ETDRS letters and decreased the median CSMT from 428 µm to a level of 279 µm, which were statistically significant (P<0.001 and P<0.001, respectively). The median change in BCVA was 4.5 ETDRS letters in the bevacizumab group and 6 ETDRS letters in the ranibizumab group (P=0.58), whereas the median changes in CSMT were 41 and 100 µm after bevacizumab and ranibizumab injections, respectively (P=0.005).

Conclusions: Bevacizumab and ranibizumab are both effective antivascular endothelial growth factor drugs preferred in the treatment of DME. Our comparison of both therapies on the same patients suggested that the effect on BCVA was not statistically different, but ranibizumab provided more decrease in CSMT.

PMID: 21631366 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2011 Apr 18. doi: 10.1111/j.1442-9071.2011.02580.x. [Epub ahead of print]

Intravitreal ranibizumab for choroidal neovascularization associated with circumscribed choroidal hemangioma.

Querques G, Forte R, Querques L, Souied EH.

Department of Ophthalmology, Hopital Intercommunal de Creteil, University Paris XII, France.

PMID: 21631680 [PubMed - as supplied by publisher]

JAMA. 2011 May 25;305(20):2053-4.

Cancer drug offers effective, cheaper option for AMD.

Stephenson J.

PMID: 21610231 [PubMed - indexed for MEDLINE]

Other treatment & diagnosis

Invest Ophthalmol Vis Sci. 2011 May 27. [Epub ahead of print]

Nicotine increases VEGF/PEDF ratio in retinal pigment epithelium: a possible mechanism for CNV in passive smokers with AMD.

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Purpose: Cigarette smoking is the strongest environmental risk factor for wet age-related macular degeneration (AMD). Inappropriate expression of pro-angiogenic vascular endothelial growth factor (VEGF) and anti-angiogenic pigment epithelium derived factor (PEDF) may cause choroidal neovascularization (CNV), key event of wet AMD resulting in vision loss. Nicotine (NT), a potent angiogenic agent abundant in second hand smoke, may play a major role in the pathogenesis of wet AMD. The purpose of this study was to evaluate the expression of nicotinic acetylcholine receptors (nAchR) in retinal pigment epithelium (RPE) and determine the effects of NT on RPE-derived VEGF and PEDF expression in the context of passive smoking.

Methods: Human RPE cells were treated with NT (10(-8)M) with or without nAchR non specific antagonist hexamethonium (HXM) (10(-5)M) for 72 hours. RPE sheets were microdissected from rats exposed to NT in drinking water (100 µg/mL) with or without HXM (40 mg/kg/day, intraperitoneal) for 72 hours. Cell death was determined by cell count and proliferation by Western blot for PCNA. nAchR expression was examined by real-time PCR and Western blot. ERK activation was evaluated by Western blot analysis. VEGF and PEDF expression was assessed by ELISA, Western blot and real-time PCR.

Results: Cultured RPE cells constitutively express nAchR α3, α10 and β1 subunits, β1 being most prevalent. nAchR α4, α5, α7 and β2 subunits were detected in RPE sheets from rats, among which α4 is the predominant subtype. NT which did not result in either cell death or proliferation, induced β1 nAchR, upregulated VEGF and downregulated PEDF expression through nAChR in ARPE-19 cells. Transcriptional activation of nAchR α4 subunit and nAChR-mediated upregulation of VEGF and PEDF were observed in RPE from rats exposed to NT.

Conclusion: NT increased VEGF-to-PEDF ratio in RPE through nAchR in vitro and in vivo which may play a key role in the progression to wet AMD in passive smokers.

PMID: 21622701 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011;5:705-13. Epub 2011 May 24.

Treatment of macular edema due to retinal vein occlusions.

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Abstract

Retinal vein occlusion (RVO) is a prevalent retinal vascular disease, second only to diabetic retinopathy. Previously there was no treatment for central retinal vein occlusion (CRVO) and patients were simply observed for the development of severe complications, generally resulting in poor visual outcomes. The only treatment for branch vein occlusion (BRVO) was grid laser photocoagulation, which reduces edema very slowly and provides benefit in some, but not all patients. Within the past year, clinical trials have

demonstrated the effects of three new pharmacologic treatments, ranibizumab, triamcinolone acetonide, and dexamethasone implants. The benefit/risk ratio is best for intraocular injections of ranibizumab, making this first-line therapy for most patients with CRVO or BRVO, while intraocular steroids are likely to play adjunctive roles. Standard care for patients with RVO has changed and will continue to evolve as results with other new agents are revealed.

PMID: 21629578 [PubMed - in process]

PMCID: PMC3104801

J Am Med Dir Assoc. 2011 May 27. [Epub ahead of print]

Vision in the Global Evaluation of Older Individuals Hospitalized Following a Fall.

Boutin T, Kergoat MJ, Latour J, Massoud F, Kergoat H.

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INTRODUCTION: The objective of this study was to verify if vision is appropriately evaluated in older individuals admitted to a Geriatric Assessment Unit following a fall.

METHODS: A retrospective clinical chart review of 158 patients from 3 university-based Geriatric Assessment Units is presented. The clinical charts of patients admitted following a fall in the Geriatric Assessment Units of 3 Montreal hospitals, between April 2006 and 2008, were reviewed. Clinical charts from age- and sex-matched controls hospitalized in the Geriatric Assessment Units during the same period but without a history of fall or fracture, were also reviewed. Pertinent sociodemographic, medical, and visual characteristics were extracted from the charts and entered into a database for analysis.

RESULTS: The mean age ± standard deviation for the cases (n = 79) and controls (n = 79) were 82.3 ± 6.2 years and 81.7 ± 6.4 years, respectively. Most falls were not a result of accidents, but rather were more often related to underlying medical problems that were multifactorial in origin. More cases than controls were taking antiarrhythmic and antidepressant medications, whereas more controls were taking calcium channel blockers. Cases were more likely to have cataracts, age-related macular degeneration, and decreased visual acuity. Although cases were referred more often than controls for an eye examination, they were not referred in a systematic fashion.

DISCUSSION: Our results indicate that more visual problems are identified in persons who fall and, even if they are referred more often than controls for an eye examination, their vision is not evaluated systematically by an eye care specialist despite current clinical recommendations.

CONCLUSION: These data indicate that eye care professionals should work more closely with the medical team to improve the overall clinical care of older individuals with a history of falls.

PMID: 21621474 [PubMed - as supplied by publisher]

Med Sci Monit. 2011 Jun 1;17(6):CS75-79.

Severe decrease in visual acuity with choroidal hypoperfusion after photodynamic therapy.

Figurska M, Wierzbowska J, Robaszkiewicz J.

Department of Ophthalmology, Military Medical Institute, Warsaw, Poland.

Background: Photodynamic therapy (PDT) is considered a selective method of treatment which works in areas of choroidal neovascularization (CNV); however, there are reports of choroidal hypoperfusion after PDT. This paper presents a clinical case of choroidal circulation disturbances caused by PDT,

accompanied by CNV progression.

Case Report: The patient, a 75-year-old woman, was qualified for PDT in the right eye - first treatment due to progression of occult CNV. Best corrected visual acuity (BCVA) in the right eye at baseline was +0.3 logMAR. After PDT, a rapid decrease in visual acuity to +0.7 logMAR in the right eye was observed, central choroidal hypoperfusion in fluorescein angiography (FA) with subretinal fluid appeared and, as a consequence, progression of neovascular age-related macular degeneration (AMD). After stabilizing the local state through conservative therapy, a decision was made to treat the right eye with intravitreal injections of vascular endothelial growth factor (VEGF) inhibitor. During a 12-month period of observation, 7 doses of ranibizumab were administered. A regression in activity of wet AMD was observed, with visual acuity of +0.6 logMAR.

Conclusions: Choroidal circulation disturbance after PDT is possible and has to be taken into account. Sporadically, it can lead to an acute decrease in visual acuity and local state. After stabilization of AF and optical coherence tomography imaging, further treatment of neovascular AMD with intravitreal injections of anti-VEGF agents should be considered.

PMID: 21629194 [PubMed - in process]

Acta Ophthalmol. 2011 Jun 1. doi: 10.1111/j.1755-3768.2011.02144.x. [Epub ahead of print]

Outer retinal cysts in age-related macular degeneration.

Wolff B, Maftouhi MQ, Mateo-Montoya A, Sahel JA, Mauget-Faÿsse M.

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Purpose: To describe novel cystic structures ('outer retinal cysts' or ORC) found in the outer retina in age-related macular degeneration (AMD).

Methods: One hundred and seventy-three consecutive eyes of 88 AMD patients were prospectively examined with spectral domain optical coherence tomography (SD-OCT). The prevalence of ORCs was searched, and their sizes and shapes were determined.

Results: SD-OCT revealed round or ovoid, intraretinal, hyporeflective cystic structures with a hyperreflective border in 60 eyes (56%) with neovascular AMD and in six eyes (21%) with atrophic AMD. These cystic structures were of different sizes and shapes. They remained stable in all the patients after a follow-up period of 6 months.

Conclusions: Outer retinal cyst is a new type of cystic structure recently identified in AMD patients. ORCs should not be confused with intraretinal exudates or cystoid cavities and therefore do not require any treatment. The histopathological nature of ORC remains to be determined. Further studies are necessary to determine their true origin.

PMID: 21631905 [PubMed - as supplied by publisher]

Rev Prat. 2011 Feb;61(2):159-64.

[Macular degeneration age-related].

[Article in French]

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Abstract

Age-related macular degeneration (ARMD) is a multifactorial disease caused by a combination of genetic and environmental factors. It is the first cause of blindness in patients over 50 in the western world. The disease has been traditionally classified into early and late stages with dry (atrophic) and wet (neovascular) forms: neovascular form is characterized by new blood vessels development under the macula (choroidal neovascularisation) which lead to a rapid decline of vision associated with metamorphopsia and requiring an urgent ophtalmological examination. Optical coherence tomography is now one of the most important part of the examination for diagnosis and treatment. Patient with age related maculopathy should consider taking a dietary supplement such that used in AREDS. The treatment of the wet ARMD has largely beneficied since year 2006 of anti-VEGF (vascular endothelial growth factor) molecules such as ranibizumab or bevacizumab given as repeated intravitreal injections. A systematic follow up each 4 to 8 week in required for several years. There is no effective treatment at the moment for dry AMD. For patients with binocular visual acuity under 60/200 rehabilitation includes low vision specialist, vision aids and psychological support.

PMID: 21618758 [PubMed - in process]

Epidemiology & pathogenesis

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

Prevalence and Causes of Visual Impairment and Blindness in an Urban Indian Population The Singapore Indian Eye Study.

Zheng Y, Lavanya R, Wu R, Wong WL, Wang JJ, Mitchell P, Cheung N, Cajucom-Uy H, Lamoureux E, Aung T, Saw SM, Wong TY.

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PURPOSE: To describe the prevalence and causes of visual impairment and blindness in an urban Indian population.

DESIGN: Population-based study.

PARTICIPANTS: Ethnic Indians aged more than 40 years living in Singapore.

METHODS: Participants underwent standardized ophthalmic assessments for visual impairment and blindness, defined using best-corrected visual acuity (BCVA) and presenting visual acuity (PVA), according to US and modified World Health Organization (WHO) definitions.

MAIN OUTCOME MEASURES: Unilateral visual impairment or blindness was defined on the basis of the worse eye, and bilateral visual impairment or blindness was defined on the basis of the better eye. Primary causes of visual impairment were determined.

RESULTS: A total of 3400 eligible individuals (75.6% response rate) participated. On the basis of US definitions, the age-standardized prevalence was 0.4% for bilateral blindness (≤20/200, better eye) and 3.4% for bilateral visual impairment (<20/40 to >20/200, better eye). Another 0.3% of bilateral blindness and 13.4% of bilateral visual impairment were correctable with refraction. Cataract was the principal cause of best-corrected bilateral blindness (60.0%) and bilateral visual impairment (65.7%). Other major causes of blindness and visual impairment included diabetic retinopathy, age-related macular degeneration, glaucoma, corneal opacity, and myopic maculopathy.

CONCLUSIONS: The prevalence of bilateral blindness and visual impairment in Indians living in Singapore is lower than estimates from populations living in India, but similar to estimates obtained from Singapore

Malay and Chinese populations. Cataract is the leading cause of blindness and visual impairment. One in 20 cases of bilateral blindness and 1 in 10 cases of bilateral visual impairment are attributable to diabetic retinopathy. These data may have relevance to many ethnic Indian persons living outside India.

PMID: 21621261 [PubMed - as supplied by publisher]

Clin Experiment Ophthalmol. 2011 Apr 18. doi: 10.1111/j.1442-9071.2011.02572.x. [Epub ahead of print]

Mannose-binding lectin as part of the complement pathway: characterisation in non-inflamed and inflamed human eyes.

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Background: Mannose-binding lectin (MBL) plays a central effector role in the lectin pathway of complement activation. Frequently occurring MBL2 polymorphisms result in MBL deficiency, which has been shown to increase susceptibility to infection. MBL2 was also recently implicated in a genome wide association study for age-related macular degeneration subtypes. We characterised MBL levels and function in non-inflamed and inflamed human eyes, and evaluated its relationship to blood MBL levels and function.

Design: Prospective, observational clinical study with controls and cases.

Participants: Twenty-seven patients with paired blood and ocular samples (aqueous and/or vitreous) including 15 controls (non-inflamed) and 12 cases (inflamed).

Methods: Blood and ocular samples were collected from controls (n = 15) with quiet eyes during elective cataract surgery and cases with inflamed eyes including proven/suspected endophthalmitis (n = 11) and herpetic retinal vasculitis (n = 1). Mannan binding and C4 deposition enzyme-linked immunosorbent assays (ELISA) were used to quantify MBL levels and function.

Main Outcome Measures: Blood and ocular MBL levels and function.

Results: Of 27 patients, ten (37%) were MBL deficient (defined as blood MBL levels <500ng/ml). Blood MBL levels ($p = 0.16$) or function ($p = 0.43$) were not significantly different between controls and cases. As expected, there was a high correlation between blood MBL levels and function ($r(2) = 0.74$). However, there was significantly more MBL in inflamed eyes than non-inflamed eyes measured as level ($p < 0.01$) or C4 deposition function ($p < 0.01$).

Conclusions: Our study demonstrated that MBL is significantly elevated in inflamed human eyes but virtually undetectable in non-inflamed control eyes, suggesting a role in sight-threatening ocular inflammation.

PMID: 21631672 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2011 Jun 1. [Epub ahead of print]

C-reactive protein and complement factor H in aged human eyes and eyes with age-related macular degeneration.

Bhutto IA, Baba T, Merges C, Juriasinghani V, McLeod DS, Lutty GA.

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Background: There is increasing evidence that inflammation and immune-mediated processes (complement activation) play an important role in age-related macular degeneration (AMD) pathogenesis. A genetic variation in the gene encoding complement factor H (CFH) and plasma levels of C-reactive protein (CRP), a systemic marker of subclinical inflammation, have consistently been shown to be associated with an increased risk for AMD. In the present study, we examined the immunolocalisation of CRP and CFH in aged control human donor eyes (n=10; mean age 79 years) and eyes with AMD (n=18; mean age 83 years).

Methods: Alkaline phosphatase immunohistochemistry was performed using polyclonal antibodies against CRP and CFH on cryopreserved tissue sections from disc/macular blocks. Three independent masked observers scored the reaction product (0-8).

Results: In aged control eyes, the retinal pigment epithelium/Bruch's membrane/choriocapillaris (RPE/BrM/CC) complex including intercapillary septa (ICS) had the most prominent immunostaining for CRP and CFH. CRP was significantly higher than controls in BrM/CC/ICS and choroidal stroma in early and wet AMD eyes ($p<0.05$). In contrast, CFH was significantly lower in BrM/CC/ICS complex of AMD choroids than in controls ($p<0.05$). Interestingly, CRP and CFH were significantly reduced in BrM/CC/ICS complex in atrophic area of macula in geographical atrophy ($p<0.05$). Drusen and basal laminar deposits were intensely positive for CRP and CFH.

Conclusion: These immunohistochemical findings show that changes in distribution and relative levels of CRP and CFH were evident in early and late AMD eyes. This suggests that high levels of CRP and insufficient CFH at the retina/choroid interface may lead to uncontrolled complement activation with associated cell and tissue damage. This study supports the hypothesis that inflammation and immune-mediated mechanisms are involved in the pathogenesis of AMD.

PMID: 21633121 [PubMed - as supplied by publisher]

Genetics

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

Smoking, Dietary Betaine, Methionine, and Vitamin D in Monozygotic Twins with Discordant Macular Degeneration: Epigenetic Implications.

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OBJECTIVE: We evaluated monozygotic twin pairs with discordant age-related macular degeneration (AMD) phenotypes to assess differences in behavioral and nutritional factors.

DESIGN: Case series.

PARTICIPANTS: Caucasian male twin pairs from the United States Twin Study of Macular Degeneration.

METHODS: Twin pairs were genotyped to confirm monozygosity. Ocular characteristics were evaluated based on fundus photographs using the Wisconsin Grading System and a 5-grade Clinical Age-Related Maculopathy Staging System. We selected twin pairs discordant in each of the following phenotypic categories: Stage of AMD (n = 28), drusen area (n = 60), drusen size (n = 40), and increased pigment area

(n = 56). The Wilcoxon signed-rank test and linear regression were used to assess associations between behavioral and nutritional characteristics and each phenotype within discordant twin pairs.

MAIN OUTCOME MEASURES: Differences in smoking and dietary factors within twin pairs discordant for stage of AMD, drusen area, drusen size, and pigment area.

RESULTS: Representative fundus photographs depict the discordant phenotypes. Pack-years of smoking were higher for the twin with the more advanced stage of AMD (P = 0.05). Higher dietary intake of vitamin D was present in the twins with less severe AMD (P = 0.01) and smaller drusen size (P = 0.05) compared with co-twins, adjusted for smoking and age. Dietary intakes of betaine and methionine were significantly higher in the twin with lower stage of AMD (P = 0.009) and smaller drusen area (P = 0.03), respectively.

CONCLUSIONS: The twin with the more advanced stage of AMD, larger drusen area, drusen size, and pigment area tended to be the heavier smoker. The twin with the earlier stage of AMD, smaller drusen size and area, and less pigment tended to have higher dietary vitamin D, betaine, or methionine intake. Results suggest that behavioral and nutritional factors associated with epigenetic mechanisms are involved in the etiology of AMD, in addition to genetic susceptibility.

PMID: 21620475 [PubMed - as supplied by publisher]

Exp Eye Res. 2011 May 20. [Epub ahead of print]

No association between the T280M polymorphism of the CX3CR1 gene and exudative AMD.

Zerbib J, Puche N, Richard F, Leveziel N, Cohen SY, Korobelnik JF, Sahel J, Munnich A, Kaplan J, Rozet JM, Souied EH.

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Abstract

Major genetic factors for age-related macular degeneration (AMD) have recently been identified as susceptibility risk factors. The CX3CR1 gene has been shown to be associated with AMD in some studies. Our purpose was to analyze the role of the T280M polymorphism of the CX3CR1 gene in a large French population, in a case-control study. 1093 patients with exudative AMD and 396 controls have been recruited and genotyped for the Y402H of CFH, rs10490924 of ARMS2 and T280M of the CX3CR1 gene. The distribution of the Y402H of CFH and of the rs10490924 of ARMS2 was significantly different between cases and controls ($p < 0.0001$). The distribution of the T280M genotypes was not significantly different in the AMD patients compared to controls ($p = 0.99$). The Odds Ratio compared to TT individuals was 1.0 (95% CI 0.8-1.3) for TM individuals and 1.0 (95% CI 0.5-2.1) for MM individuals. The M allele frequency was 0.157 in cases and 0.154 in controls ($p = 0.87$). Our study exclude an association between the T280M of the CX3CR1 gene and exudative AMD in a French population.

PMID: 21621535 [PubMed - as supplied by publisher]

Pre-clinical

Eur J Pharmacol. 2011 May 20. [Epub ahead of print]

Anti-angiogenic effects of the receptor tyrosine kinase inhibitor, pazopanib, on choroidal neovascularization in rats.

Yafai Y, Yang XM, Niemeyer M, Nishiwaki A, Lange J, Wiedemann P, King AG, Yasukawa T, Eichler W.

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Abstract

Neovascularization in the eye is a major cause of irreversible vision loss. The present study was undertaken to determine mechanisms through which pazopanib, a drug that targets multiple receptor tyrosine kinases such as VEGF receptors, inhibits angiogenesis and experimental choroidal neovascularization (CNV). Pazopanib inhibited VEGF expression by retinal pigment epithelium (RPE) cells and choroidal endothelial cells (CEC), decreased VEGF-induced cellular migration in a dose-dependent manner and suppressed extracellular signal-regulated kinase (ERK)-1/-2 phosphorylation. To assess the impact of pazopanib in vivo, CNV was induced in rats by rupturing the Bruch's membrane by laser coagulation. These experiments demonstrated that twice-daily topical eye drop treatment significantly ($P<0.001$) decreased leakage from photocoagulated lesions by 89.5%. Furthermore, the thickness of the developed CNV lesions was significantly inhibited by 71.7% ($P<0.001$) in pazopanib-treated eyes, and immunoreactivity of VEGF was lower than in control eyes. Our data suggest that pazopanib is a promising inhibitor of angiogenesis leading to an effective inhibition of CNV development in vivo. This activity can be largely ascribed to the down-regulation of VEGF release in the retina as well as to impaired VEGF-induced signaling and chemotaxis. Using a convenient topical dosing regimen, pazopanib may prove useful for treating a variety of ocular neovascular diseases such as neovascular age-related macular degeneration.

PMID: 21620822 [PubMed - as supplied by publisher]