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Drug treatment

Ophthalmology. 2012 Sep 25. pii: S0161-6420(12)00660-4. doi: 10.1016/j.ophtha.2012.07.026. [Epub ahead of print]

The SECURE Study: Long-Term Safety of Ranibizumab 0.5 mg in Neovascular Age-Related Macular Degeneration.

Silva R, Axer-Siegel R, Eldem B, Guymer R, Kirchhof B, Papp A, Seres A, Gekkieva M, Nieweg A, Pilz S; SECURE Study Group.

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OBJECTIVE: To evaluate long-term safety of intravitreal ranibizumab 0.5-mg injections in neovascular age-related macular degeneration (nAMD).

DESIGN: Twenty-four-month, open-label, multicenter, phase IV extension study.

PARTICIPANTS: Two hundred thirty-four patients previously treated with ranibizumab for 12 months in the EXCITE/SUSTAIN study.

METHODS: Ranibizumab 0.5 mg administered at the investigator's discretion as per the European summary of product characteristics 2007 (SmPC, i.e., ranibizumab was administered if a patient experienced a best-corrected visual acuity [BCVA] loss of >5 Early Treatment Diabetic Retinopathy Study letters measured against the highest visual acuity [VA] value obtained in SECURE or previous studies [EXCITE and SUSTAIN], attributable to the presence or progression of active nAMD in the investigator's opinion).

MAIN OUTCOME MEASURES: Incidence of ocular or nonocular adverse events (AEs) and serious AEs, mean change in BCVA from baseline over time, and the number of injections.

RESULTS: Of 234 enrolled patients, 210 (89.7%) completed the study. Patients received 6.1 (mean) ranibizumab injections over 24 months. Approximately 42% of patients had 7 or more visits at which ranibizumab was not administered, although they had experienced a VA loss of more than 5 letters, indicating either an undertreatment or that factors other than VA loss were considered for retreatment decision by the investigator. The most frequent ocular AEs (study eye) were retinal hemorrhage (12.8%; 1 event related to study drug), cataract (11.5%; 1 event related to treatment procedure), and increased intraocular pressure (6.4%; 1 event related to study drug). Cataract reported as serious due to hospitalization for cataract surgery occurred in 2.6% of patients; none was suspected to be related to study

drug or procedure. Main nonocular AEs were hypertension and nasopharyngitis (9.0% each). Arterial thromboembolic events were reported in 5.6% of the patients. Five (2.1%) deaths occurred during the study, none related to the study drug or procedure. At month 24, mean BCVA declined by 4.3 letters from the SECURE baseline.

CONCLUSIONS: The SECURE study showed that ranibizumab administered as per a VA-guided flexible dosing regimen recommended in the European ranibizumab SmPC at the investigator's discretion was well tolerated over 2 years. No new safety signals were identified in patients who received ranibizumab for a total of 3 years. On average, patients lost BCVA from the SECURE study baseline, which may be the result of disease progression or possible undertreatment.

PMID: 23021093 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Sep 27. pii: S0002-9394(12)00507-7. doi: 10.1016/j.ajo.2012.06.031. [Epub ahead of print]

Four-Year Treatment Results of Neovascular Age-Related Macular Degeneration With Ranibizumab and Causes for Discontinuation of Treatment.

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PURPOSE: To evaluate 4-year treatment results of neovascular age-related macular degeneration with ranibizumab using a variable dosing regimen.

DESIGN: Retrospective, single-center chart review.

METHODS: This was a retrospective single-center study that included 855 patients with neovascular age-related macular degeneration receiving treatment with ranibizumab during a 4-year period. Included in the study were patients with a minimum follow-up of 15 months and all patients who terminated treatment regardless of follow-up.

RESULTS: A total of 1321 patients were treated over the 4-year period, and 855 patients were eligible for inclusion. Of those, 456 patients were still receiving active treatment, whereas 399 patients had discontinued treatment. Overall treatment results showed a significant decrease in vision from 53.2 Early Treatment Diabetic Retinopathy Study letters (range, 1 to 85 letters) to 50.5 letters (range, 1 to 87 letters; $P < .001$). Mean follow-up was 23.3 months (range, 4 to 48 months). The reason for discontinuing treatment in 181 patients was no signs of activity, whereas 113 patients were judged to be nontreatable. Thirty-six patients declined further treatment for various reasons.

CONCLUSIONS: This report shows that when follow-up extends beyond 2 to 3 years, visual acuity does seem to decrease. Our data show that different responder groups can be identified: bad or nonresponders (approximately 15% of all patients) and good responders (approximately 21% of all patients). These 2 groups in general can be identified within the first 2 years of treatment, whereas the third group of regular responders (approximately 64% of all patients) require continuous monitoring and treatment for years.

PMID: 23022167 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Sep 27. pii: S0002-9394(12)00497-7. doi: 10.1016/j.ajo.2012.07.001. [Epub ahead of print]

Intravitreal Ranibizumab for Pigment Epithelium Detachment with Subfoveal Occult Choroidal Neovascularization: A Prospective 24-Month Case Series.

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PURPOSE: To assess the effects of intravitreal ranibizumab injection in patients affected by pigment epithelial detachment associated with occult subfoveal choroidal neovascularization.

DESIGN: Prospective, interventional case series.

METHODS: Participants: Forty eyes of 40 patients were considered for the purpose of the study. Consecutive patients were recruited for a 24-month study. All patients underwent a complete ophthalmic examination, including best-corrected visual acuity on Early Treatment Diabetic Retinopathy Study (ETDRS) charts. After a 3-monthly loading phase, further intravitreal ranibizumab injections were administered on the basis of detection of any type of fluid on optical coherence tomography. Primary outcome measures: Changes in mean best-corrected visual acuity at 12 and 24 months and the proportion of eyes losing fewer than 15 letters (corresponding to 3 ETDRS lines) from baseline visual acuity. Secondary outcome measures: Changes in central macular thickness on optical coherence tomography and variation in mean area of the entire lesion.

RESULTS: Forty patients were included. Mean best-corrected visual acuity decreased from 20/66 (58 ETDRS letters) to 20/83 (53 letters) at 12 months and 20/112 (489 ETDRS letters) at 24 months (P = .003). Eighty percent and 67.5% of eyes lost fewer than 3 lines at 12 and 24 months, respectively. Mean central macular thickness passed from 545 μm to 428 μm at 12 months and 426 μm at 24 months. Mean lesion area changed from 6826 μm(2) to 6312 μm(2) at 12 months and 6010 μm(2) at 24 months.

CONCLUSIONS: The treatment of pigment epithelial detachment associated with occult subfoveal choroidal neovascularization with intravitreal ranibizumab injection after a 3-monthly loading phase and pro re nata strategy can lead to partial results over a 24-month follow-up. Further investigations are warranted to establish the best therapeutic approach to this disease.

PMID: 23022164 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Sep 27. pii: S0002-9394(12)00505-3. doi: 10.1016/j.ajo.2012.07.009. [Epub ahead of print]

Retinal Functional Changes Measured by Microperimetry in Neovascular Age-Related Macular Degeneration Treated With Ranibizumab.

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PURPOSE: To evaluate the retinal functional changes measured by scanning laser ophthalmoscope microperimetry in neovascular age-related macular degeneration treated with ranibizumab injections.

DESIGN: Prospective, interventional case series.

METHODS: A total of 42 eyes of 39 patients with neovascular age-related macular degeneration were included. After an initial 3 loading injections of ranibizumab, 0.5 mg per injection per month, injection was performed as needed. Evaluation of best-corrected visual acuity, microperimetry, and optical coherence

tomography were performed before treatment and 3 months, 6 months, and 12 months after treatment. According to the appearance of the subfoveal choroidal neovascular membrane on fluorescein angiography, the study group was divided into patients with a predominantly or purely classic choroidal neovascular membrane, those with a minimally classic choroidal neovascular membrane, and patients with occult choroidal neovascular membrane.

RESULTS: In all the subjects, mean retinal sensitivity of the central 12-degree area had increased significantly from 4.89 ± 3.1 dB to 9.82 ± 2.1 dB at month 12 (P = .01). The number of absolute scotoma points decreased significantly from 11.3 ± 3.2 to 5.9 ± 2.4 at month 12 (P = .01). However, in the subgroup analysis, the mean retinal sensitivity improvement, decreased absolute scotoma size, best-corrected visual acuity improvement, and central macular thickness improvement did not differ significantly among the groups.

CONCLUSIONS: Intravitreal 0.5 mg ranibizumab therapy improves retinal function, quantified not only by visual acuity, but also by mean retinal sensitivity and fixation stability, as assessed by scanning laser ophthalmoscope microperimetry. Measurement of retinal sensitivity may facilitate evaluation of the effectiveness of intravitreal ranibizumab treatment in patients with neovascular age-related macular degeneration.

PMID: 23022163 [PubMed - as supplied by publisher]

Retina. 2012 Sep 27. [Epub ahead of print]

INVESTIGATION OF ORAL FENRETINIDE FOR TREATMENT OF GEOGRAPHIC ATROPHY IN AGE-RELATED MACULAR DEGENERATION.

Mata NL, Lichter JB, Vogel R, Han Y, Bui TV, Singerman LJ.

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BACKGROUND: Excessive accumulation of retinol-based toxins has been implicated in the pathogenesis of geographic atrophy (GA). Fenretinide, an orally available drug that reduces retinol delivery to the eye through antagonism of serum retinol-binding protein (RBP), was used in a 2-year trial to determine whether retinol reduction would be effective in the management of geographic atrophy.

METHODS: The efficacy of fenretinide (100 and 300 mg daily, orally) to slow lesion growth in geographic atrophy patients was examined in a 2-year, placebo-controlled double-masked trial that enrolled 246 patients at 30 clinical sites in the United States.

RESULTS: Fenretinide treatment produced dose-dependent reversible reductions in serum RBP-retinol that were associated with trends in reduced lesion growth rates. Patients in the 300 mg group who achieved serum retinol levels of ≤1 μM (≤2 mg/dL RBP) showed a mean reduction of 0.33 mm in the yearly lesion growth rate compared with subjects in the placebo group (1.70 mm/year vs. 2.03 mm/year, respectively, P = 0.1848). Retinol-binding protein reductions <2 mg/dL correlated with further reductions in lesion growth rates (r = 0.478). Fenretinide treatment also reduced the incidence of choroidal neovascularization (approximately 45% reduction in incidence rate in the combined fenretinide groups vs. placebo, P = 0.0606). This therapeutic effect was not dose dependent and is consistent with anti-angiogenic properties of fenretinide, which have been observed in other disease states. CONCLUSION: The findings of this study and the established safety profile of fenretinide in chronic dosing regimens warrant further study of fenretinide in the treatment of geographic atrophy.

PMID: 23023528 [PubMed - as supplied by publisher]

Drugs Aging. 2012 Oct 5. [Epub ahead of print]

Aflibercept for Intravitreal Injection : In Neovascular Age-Related Macular Degeneration.

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Abstract

Aflibercept is a recombinant human fusion protein that acts as a soluble decoy receptor for vascular endothelial growth factor (VEGF) family members VEGF-A, VEGF-B and placental growth factor, thereby preventing these ligands from binding to, and activating, their cognate receptors. The efficacy of intravitreal aflibercept in the treatment of wet (neovascular) age-related macular degeneration has been compared with that of intravitreal ranibizumab, the current gold standard for this indication, in two pivotal phase III studies of virtually identical design (VIEW 1 and 2). In both trials, the recommended regimen of aflibercept [2 mg every second month (after three initial monthly doses)] was shown to be noninferior to the recommended regimen of ranibizumab (0.5 mg every month) in terms of the primary endpoint of the proportion of patients who maintained their vision after 1 year of treatment; similar results were seen when monthly dosing with aflibercept (0.5 or 2 mg) was compared with ranibizumab. Over a period of 96 weeks in the VIEW studies, patients receiving the recommended regimen of aflibercept during the first year followed by modified quarterly treatment during the second year had a similar visual acuity gain to those receiving the recommended regimen of ranibizumab during first year followed by modified quarterly treatment during the second year, but on average required five fewer injections. Aflibercept was generally well tolerated in the VIEW studies; the ocular and non-ocular adverse event profile of the drug was similar to that of ranibizumab.

PMID: 23038609 [PubMed - as supplied by publisher]

Curr Neurovasc Res. 2012 Sep 27. [Epub ahead of print]

The Challenges for Drug Development: Cytokines, Genes, and Stem Cells.

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Abstract

The development of new treatment strategies can offer exciting possibilities for individuals with neurodegenerative disorders, especially if destructive disabilities can be eliminated. However, drug development is an intricate process and can have multiple components that range from assessing an agent's role upon targeted cellular pathways to assessing a drug's ability to prevent or reverse the progression of a particular disease. Along this drug development course one must consider not only the efficacy of a drug, but also the toxicity profile of the agent. Examination of novel agents for the nervous system, such as erythropoietin (EPO), can be illustrative for the considerations that unfold during drug development. As a cytokine and growth factor, EPO is produced and secreted in several organs throughout the body that include the brain, liver, and uterus and is present in the breath of individuals. Although EPO is currently approved by the Food and Drug Administration for the treatment of anemia, the presence of EPO and its receptor in the nervous system has generated an immense amount of interest to target EPO and its downstream pathways for novel therapeutic strategies against neurodegenerative disorders. EPO can protect neurons during acute injury from oxidative stress, stroke, spinal cord ischemia, retinal disease, and demyelinating disease. During chronic neurodegenerative disorders such as cognitive loss and Alzheimer's disease, EPO can prevent cell toxicity, reduce β-amyloid burden, and lead to memory improvements. In

models of Parkinson's disease, EPO represses expression of the pro-apoptotic protein p53 up-regulated modulator of apoptosis (PUMA) and prevents L-3, 4-dihydroxyphenylalanine (L-DOPA) toxicity through reductions in caspase 3 activity.

EPO also has been shown in animal models to have increased expression during electroconvulsive therapy and reduce depressive behavior. In studies with seizures, EPO reduces seizure duration and protects against hippocampal cell loss. At the cellular level, EPO can modulate a number of components in the apoptotic cascade to avert cell death. EPO prevents mitochondrial depolarization and the subsequent release of cytochrome c. EPO can control mitochondrial signaling through Bad, Bax, Puma and blocks Apaf -1 activation. EPO also prevents the early activation of several caspases such as caspase 1, caspase 3, and caspase 9. New work has revealed that EPO also relies upon mammalian target of rapamycin (mTOR) signaling for the neuronal differentiation of post-mortem neural precursors. Retinal progenitor cells have been shown to be resistant to hypoxia when exposed to EPO that leads to mTOR activation. EPO through wingless (Wnt1) signaling can activate mTOR to block apoptotic cell death in inflammatory cells. In cell models of Alzheimer's disease, amyloid degeneration of microglia is limited by EPO through activation of mTOR pathways. Yet, EPO can have clinical limitations. Excessive over-expression of EPO may abolish any protective effects and lead to thrombotic injury. EPO may be contraindicated during severe hypertension since EPO may raise mean arterial blood pressure. As a result, in an effort to limit some of these disadvantages of EPO, analogues of EPO are also under consideration that are absent of erythrogenic properties. In this issue of Current Neurovascular Research, we prevent novel studies that are highly relevant for drug development, and in particular for EPO.

Lagarto et al. examine the toxicology profile of EPO with a nasal formulation. The authors show that this formulation may have a high potential for clinical applications since the nasal formulation was without erythrogenic properties, hematological side effects, antibody formation, or weight loss after a fourteen-day treatment. Given the role that EPO may have in governing the wingless and mTOR pathways to promote neuroprotection, the article by Shang et al. provides us with new insight upon the downstream wingless pathway involving Wnt1 inducible signaling pathway protein 1 (WISP1) and mTOR signaling. These investigators show that in a cellular model of Alzheimer's disease WISP1 is protective against amyloid toxicity, activates mTOR, and controls the regulatory mTOR component proline rich Akt substrate 40 kDa (PRAS40), identifying these novel targets for new strategies directed against Alzheimer's disease and related disorders. The article by Lu et al. brings us to the potential role of stem cell therapy for neuromyelitis optica. The authors demonstrate that transplanted human umbilical cord-derived mesenchymal stem cells, known to secrete growth factors and cytokines such as EPO, in a small group of patients with neuromyelitis optica lead to clinical improvement that may be secondary to modulation of B-cell and T-cell activities.

The work by Sharma et al. compliments this study by examining the role of the vascular endothelial growth factor 2 (VEGF2) gene in the pathogenesis of age-related macular degeneration. Articles by Ciancarelli et al., Fassbender et al., Lahoti et al., and Kimura et al. extend the work of these studies to examine for us the role of oxidative stress and antibody formation in clinical studies with neuro-rehabilitation and in experimental studies with spinal cord injury and apoptotic signaling. Our review articles by Bhutani and Anad, and by Zheng et al. provide further analysis for drug development in relation to the role of biomarkers and the treatment of subarachnoid hemorrhage. The studies presented in this issue of Current Neurovascular Research provide an enticing perspective for the varied parameters that can encompass drug development as well as help us comprehend the need to effectively translate basic cellular mechanisms into useful and safe clinical treatments, a challenge never to be under estimated or assumed until properly powered clinical trials are undertaken.

PMID: 23030554 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2012 Oct;47(5):e15-7. doi: 10.1016/j.jcjo.2012.03.032. Epub 2012 Jul 6.

Long-term ranibizumab treatment for choroidal neovascularization secondary to serpiginous choroiditis.

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Other treatment & diagnosis

Ophthalmology. 2012 Sep 29. pii: S0161-6420(12)00670-7. doi: 10.1016/j.ophtha.2012.07.035. [Epub ahead of print]

Design and Evaluation of a Customized Reading Rehabilitation Program for Patients with Age-Related Macular Degeneration.

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PURPOSE: To evaluate the efficacy of a reading rehabilitation program (RRP) specifically designed for patients with impaired central vision from age-related macular degeneration (AMD) and the impact of the program on the quality of life (QoL) and to determine any predictable reading performance improvements between visits.

DESIGN: Prospective case series.

PARTICIPANTS: Forty-one patients with AMD who attended to the Institute of Applied Ophthalmobiology Eye Institute.

METHODS: An ad hoc-created RRP comprising 4 customized in-office training and in-home training visits over 6 weeks was undertaken by AMD patients. The RRP was based on the principle of stepwise progressive goal achievement: the difficulty of training tasks increased depending on the success obtained when performing previous easier ones. Reading performance was evaluated during each in-office training visit, and the individual's perception of his or her QoL was assessed before and after the RRP. Reading performance parameters were assessed to evaluate RRP effectiveness.

MAIN OUTCOME MEASURES: Best-corrected visual acuity (BCVA), reading speed, reading duration, near visual acuity (VA), font size, and the World Health Organization Quality of Life (WHOQOL-BREF) questionnaire scores. The effect sizes (mean differences and standard deviations) also were calculated.

RESULTS: The mean distance BCVA was 0.81±0.29 logarithm of the minimum angle of resolution units. The mean near VA with the appropriate low-vision aid was 0.91±0.18 (M notation) at baseline. The mean near magnification was 4.32±1.15 at the last in-office visit. The mean reading speed, reading duration, and font size improvement after the reading rehabilitation program were 48.31±22.06 words per minute ($P<0.001$), 35.46±15.68 minutes ($P<0.001$), and -4.08±2.19 font points ($P<0.001$), respectively. The effect sizes of reading speed, reading duration, and font size after the last visit were 2.19, 2.26, and -1.86, respectively. The final score of each WHOQOL-BREF domain improved significantly ($P\leq0.004$) after the RRP. The increased ability to read a smaller font size was correlated with improvement in the physical health domain score of the WHOQOL-BREF ($r = 0.35$; $P = 0.04$).

CONCLUSIONS: This customized RRP significantly enhanced reading performance and perceived QoL in patients with AMD. The improvement between visits seemed to be consistent.

PMID: 23031670 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2012 Sep 27. pii: S0002-9394(12)00515-6. doi: 10.1016/j.ajo.2012.07.018. [Epub ahead of print]

Relationship Between Clinical Characteristics of Polypoidal Choroidal Vasculopathy and Choroidal Vascular Hyperpermeability.

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PURPOSE: To investigate the relationship between the clinical characteristics of polypoidal choroidal vasculopathy (PCV) and choroidal vascular hyperpermeability seen on indocyanine green angiography.

DESIGN: Retrospective, consecutive, interventional case series.

METHODS: We reviewed the medical records and the angiograms of 89 patients with PCV. The relationship between choroidal vascular hyperpermeability and background factors, associated clinical manifestations, and treatment responses to intravitreal injections of ranibizumab were evaluated.

RESULTS: Of the 89 patients with PCV, 31 patients (34.8%) demonstrated choroidal vascular hyperpermeability. The patients with choroidal vascular hyperpermeability more frequently showed bilateral neovascular membrane than those without choroidal vascular hyperpermeability (P=.009) and had a significant relationship with a history of central serous chorioretinopathy (CSC) (P=.01). Of the 98 eyes with treatment-naïve PCV, 34 eyes with choroidal vascular hyperpermeability demonstrated significantly greater subfoveal thickness than the 64 eyes without choroidal vascular hyperpermeability (P < .001). However, no significant relationship was found between choroidal vascular hyperpermeability and the other biomicroscopic and angiographic phenotypes of PCV. Three monthly intravitreal injections of ranibizumab were performed on 57 patients with treatment-naïve PCV, and the presence of choroidal vascular hyperpermeability was significantly related to the persistent retinal fluid 1 month after the third ranibizumab injection (P=.01).

CONCLUSIONS: The patients with PCV associated with choroidal vascular hyperpermeability more frequently demonstrated bilateral neovascular membrane, a history of CSC, a thickened choroid, and poor responses to intravitreal injections of ranibizumab than those without choroidal vascular hyperpermeability.

PMID: 23022162 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2012 Aug;90(5):e399-403. doi: 10.1111/j.1755-3768.2012.02423.x.

Comparison of macular pigment in patients with age-related macular degeneration and healthy control subjects - a study using spectral fundus reflectance.

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Purpose: Previous studies have reported an age-dependent decline of macular pigment optical density (MPOD) as well as a relative lack of MPOD in age-related macular degeneration (AMD). Results are, however, strongly dependent on the technique used. In this study, we investigated the age dependence of MPOD using spectral fundus reflectance. In addition, we hypothesized that patients with AMD have a reduced MPOD as compared to healthy controls.

Methods: A total of 85 healthy subjects and 96 patients with AMD were included in this study. The healthy

control subjects showed a wide range of ages (mean, 51.6 years; range, 21-79 years). Patients with AMD were significantly older (mean, 71.2 years; range, 50-89 years). Spectral fundus reflectance of the fovea was measured in a 2.3° detection field with a custom built fundus reflectometer. Calculation of MPOD was based on a previously published fundus reflectance model.

Results: Patients with AMD showed a reduced MPOD (0.35 ± 0.12) as compared to the healthy control group (0.39 ± 0.12, p = 0.013 between groups). No age dependence of MPOD (r = -0.14, p = 0.19) was found in the healthy control group. In the AMD group, however, MPOD declined with age (r = -0.24, p = 0.019).

Conclusions: This study indicates that MPOD is reduced in patients with AMD. In addition, the data of this study indicate that MPOD is age dependent in AMD patients, but not in healthy controls. Taken together with data indicating that lutein supplementation increases MPOD, this provides a rationale for supplementation of the macular pigments in patients with AMD, although long-term clinical outcome data are lacking.

PMID: 23035764 [PubMed - in process]

Optom Vis Sci. 2012 Oct 2. [Epub ahead of print]

Smoking and Age-Related Macular Degeneration: Biochemical Mechanisms and Patient Support.

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ABSTRACT: A small percentage of the population associates smoking with ocular disease. Most optometrists do not stress the importance of smoking cessation to their patients, and the centrality of smoking regarding the risk for ocular disease is not emphasized in optometric education. Age-related macular degeneration has strong epidemiological associations with smoking, and so serves as an appropriate model for the adverse effects of cigarette smoke on the eye. This article aims to provide basic scientific information to optometrists and optometry students so that they can better understand the pathogenesis of age-related macular degeneration and provide education and support to their patients wishing to stop smoking.

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Invest Ophthalmol Vis Sci. 2012 Oct 2. [Epub ahead of print]

Impaired mesopic visual acuity in eyes with early age-related macular degeneration.

Puell MC, Barrio AR, Palomo-Alvarez C, Gomez-Sanz FJ, Clement-Corral A, Perez-Carrasco MJ.

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PURPOSE: To determine photopic and mesopic distance high-contrast visual acuity (HC-VA) and low-contrast visual acuity (LC-VA) in eyes with early age-related macular degeneration (AMD).

METHODS: Measurements were made in 22 subjects with early AMD and 28 healthy control subjects. Inclusion criteria included a photopic HC-VA of 20/25 or better. Distance VA was measured using HC (96%) and LC (10%) Bailey-Lovie logMAR letter charts under photopic (85 cd/m2) and mesopic (0.1 to 0.2 cd/m2) luminance conditions.

RESULTS: Mean mesopic distance HC-VA and LC-VA were significantly worse (0.1 logMAR and 0.28

logMAR respectively) in the early AMD group than control group. Under mesopic conditions, the mean difference between LC-VA and HC-VA was significantly greater in the early AMD (0.45 logMAR) than control group (0.27 logMAR). Mean differences between mesopic versus photopic HC-VA and mesopic versus photopic LC-VA were significantly greater in the early AMD than control group (0.13 and 0.32 logMAR of difference between the means respectively). Sensitivity and specificity were significantly greater for mesopic LC-VA than for mesopic HC-VA (Receiver Operating Characteristics, AUC, 0.94±0.030 and 0.76 ±0.067, respectively). AUC values for photopic HC- and LC-VA were below 0.70.

CONCLUSIONS: Visual acuity testing under low luminance conditions emerged as an optimal quantitative measure of retinal function in early AMD.

PMID: 23033386 [PubMed - as supplied by publisher]

Pathogenesis

Curr Neurovasc Res. 2012 Sep 19. [Epub ahead of print]

SINGLE NUCLEOTIDE POLYMORPHISM AND SERUM LEVELS OF VEGFR2 ARE ASSOCIATED WITH AGE RELATED MACULAR DEGENERATION.

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Abstract

Age-related macular degeneration (AMD) is a leading cause of blindness and is the third leading cause of blindness. Genetic factors are known to influence an individuals risk for developing AMD. Linkage has earlier been shown to the vascular endothelial growth factor 2 (VEGF2) gene and AMD. To examine the role of VEGFR2 in north Indian population, we conducted a case control study. Total 176 subjects were enrolled in a case-control genetic study. Real-Time PCR was used to analyzed the SNPs (rs1531289 and rs2305948) of VEGFR-2 gene. ELISA was conducted to determine the levels of VEGFR2. A non-parametric Mann-Whitney-U test was applied for comparison of the ELISA levels and Pearsons Chi-square test was applied to study the association of polymorphism between various groups. The single SNP (rs1531289) AG genotype was significantly associated with AMD (OR= 2.13, 95%CI= 1.011-4.489, P=0.047). VEGFR2 levels were found to be increased significantly in AMD patients as compared to normal controls. We also found significant increase in the levels of wet AMD as compare to dry AMD. This study demonstrates higher levels of VEGFR2 and higher frequency of AG (rs1531289) genotype in AMD patient population, suggesting the role of VEGFR-2 in pathogenesis of AMD.

PMID: 23030506 [PubMed - as supplied by publisher]

PLoS One. 2012;7(9):e45801. doi: 10.1371/journal.pone.0045801. Epub 2012 Sep 20.

Interleukin 27 Induces the Expression of Complement Factor H (CFH) in the Retina.

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Abstract

Complement factor H (CFH) is a central regulator of the complement system and has been implicated in the

etiology of age-related macular degeneration (AMD), a leading cause of blindness in the elderly. In view of previous studies showing that reduced expression of CFH in the retina is a risk factor for developing AMD, there is significant interest in understanding how CFH expression is regulated in the retina. In this study, we have shown that the anti-inflammatory cytokine, IL-27, induced CFH expression in mouse retinal cells and human retinal pigmented epithelial cells (RPE) through STAT1-mediated up-regulation of Interferon Regulatory Factor-1 (IRF-1) and IRF-8. We further show that cells in the ganglion and inner-nuclear layers of the retina constitutively express IRF-1 and IRF-8 and enhanced CFH expression in the retina during ocular inflammation correlated with significant increase in the expression of IRF-1, IRF-8 and IL-27 (IL-27p28 and Ebi3). Our data thus reveal a novel role of IL-27 in regulating complement activation through up-regulation of CFH and suggest that defects in IL-27 signaling or expression may contribute to the reduction of CFH expression in the retina of patients with AMD.

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New Biomarker for Neovascular Age-Related Macular Degeneration: Eotaxin-2.

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Abstract

Recently, eotaxin-CCR3 was reported to play an important role in choroidal neovascularization (CNV) development and was documented to be superior than vascular endothelial growth factor-A treatment when tested in CNV animals. As eotaxin studies are lacking in the human age-related macular degeneration (AMD) patients, we sought to determine whether eotaxin-2 (CCL24) has any association with inflammatory processes that occur in CNV. CCL24 levels were determined by enzyme linked immunosorbant assay (ELISA) after normalization to total serum protein and levels of ELISA were correlated to various risk factors in about 133 AMD patients and 80 healthy controls. The CCL24 levels were significantly higher in wet AMD patients as compared with dry AMD and normal controls. There was a significant difference when compared among wet AMD patients (i.e., minimally classic, predominantly classic, and occult). We also report significant difference in the CCL24 levels of Avastin-treated and untreated AMD patients. This study shows that CCL24 levels were found to be significantly increased in AMD patients despite Avastin treatment as compared with normal controls and those without Avastin, indicating that CCL24 may have an association with CNV and may be an important target to validate future therapeutic approaches in AMD in tandem with Avastin treatment.

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Vascular Endothelial Growth Factor A in Intraocular Vascular Disease.

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Abstract

The vascular beds supplying the retina may sustain injury as a result of underlying disease such as

diabetes, and/or the interaction of genetic predisposition, environmental insults, and age. The vascular pathologic features observed in different intraocular vascular diseases can be categorized broadly as proliferation, exemplified by proliferative diabetic retinopathy, leakage such as macular edema secondary to retinal vein occlusion, or a combination of proliferation and leakage, as seen in neovascular age-related macular degeneration (AMD). The World Health Organization has identified diabetic retinopathy and AMD as priority eye diseases for the prevention of vision loss in developed countries. The pathologic transformations of the retinal vasculature seen in intraocular vascular disease are associated with increased expression of vascular endothelial growth factor A (VEGF), a potent endothelial-specific mitogen. Furthermore, in model systems, VEGF alone is sufficient to trigger intraocular neovascularization, and its inhibition is associated with functional and anatomic improvements in the affected eye. Therapeutic interventions with effect on VEGF include intraocular capture and neutralization by engineered antibodies or chimeric receptors, downregulation of its expression with steroids, or alleviation of retinal ischemia, a major stimulus for VEGF expression, with retinal ablation by laser treatment. Data from prospective randomized clinical trials indicate that VEGF inhibition is a potent therapeutic strategy for intraocular vascular disease. These findings are changing clinical practice and are stimuli for further study of the basic mechanisms controlling intraocular angiogenesis. Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.

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Genetics

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A NOVEL MUTATION AT THE N-TERMINAL DOMAIN OF THE TIMP3 GENE IN SORSBY FUNDUS DYSTROPHY.

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PURPOSE: To report a novel mutation occurring in the N-terminal domain of the tissue inhibitor of metalloproteinase 3 (TIMP3) gene in Sorsby fundus dystrophy.

METHODS: Retrospective review of medical records of two patients who had clinical features consistent with Sorsby fundus dystrophy. Genetic testing confirmed a mutation in the TIMP3 gene in both patients.

RESULTS: Both patients had findings of drusenlike deposits, retinal pigment epithelial and photoreceptor atrophy, and bilateral, recurrent choroidal neovascularization. A strong family history of early onset macular degeneration was present in both. The patients developed choroidal neovascularization at the age of 45 and 48 years, and both had multiple recurrences in both eyes. Genetic testing in both patients confirmed a heterozygous nucleotide change of C113G, causing a Ser38Cys change in Exon 1 of the N-terminal domain of the TIMP3 gene.

CONCLUSION: All previously reported mutations in Sorsby fundus dystrophy occur at Exon 5 in the C-terminal domain. We report 2 patients with novel mutations in Exon 1 of the N-terminal domain. Although the mutation occurs at a different location on the TIMP3 gene, the clinical features are similar to other reported patients with Sorsby fundus dystrophy. This finding assists in understanding the pathogenesis of this disorder.

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Correction of Phenotype Misclassification Based on High-Discrimination Genetic Predictive Risk Models.

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Abstract

Misclassification of phenotype status can seriously affect accuracy in association studies, including studies of genetic risk factors. A common problem is the classification of participants as nondiseased because of insufficient diagnostic workup or because participants have not been followed up long enough to develop disease. Some validated predictive models may have high discrimination in predicting disease. We suggest that information from such models can be used to predict the risk that a nondiseased participant will eventually develop disease and to recode the status of participants predicted to be at highest risk. We evaluate conditions under which recoding results in a maximal net improvement in the accuracy of phenotype classification. Net improvement is expected only when the positive likelihood ratio of the predictive model is larger than the inverse of the odds of disease among apparently nondiseased controls. We conducted simulations to probe the impact of reclassification on the power to detect new risk factors under several scenarios of classification accuracy of the previously developed models. We also apply this framework to a validated model of progression to advanced age-related macular degeneration that uses genetic and nongenetic variables (area under the curve = 0.915). In the training cohort (n = 2,937) and a separate validation cohort (n = 1,227), 195-272 and 78-91 nonprogressor participants, respectively, were reclassified as progressors. Correction of phenotype misclassification based on highly informative predictive models may be helpful in identifying additional genetic and other risk factors, when there are validated risk factors that provide strong discriminating ability.

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Diet

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Vitamin A supplementation ameliorates obesity-associated retinal degeneration in WNIN/Ob rats.

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OBJECTIVE: Obesity is associated with various health afflictions, including ocular complications such as diabetic retinopathy, high intraocular pressure, cataracts, and macular degeneration. We previously reported progressive retinal degeneration after the onset of obesity in the spontaneously obese rat (WNIN/Ob) model. In the present study, we investigated vitamin A supplementation to ameliorate obesity-associated retinal degeneration in the WNIN/Ob rat.

METHODS: Five-month-old male WNIN/Ob obese (O) and lean (L) control rats were fed with vitamin A 2.6 mg (L/O-I), 26 mg (L/O-II), 52 mg (L/O-III), and 129 mg (L/O-IV) per kilogram of diet as retinyl palmitate for 4 mo 2 wk. Retinal morphology and retinal gene expression were assessed by histologic, immunohistochemical, and real-time polymerase chain reaction methods.

RESULTS: Supplementation of vitamin A at 26 or 52 mg significantly modulated the expression of retinal genes in the O but not in the L phenotype. Vitamin A supplementation significantly upregulated the expression of genes, such as rhodopsin, rod arrestin, phosphodiesterase, transducins, and fatty acid elongase-4, that were otherwise downregulated in O rat retina. The expression of glial fibrillary acidic protein was downregulated by vitamin A feeding in O rat retina. The immunohistochemical and histologic findings corroborated the gene expression data. The effects were significant at a 26- or 52-mg dose of vitamin A.

CONCLUSION: Vitamin A supplementation alleviated obesity-associated retinal degeneration in the WNIN/Ob rat.

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