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Issue 45

Monday September 5 , 2011

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Drug treatment

Ophthalmology. 2011 Aug 26. [Epub ahead of print]

Incidence of Retinal Pigment Epithelial Tears after Intravitreal Ranibizumab Injection for Neovascular Age-Related Macular Degeneration.

Cunningham ET Jr, Feiner L, Chung C, Tuomi L, Ehrlich JS.

California Pacific Medical Center and the Department of Ophthalmology, Stanford University School of Medicine, Stanford, California.

OBJECTIVE: To explore the association between treatment for neovascular age-related macular degeneration (AMD) and incidence and timing of retinal pigment epithelium (RPE) tears in ranibizumab-treated patients versus control treatment.

DESIGN: Results from 3 phase III clinical trials (ANti-VEGF antibody for the treatment of predominantly classic CHORoidal neovascularization in age-related macular degeneration [ANCHOR], Minimally classic/occult trial of the Anti-VEGF antibody Ranibizumab In the treatment of Neovascular Age-related macular degeneration [MARINA], and A Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age-Related Macular Degeneration [PIER]) were retrospectively reviewed to identify patients who developed RPE tears during the study period, detected on fluorescein angiography performed at prespecified intervals.

PARTICIPANTS: Patients with baseline and post-baseline angiographic assessments.

METHODS: Patients received intravitreal ranibizumab (0.3 or 0.5 mg) or control treatment (verteporfin photodynamic therapy [PDT] in ANCHOR and sham intravitreal injections in ANCHOR, MARINA, and PIER).

MAIN OUTCOME MEASURES: Incidence and timing of RPE tears during the treatment period.

RESULTS: Data from 1298 patients were analyzed. No statistically significant differences in RPE tear incidence were observed. The pooled rate of RPE tears was 1.8% with 0.5 mg ranibizumab, 3.0% with 0.3 mg ranibizumab, and 1.6% in the control group. Most (76%; 16/21) RPE tears in ranibizumab-treated patients were identified within 3 months of initiating treatment, whereas the majority (80%; 4/5) of late-onset RPE tears occurred in control patients. In patients who developed RPE tears, better visual acuity (VA) outcomes were observed in those treated with ranibizumab versus control treatment.

CONCLUSIONS: As studied in these trials, no statistically significant differences in the incidence of RPE

tears within a 2-year treatment period were observed in patients who received ranibizumab (0.5 or 0.3 mg) versus control treatment, although most RPE tears with ranibizumab occurred within 3 months of initiating treatment. Mean VA was better in patients who developed RPE tears while receiving ranibizumab than in those who received control treatment, suggesting a potential benefit of continued ranibizumab therapy in patients with neovascular AMD who developed RPE tears.

PMID:21872935 [PubMed - as supplied by publisher]

Methods Mol Biol. 2011;763:403-15.

Evaluation of VEGF-Induced Vascular Permeability in Mice.

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Abstract

Vascular endothelial growth factor (VEGF) is a potent inducer of angiogenesis and vascular leak involved in development, wound healing, tumor growth, macular degeneration, and ischemia. Studying the effects of VEGF in vitro is not always sufficient to approximate the complex in vivo response that involves multiple cell types within functioning tissues. Treating mice with an intravenous injection of recombinant VEGF produces a rapid and transient biochemical response that is accompanied by a series of ultrastructural changes. Similar events are induced by hypoxia-induced VEGF in the heart following myocardial infarction or by tumor cell-released VEGF during metastasis. Studying how intact blood vessels respond to VEGF will augment the further development of antipermeability strategies to improve disease progression in a number of pathologies.

PMID:21874467 [PubMed - in process]

Med Sci Monit. 2011 Aug 22;17(9):CR485-490.

Effectiveness of ranibizumab intravitreal injections for exudative age-related macular degeneration treatment: 12-month outcomes.

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

Background: The aim of this paper was to evaluate functional and anatomical results of intravitreal ranibizumab injections and the course of exudative age-related macular degeneration (AMD) treatment over a 12-month observation period.

Material/Methods: In 25 patients with active dominantly classic exudative AMD, treatment was performed according to the following schedule: 3 intravitreal injections of 0.5 mg ranibizumab at monthly intervals (saturation phase); further injections were based on activity of the neovascular process. Changes in VA and central retinal thickness (CRT) during treatment were evaluated with ANOVA testing.

Results: Mean pre-treatment best corrected visual acuity was 0.73±0.27 logMAR. After the third ranibizumab injection the best results, 0.54±0.27 logMAR, were seen; 12-month results were 0.58±0.26 logMAR. Patients had a mean improvement of 10.6 letters at 12 months. In 92% of patients stabilization or improvement of vision was observed. The mean number of injections in the 12-month period was 6. Baseline mean CRT was 351.12±74.15 µm. After the first ranibizumab injection it decreased significantly to 221.96±60.85 µm, after the third injection it was 200.80±47.63 µm, and after 12 months it was 213.16±44.37 µm. Mean correlations between baseline average CRT and baseline average VA measured

in ETDRS letters (p=0.017) and in logMAR scale (p=0.033) and between average CRT after the third injection and average VA in logMAR scale after the third injection (p=0.047) were noted.

Conclusions: Treatment with intravitreal ranibizumab injections according to the presented scheme provides AMD patients with a chance of stabilization and improvement of the topical state, with a lower number of injections and preserved topical and general safety. Our results suggest that regular monthly controls are necessary to be able react rapidly to the smallest signs of deterioration, not only in visual acuity, but also in OCT images.

PMID:21873944 [PubMed - in process] Related citations

Acta Ophthalmol. 2011 Aug 23. doi: 10.1111/j.1755-3768.2011.02237.x. [Epub ahead of print]

Circulating antiretinal antibodies predict the outcome of anti-VEGF therapy in patients with exudative age-related macular degeneration.

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Purpose: To determine serum antiretinal antibody (ARA) levels in response to treatment with intravitreal bevacizumab of exudative age-related macular degeneration (AMD).

Methods: The study comprised 22 patients treated with intravitreal bevacizumab (Avastin) 1.25 mg. In all patients, serum ARA levels were assessed by indirect immunofluorescence on normal monkey retina substrate. The ophthalmic examination including best corrected visual acuity (BCVA), fundoscopy, fluorescein angiography, optical coherence tomography (OCT) and immunohistochemical investigations. These were repeated at 4-week intervals during a loading phase of antiangiogenic therapy. Sera of 22 sex- and age-matched healthy subjects were used as controls for immunohistochemical studies.

Results: Before bevacizumab therapy, ARAs were detected in the sera of all patients at titres ranging from 1:40 to 1:1280. The titres were significantly higher ($p < 0.01$) than in controls (1:10-1:40). There was no significant correlation between serum ARA titres and neither the type nor the dimensions of choroidal neovascularization, as well as central retinal thickness. Following treatment, all patients demonstrated significant decrease in ARA levels. This correlated with improvement of BCVA, decreased leakage of fluorescein and reduction of subretinal fluid on OCT.

Conclusion: Serum ARA levels demonstrate a dynamic change which occurs in parallel with clinical outcomes of antiangiogenic therapy. They also may act as markers of the therapeutic benefits of vascular endothelial growth factor inhibition.

PMID:21883989 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011;5:1151-65. Epub 2011 Aug 18.

Emerging nonsurgical methods for the treatment of vitreomacular adhesion: a review.

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Abstract

With the dissemination of optical coherence tomography over the past two decades, the role of persistent vitreomacular adhesion (VMA) in the development of numerous macular pathologies - including idiopathic macular hole, vitreomacular traction syndrome, cystoid and diabetic macular edema, neovascularization in diabetic retinopathy and retinal vein occlusion, exudative age-related macular degeneration, and myopic traction maculopathy - has been established. While invasive vitreoretinal procedures have long been utilized to address complications related to these disorders, such an approach is hampered by incomplete vitreoretinal separation and vitreous removal, surgical complications, and high costs. In light of such limitations, investigators have increasingly looked to nonsurgical means for the treatment of persistent pathologic VMA. Chief among these alternative measures is the intravitreal application of pharmacologic agents for the induction of vitreous liquefaction and/or vitreoretinal separation, an approach termed pharmacologic vitreolysis. This article aims to review the available evidence regarding the use of pharmacologic agents in the treatment of VMA-related pathology. In addition, a discussion of vitreous molecular organization and principles of physiologic posterior vitreous detachment is provided to allow for a consideration of vitreolytic agent mode of action and molecular targets.

PMID: 21887098 [PubMed - in process]

J Cell Mol Med. 2011 Sep 1. doi: 10.1111/j.1582-4934.2011.01440.x. [Epub ahead of print]

Angiostatic kinase inhibitors to sustain photodynamic angio-occlusion.

Nowak-Sliwinska P, Weiss A, Beijnum JR, Wong TJ, Ballini JP, Lovisa B, Bergh HV, Griffioen AW.

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Abstract

Targeted angiostatic therapy receives major attention for the treatment of cancer and exudative age-related macular degeneration (AMD). Photodynamic therapy (PDT) has been used as an effective clinical approach for these diseases. Since PDT can cause an angiogenic response in the treated tissue, combination of PDT with anti-angiogenic compounds should lead to improved therapy. The current study was undertaken to test the clinically used small molecule kinase inhibitors Nexavar(®) (sorafenib), Tarceva(®) (erlotinib), and Sutent(®) (sunitinib) for this purpose, and compare the results to the combination of Visudyne(®) -PDT with Avastin(®) (bevacizumab) treatment. When topically applied to the chicken chorioallantoic membrane (CAM) at embryo development day (EDD) 7, a clear inhibition of blood vessel development was observed, with sorafenib being most efficient. To investigate combination with phototherapy, Visudyne(®) -PDT was first applied on EDD11 to close all <100 μm vessels. Application of angiostatics after PDT resulted in a significant decrease in vessel regrowth in terms of reduced vessel density and number of branching points/ mm(2) . While for all compounds the 50% effective dose (ED(50)) was approximately 10-fold lower, sorafenib also outperformed the other compounds. In vitro, all kinase inhibitors decreased the viability of human umbilical vein endothelial cells (HUVEC). Sunitinib convincingly inhibited the in vitro migration of endothelial cells. These results suggest the therapeutic potential of these compounds for application in combination with PDT in anti-cancer approaches, and possibly also in the treatment of other diseases where angiogenesis plays an important role.

PMID:21880113 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Br J Ophthalmol. 2011 Aug 26. [Epub ahead of print]

Development and validation of a computer-aided diagnostic tool to screen for age-related macular degeneration by optical coherence tomography.

Serrano-Aguilar P, Abreu R, Antón-Canalís L, Guerra-Artal C, Ramallo-Fariña Y, Gómez-Ulla F, Nadal J.

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Background: To develop and assess the technical validity of new computer-aided diagnostic software (CAD) for automated analyses of optical coherence tomography (OCT) images for the purpose of screening for neovascular age-related macular degeneration.

Methods: Artificial visual techniques were used to develop the CAD in two steps: normalisation and feature vector extraction from OCT images; and training and classification by means of decision trees. Technical validation was performed by a retrospective study design based on OCT images randomly extracted from clinical charts. Images were classified as normal or abnormal to serve for screening purposes. Sensitivity, specificity, positive predictive values and negative predictive values were obtained.

Results: The CAD was able to quantify image information by working in the perceptually uniform hue-saturation-value colour space. Particle swarm optimisation with Haar-like features is suitable to reveal structural features in normal and abnormal OCT images. Decision trees were useful to characterise normal and abnormal images using feature vectors obtained from descriptive statistics of detected structures. The sensitivity of the CAD was 96% and the specificity 92%.

Conclusions: This new CAD for automated analysis of OCT images offers adequate sensitivity and specificity to distinguish normal OCT images from those showing potential neovascular age-related macular degeneration. These results will enable its clinical validation and a subsequent cost-effectiveness assessment to be made before recommendations are made for population-screening purposes.

PMID:21873314 [PubMed - as supplied by publisher]

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

Semi-automated image processing method for identification and quantification of geographic atrophy in age-related macular degeneration.

Schmitz-Valckenberg S, Brinkmann CK, Alten F, Herrmann P, Stratmann NK, Göbel AP, Fleckenstein M, Diller M, Jaffe GJ, Holz FG.

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Purpose: To determine intra- and interobserver longitudinal measurement variability of novel semi-automated software for quantification of age related macular degeneration-associated geographic atrophy (GA) based on confocal scanning laser ophthalmoscopy fundus autofluorescence (FAF) imaging.

Methods: Three-field FAF (exc 488 nm, em 500-700 nm), near-infrared reflectance (820 nm) and blue reflectance (488 nm) images (Spectralis HRA+OCT, Heidelberg Engineering, Germany) of 30 GA subjects were recorded according to a standardized protocol at baseline, after 6 and 12 months. At all visits, GA area was analyzed on central FAF images by seven independent readers using semi-automated software (RegionFinder(TM), Heidelberg Engineering) The software allows a direct export of FAF images from the database, semi-automated detection of atrophic areas by shadow correction, vessel detection and selection of seed points.

Results: The mean size of atrophy at baseline and the mean progression rate were 5.96 mm(2) (range,

1.80-15.87) and 1.25 mm(2)/year (0.42-2.93), respectively. Mean difference of interobserver agreement (Bland-Altman statistics) ranged between -0.25 to 0.30 mm(2) for the baseline visit and between -0.14 to 0.11 mm(2)/year for the atrophy progression rate. Corresponding reflectance images were helpful for lesion boundary discrimination, particularly for evaluation of foveal GA involvement and when the image quality was poor.

Conclusions: The new image processing software offers an accurate, reproducible and time-efficient identification and quantification of outer retinal atrophy and its progression over time. It facilitates measurements both in natural history studies and in interventional trials to evaluate new pharmacological agents designed to limit GA enlargement.

PMID:21873669[PubMed - as supplied by publisher]

Retina. 2011 Aug 12. [Epub ahead of print]

Comparison of choroidal thickness among patients with healthy eyes, early age-related maculopathy, neovascular age-related macular degeneration, central serous chorioretinopathy, and polypoidal choroidal vasculopathy.

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PURPOSE: To compare choroidal thicknesses among eyes with early age-related maculopathy (ARM), neovascular age-related macular degeneration, polypoidal choroidal vasculopathy, and central serous chorioretinopathy.

METHODS: Patients with age-related maculopathy (37 eyes), neovascular age-related macular degeneration (24 eyes), polypoidal choroidal vasculopathy (12 eyes), and central serous chorioretinopathy (31 eyes) underwent spectral-domain optical coherence tomography evaluations using a choroid scanning protocol. A horizontal linear section comprising 50 averaged scans was obtained of each macula. The choroidal thickness was measured from the outer border of the retinal pigment epithelium to the inner scleral border. Twenty-nine subjects with healthy eyes served as a control group. Analysis of covariance tests were performed to evaluate the effects of various diagnoses on choroidal thickness after removal of variance (covariates = gender, age, and refractive error).

RESULTS: Among the different covariates, age was associated with choroidal thickness (fovea: $F = 12.067$, $P = 0.001$). After controlling for age differences, the choroid was thicker in polypoidal choroidal vasculopathy (319.92 ± 68.66 μm) and central serous chorioretinopathy (367.81 ± 105.56 μm) patients than in controls (241.97 ± 66.37 μm) and age-related maculopathy patients (186.62 ± 64.02 μm). However, there were no significant differences in mean choroidal thickness between neovascular age-related macular degeneration (226.46 ± 102.87 μm) and any of the other diagnoses.

CONCLUSION: The choroid was thicker in eyes with polypoidal choroidal vasculopathy or central serous chorioretinopathy than in control or age-related maculopathy groups.

PMID:21878855 [PubMed - as supplied by publisher]

Klin Monbl Augenheilkd. 2011 Aug 26. [Epub ahead of print]

[Photocoagulation of Age-Related Juxtapapillary Choroidal Neovascularisation.]

[Article in German]

Butros S, Cucera A, Lang GE.

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BACKGROUND: The aim of this study was to evaluate retrospectively the clinical outcome of retinal photocoagulation of age-related juxtapapillary choroidal neovascularisation (CNV) with macular oedema. Juxtapapillary CNV represents a rare form of extrafoveal CNV in age-related macular degeneration (AMD).

PATIENTS AND METHODS: In 15 eyes of 14 patients with age-related juxtapapillary choroidal neovascularisation, CNV was treated with several rows of frequency doubled Nd:YAG laser (532 nm) irradiation to protect the fovea. Classification of the CNV was performed with fluorescein angiography. Best corrected visual acuity was determined before and after photocoagulation. Follow-up time was 1 - 32 months.

RESULTS: In 13 eyes the juxtapapillary CNV was occult (87 %), one eye had a classic, one eye a minimally classic form. In 13 eyes (87 %) the centre of the fovea showed macular oedema in spite of the extrafoveal location of the CNV. Of these 13 eyes, in 10 eyes (77 %) visual acuity increased after photocoagulation. 7 eyes (53 %) had an increase in visual acuity of 1 or 2 lines, 3 eyes of ≥ 4 lines. 2 eyes showed a stable visual acuity, in 1 eye visual acuity deteriorated after photocoagulation. In 2 eyes without foveal involvement of macular oedema, CNV was located in the papillo-macular bundle and threatened the centre of the fovea. Postoperative visual acuity in theses eyes was stable after 1 and 5 months.

CONCLUSION: The therapeutic benefit of photocoagulation of juxta- and extrafoveal classic CNV has already been proven. According to our results, photocoagulation is an effective therapeutic approach in the treatment of age-related juxtapapillary CNV especially, in the occult form, when the fovea is threatened by or involved in the macular oedema.

PMID:21874630 [PubMed - as supplied by publisher]

Retina. 2011 Aug 12. [Epub ahead of print]

QUANTIFICATION OF FLUORESCEIN-STAINED DRUSEN ASSOCIATED WITH AGE-RELATED MACULAR DEGENERATION.

Friedman D, Parker JS, Kimble JA, Delori FC, McGwin G Jr, Curcio CA.

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BACKGROUND: Previous studies of age-related macular degeneration have not quantified the number of drusen that accumulate fluorescein. Histopathologic studies have demonstrated druse subregions with different degrees of hydrophobicity, and these subregions might potentially exhibit different degrees of fluorescein uptake.

METHODS: We evaluated macular drusen from 35 age-related macular degeneration patients by measuring druse area in color digital images and fluorescein angiograms, using 2 morphometric methods.

RESULTS: Of 828 drusen evaluated, 405 had a corresponding fluorescein angiogram signal. About half of all drusen per eye (49.57%) stained in each participant. Among fluorescein-stained drusen, druse size measured in color images did not differ significantly from the sizes measured in corresponding fluorescein images (P = 0.8105), across the range of druse sizes.

CONCLUSION: These findings indicate that our understanding of drusen subregion staining may not directly correlate to in vivo observations of macular drusen in age-related macular degeneration.

PMID:21878853 [PubMed - as supplied by publisher]

Optometry. 2011 Aug 26. [Epub ahead of print]

Peripapillary subretinal neovascular membranes: A review.

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Abstract

Peripapillary subretinal neovascular membranes (PSRNVM) are most commonly associated with age-related macular degeneration and idiopathic causes in older patients. In younger patients, it has been linked to a wide variety of other conditions. As with the more commonly occurring macular form of choroidal neovascular membranes, PSRNVM can also lead to severe vision loss. Therefore, clinicians must take care to avoid overlooking this event to provide appropriate management and treatment. Current knowledge of PSRNVM suggests the importance of regular examinations of the affected eye in both treated and untreated cases to watch for progression and recurrence, which are unpredictable, and also of the fellow eye because there is a high risk of bilateral involvement.

PMID:21873121 [PubMed - as supplied by publisher]

Tsitologiia. 2011;53(6):505-12.

[Adult human retinal pigment epithelial cells - a potential source of cells for regeneration retina].

[Article in Russian]

[No authors listed]

Abstract

Retinal pigment epithelium (RPE) arises from neuroectoderm and plays a key role in support of photoreceptor functions. Several degenerative eye diseases, such as macular degeneration or retinitis pigmentosa, are associated with impaired RPE function that may lead to photoreceptor loss and blindness. RPE cell culture derived from adult human eyes autopsy could be an important source for transplantation to cure such retinal degenerative diseases. RPE cells subsequent isolation and maintenance in culture are described. Besides the results of immunocytochemical analysis that characterizes dedifferentiated state of cultured adult human RPE cells are given. Our findings demonstrate that mature human RPE cells have the capacity to express neural markers in response to conditions that promote dedifferentiation.

PMID:21870507 [PubMed - in process]

Nihon Ganka Gakkai Zasshi. 2011 Aug;115(8):681-5.

[Long-term outcome of radiation therapy for exudative age-related macular degeneration in Japan].

[Article in Japanese]

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PURPOSE: To evaluate the long-term outcome of radiation therapy in eyes with exudative age-related macular degeneration (AMD).

METHODS: Eighty eyes of 80 patients (54 men and 26 women) with exudative AMD, which underwent radiation therapy with a photon beam of 20 Gy (2 Gy per day for 10 days) between 1998 and 2003, were retrospectively reviewed. Average age was 69 +/- 8.1 and follow-up period was 66 months. Best-corrected visual acuity (BCVA), additional therapies and complications were assessed.

RESULTS: Mean duration till the best value of postoperative BCVA could be reached was 10 months. The best BCVA was improved in 20 eyes (25.0%), stabilized in 56 eyes (70.0%), and deteriorated in 4 eyes (5.0%). On the final visit visual improvement was observed in 9 (11.3%), stabilization in 25 (31.3%), and deterioration in 46 eyes (57.5%). Additional therapies for exudative AMD were performed in 24 eyes (30.0%). Severe subretinal hemorrhage was observed in 9 eyes (11.3%), which resulted in severe vision loss despite additional vitrectomy.

CONCLUSIONS: Low-dose radiation therapy for exudative AMD achieved short-term efficacy but seemed less effective in the long-term.

PMID:21882584 [PubMed - in process]

Invest Ophthalmol Vis Sci. 2011 Sep 1;52(9):7012-8. Print 2011.

Preferential hyperacuity perimeter as a functional tool for monitoring exudative age-related macular degeneration in patients treated by intravitreal ranibizumab.

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Purpose: To analyze the response to anti vascular endothelial growth factor (VEGF) treatment for exudative age-related macular degeneration (AMD), with respect to changes in the Preferential Hyperacuity Perimeter (PHP), best-corrected visual acuity (BCVA), and spectral-domain optical coherence tomography (SD-OCT), and to investigate whether the PHP score predicts the need for reinjection.

Methods: Consecutive patients with newly diagnosed exudative AMD underwent the PHP metamorphopsia test, BCVA, and SD-OCT at five time points after initiation of ranibizumab therapy (0.05 mL/0.5 mg). At the third and sixth months, reevaluation for additional injections was done. The relationships between PHP, BCVA, and SD-OCT parameters over time as well as their ability to predict the need for reinjection were examined.

Results: Analysis included 17 eyes (17 patients, 70% females; mean age, 83.2 years). The mean PHP metamorphopsia test score improved from 25.6 ± 41 (baseline) to 10.7 ± 20.1 ($P < 0.05$) over 6 months, after a mean of 4.2 (±1.0) injections. Mean reduction in SD-OCT parameters well reflected the functional improvements as evaluated by PHP (Spearman correlation = 0.9, $P < 0.05$). Mean BCVA did not improve over 6 months (0.6 vs. 0.58 logMAR), and neither correlated with SD-OCT morphologic changes (Spearman correlation = 0.1, $P > 0.05$) nor with PHP functional changes (Spearman correlation = 0.1, $P > 0.05$). The PHP predicted the need for reinjection with an accuracy of 75% (sensitivity, 83 ± 12%; specificity, 67 ± 15%), whereas a combination of all the measurements (PHP, BCVA, and SD-OCT) yielded an accuracy of 87% (sensitivity, 83 ± 12%; specificity, 90 ± 10%).

Conclusions: Improvement in the metamorphopsia test score after intravitreal injections of ranibizumab, as well as its ability to predict the need for retreatment, suggest that PHP may be used to monitor response to anti-VEGF therapy in patients with exudative AMD.

PMID:21885622 [PubMed - in process]

Clin Ophthalmol. 2011;5:1095-106. Epub 2011 Aug 9.

High-resolution wide-field imaging of perfused capillaries without the use of contrast agent.

Nelson DA, Burgansky-Eliash Z, Barash H, Loewenstein A, Barak A, Bartov E, Rock T, Grinvald A.

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PURPOSE: Assessment of capillary abnormalities facilitates early diagnosis, treatment, and follow-up of common retinal pathologies. Injected contrast agents like fluorescein are widely used to image retinal capillaries, but this highly effective procedure has a few disadvantages, such as untoward side effects, inconvenience of injection, and brevity of the time window for clear visualization. The retinal function imager (RFI) is a tool for monitoring retinal functions, such as blood velocity and oximetry, based on intrinsic signals. Here we describe the clinical use of hemoglobin in red blood cells (RBCs) as an intrinsic motion-contrast agent in the generation of detailed noninvasive capillary-perfusion maps (nCPMs).

PATIENTS AND METHODS: Multiple series of nCPM images were acquired from 130 patients with diabetic retinopathy, vein occlusion, central serous retinopathy, age-related macular degeneration, or metabolic syndrome, as well as from 37 healthy subjects. After registration, pixel value distribution parameters were analyzed to locate RBC motion.

RESULTS: The RFI yielded nCPMs demonstrating microvascular morphology including capillaries in exquisite detail. Maps from the same subject were highly reproducible in repeated measurements, in as much detail and often better than that revealed by the very best fluorescein angiography. In patients, neovascularization and capillary nonperfusion areas were clearly observed. Foveal avascular zones (FAZ) were sharply delineated and were larger in patients with diabetic retinopathy than in controls (FAZ diameter: 641.5 ± 82.3 versus 463.7 ± 105 μm; $P < 0.001$). Also visible were abnormal vascular patterns, such as shunts and vascular loops.

CONCLUSION: Optical imaging of retinal capillaries in human patients based on motion contrast is noninvasive, comfortable, safe, and can be repeated as often as required for early diagnosis, treatment guidance, and follow up of retinal disease progression.

PMID:21887088 [PubMed - in process]

Epidemiology

Br J Ophthalmol. 2011 Aug 28. [Epub ahead of print]

Trends over time and geographical variation in rates of intravitreal injections in England.

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Aims: The recent emergence of antivascular endothelial growth factor (anti-VEGF) drugs has led to increased numbers of patients undergoing intravitreal injection for age-related macular degeneration (AMD). The aims of this study were to report on trends over time and geographical variation in intravitreal injection rates in England, and consider the implications for publicly funded health services of introducing new and expensive treatments.

Methods: Hospital episode statistics were analysed for annual treatment rates of intravitreal injection between the NHS financial years of 1989/1990 and 2008/1999.

Results: Annual injection rates increased from 0.4 episodes (95% CI 0.37 to 0.49) per 100 000 population in 1989/1990 to 10.7 (10.4-11.0) in 2006/2007. Rates then rose exponentially to 59.5 (58.8-60.2) in 2008/2009, with increasing use of multiple injections per person. The largest growth in injection rates was

found in older people, and for AMD. Numbers of treatment episodes increased from 203 (1989/1990) to 30 458 (2008/2009). Geographical analysis showed a very wide variation across local authority areas in injection rates, from 0.9 (0.2-2.2) to 42.2 (38.9-45.7) people per 100 000 population in 2005-2008.

Conclusion: Rates of intravitreal injection increased exponentially from 2006/2007. This followed the US Food and Drug Association licensing of ranibizumab for the treatment of neovascular AMD (2006), and its recommendation by National Institute for Health and Clinical Excellence (2008). This study demonstrates some of the major issues which arise with the emergence of expensive new treatments, including speed and cost of adoption, geographical variation in access, and implications for licensing, commissioning and health financing in an ageing society.

PMID:21875871 [PubMed - as supplied by publisher]

Pathogenesis

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

The small GTPase Rap1 is a novel regulator of RPE cell barrier function.

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Purpose: To determine whether the small GTPase Rap1 regulates the formation and maintenance of the retinal pigment epithelial (RPE) cell junctional barrier.

Methods: We utilized ARPE-19 as an in vitro model to study RPE barrier properties. To dissect the role of Rap1, we used two techniques to inhibit Rap1 function: overexpression of RapGAP, which acts as a negative regulator of endogenous Rap1 activity, and treatment with engineered, adenovirally-transduced microRNAs to knockdown Rap1 protein expression. Transepithelial electrical resistance (TER) and real-time cellular analysis (RTCA) of impedance were used as readouts for barrier properties. Immunofluorescence microscopy was used to visualize localization of cadherins under steady-state conditions and also during junctional reassembly following calcium switch. Finally, choroidal endothelial cell (CEC) migration across RPE monolayers was quantified under conditions of Rap1 inhibition in RPE.

Results: Knockdown of Rap1 or inhibition of its activity in RPE reduces TER and electrical impedance of ARPE-19 monolayers. The loss of barrier function is also reflected by the mislocalization of cadherins and formation of gaps within the monolayer. TER measurement and immunofluorescent staining of cadherins after a calcium switch indicate that junctional reassembly kinetics are also impaired. Furthermore, CEC transmigration is significantly higher in Rap1-knockdown ARPE-19 monolayers compared to control.

Conclusions: Rap1 GTPase is an important regulator of RPE cell junctions, and is required for maintenance of barrier function. Our observation that RPE monolayers lacking Rap1 allow greater transmigration of CECs suggests a possible role for potentiating choroidal neovascularization during the pathology of neovascular age-related macular degeneration.

PMID:21873678 [PubMed - as supplied by publisher]

Retina. 2011 Aug 25. [Epub ahead of print]

THE ASSOCIATION BETWEEN DRUSEN EXTENT AND FOVEOLAR CHOROIDAL BLOOD FLOW IN AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To investigate the relationship between drusen extent and foveolar choroidal blood flow in nonexudative age-related macular degeneration.

METHODS: Total drusen area, average druse area, and total drusen number were determined using a computer program developed to quantify the extent of manually outlined drusen from fundus photographs of 157 patients (239 eyes) with nonexudative age-related macular degeneration. Laser Doppler flowmetry was used to assess relative choroidal blood velocity (ChBVel), volume (ChBVol), and flow (ChBFlow) in the center of the fovea.

RESULTS: We found a significant inverse relationship between total drusen area and ChBVol or ChBFlow. For every 1-mm increase in total drusen area, ChBVol decreased by 0.0061 arbitrary units (P = 0.03) and ChBFlow decreased by 0.23 arbitrary units (P = 0.049). Average druse area was also significantly inversely related to ChBVol and ChBFlow. For every 0.01-mm increase in average druse area, the ChBVol decreased by 0.0149 arbitrary units (P = 0.001) and the ChBFlow decreased by 0.4951 arbitrary units (P = 0.003). Adjustment for age weakened the significance, although it remained strong for average druse area versus ChBFlow (P = 0.017) and ChBVol (P = 0.004). The computer-aided quantification of drusen used in this study showed high intra- and intergrader agreement.

CONCLUSION: In patients with nonexudative age-related macular degeneration, there is an association between increased drusen extent and decreased ChBVol and ChBFlow. This suggests the presence of ischemia and possibly the reason why patients with high-risk drusen are prone to advanced disease.

PMID:21878837 [PubMed - as supplied by publisher]

Chem Res Toxicol. 2011 Aug 26. [Epub ahead of print]

The Discovery of Carboxyethylpyrroles (CEPs): Critical Insights into AMD, Autism, Cancer, and Wound Healing from Basic Research on the Chemistry of Oxidized Phospholipids.

Salomon RG, Hong L, Hollyfield J.

Abstract

Basic research, exploring the hypothesis that 2-(ω-carboxyethyl)pyrrole (CEP) modifications of proteins are generated nonenzymatically in vivo is delivering a bonanza of molecular mechanistic insights into age-related macular degeneration, autism, cancer, and wound healing. CEPs are produced through covalent modification of protein lysyl ε-amino groups by γ-hydroxyalkenal phospholipids that are formed by oxidative cleavage of docosahexaenoyl of phospholipids. Chemical synthesis of CEP-modified proteins and the production of highly specific antibodies that recognize them preceded and facilitated their detection in vivo and enabled exploration of their biological occurrence and activities. This investigational approach - from the chemistry of biomolecules to disease phenotype - is proving remarkably productive.

PMID:21875030 [PubMed - as supplied by publisher]

Pathol Int. 2011 Sep;61(9):528-35. doi: 10.1111/j.1440-1827.2011.02695.x. Epub 2011 Aug 1.

Macrophage polarization in the maculae of age-related macular degeneration: A pilot study.

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Abstract

Macrophages can be polarized to exhibit either pro-inflammatory M1 or pro-angiogenic M2 phenotypes, but have high phenotypic plasticity. This pilot study investigated macrophage polarization in the macular retina and choroid of age-related macular degeneration (AMD) and non-AMD subjects, as well as in AMD choroidal neovascular membranes (CNVM). All specimens were evaluated for routine histopathology. Quantitative real-time polymerase chain reaction for representative M1 (CXCL11) and M2 (CCL22) transcripts were performed on macular choroidal trephines (MCT) of 19 AMD and nine non-AMD eye bank eyes, on the microdissected macular retinal cells from the archived slides of five geographic atrophic AMD, five exudative/neovascular AMD, and eight normal autopsied eyes, and on microdissected inflammatory cells from two surgically removed CNVM that did not respond to anti-vascular endothelial growth factor (VEGF) therapy. High M2-chemokine transcript and a low ratio of M1 to M2 chemokine transcript were found in aging non-AMD MCT. Advanced AMD maculae had a higher M1 to M2 chemokine transcript ratio compared to normal autopsied eyes. Macrophages in the two CNVM of patients unresponsive to anti-VEGF therapy were polarized toward either M1 or M2 phenotypes. The number of M2 macrophages was increased compared to M1 macrophages in normal aging eyes. A pathological shift of macrophage polarization may play a potential role in AMD pathogenesis.

PMID:21884302 [PubMed - in process]

Hum Mutat. 2011 Aug 31. doi: 10.1002/humu.21577. [Epub ahead of print]

Evidence of association of APOE with age-related macular degeneration - a pooled analysis of 15 studies.

McKay GJ, Patterson CC, Chakravarthy U, Dasari S, Klaver CC, Vingerling JR, Ho L, de Jong PT, Fletcher AE, Young IS, Seland JH, Rahu M, Soubrane G, Tomazzoli L, Topouzis F, Vioque J, Hingorani AD, Sofat R, Dean M, Sawitzke J, Seddon JM, Peter I, Webster AR, Moore AT, Yates JR, Cipriani V, Fritsche LG, Weber BH, Keilhauer CN, Lotery AJ, Ennis S, Klein ML, Francis PJ, Stambolian D, Orlin A, Gorin MB, Weeks DE, Kuo CL, Swaroop A, Othman M, Kanda A, Chen W, Abecasis GR, Wright AF, Hayward C, Baird PN, Guymer RH, Attia J, Thakkinstian A, Silvestri G.

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Abstract

Age-related macular degeneration (AMD) is the most common cause of incurable visual impairment in high-income countries. Previous studies report inconsistent associations between AMD and apolipoprotein E (APOE), a lipid transport protein involved in low-density cholesterol modulation. Potential interaction between APOE and sex, and smoking status, has been reported. We present a pooled analysis (n = 21,160) demonstrating associations between late AMD and APOε4 (OR = 0.72 per haplotype; CI: 0.65-0.74; P = 4.41×10(-11)) and APOε2 (OR = 1.83 for homozygote carriers; CI: 1.04-3.23; P = 0.04), following adjustment for age-group and sex within each study and smoking status. No evidence of interaction between APOE and sex or smoking was found. Ever smokers had significant increased risk relative to never smokers for both neovascular (OR = 1.54; CI: 1.38-1.72; P = 2.8×10(-15)) and atrophic (OR = 1.38; CI: 1.18-1.61; P = 3.37×10(-5)) AMD but not early AMD (OR = 0.94; CI: 0.86-1.03; P = 0.16), implicating smoking as a major contributing factor to disease progression from early signs to the visually disabling late forms. Extended haplotype analysis incorporating rs405509 did not identify additional risks beyond ε2 and ε4 haplotypes. Our expanded analysis substantially improves our understanding of the association between the APOE locus and AMD. It further provides evidence supporting the role of cholesterol modulation, and low-density cholesterol specifically, in AMD disease etiology.

PMID:21882290 [PubMed - as supplied by publisher]

Genetics

Br J Ophthalmol. 2011 Aug 26. [Epub ahead of print]

Production of ELOVL4 transgenic pigs: a large animal model for Stargardt-like macular degeneration.

Sommer JR, Estrada JL, Collins EB, Bedell M, Alexander CA, Yang Z, Hughes G, Mir B, Gilger BC, Grob S, Wei X, Piedrahita JA, Shaw PX, Petters RM, Zhang K.

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Background: Truncation mutations in the elongation of very long chain fatty acids-4 (AF277094, MIM #605512) (ELOVL4) gene cause Stargardt-like macular dystrophy type 3 (STGD3). Mice expressing truncated ELOVL4 develop rapid retinal degeneration, but are poor STGD3 models since mice lack a macula. Photoreceptor topography in the pig retina is more similar to that in humans as it includes the cone rich, macula-like area centralis. The authors generated transgenic pigs expressing human disease-causing ELOVL4 mutations to better model the pathobiology of this macular disease.

Methods: Pronuclear DNA microinjection and somatic cell nuclear transfer were used to produce transgenic pigs for two different ELOVL4 mutations: the 5 base pair deletion (5 bpdel) and the 270 stop mutation (Y270terEYFP). Retinal transgene expression, morphology and electrophysiology were examined.

Results: The authors obtained four lines of Y270terEYFP and one line of 5 bpdel transgenic animals. Direct fluorescence microscopy indicated that the Y270terEYFP protein is expressed in photoreceptors and mislocalised within the cell. Immunohistochemical examination of transgenic pigs showed photoreceptor loss and disorganised inner and outer segments. Electroretinography demonstrated diminished responses in both transgenic models.

Conclusions: These transgenic pigs provide unique animal models for examining macular degeneration and STGD3 pathogenesis.

PMID:21873315 [PubMed - as supplied by publisher]

Discov Med. 2011 Aug;12(63):159-67.

Pharmacogenomics in ophthalmology.

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Abstract

Inter-individual variation in drug response and adverse drug reactions (ADRs) are well known in medicine. This individual variation in drug response could be at least, in part, due to genetic diversity among individuals. Although substantial studies that connect genetic variants to inter-individual variation in drug response have been documented in several diseases such as cancer and heart diseases, such studies are slowly progressing in ophthalmology. In recent years, advancement in technologies has led to the identification of genes associated with several eye disorders. At the same time, some small-scale studies have demonstrated the association of various genotypes or haplotypes with response to drug therapies. However, its integration into clinical practice in ophthalmology is not possible at present. This is because there are many challenging questions that remain to be addressed. For instance, in the case of complex disorders a single gene study is not enough. Multiple genes, environmental factors, multiple single nucleotide polymorphisms (SNPs), and rare or low frequency variants may contribute to the disease and

they must be considered. The functional aspects of many genetic variants are not known. This raises questions of their biological importance and their clinical usefulness. In addition, there are legal, ethical, and social issues that need to be regulated. Moreover, physicians and patients must be educated about the limitation and sensitivity of genetic testing. At present pharmacogenetic studies in ophthalmology are still in their infancy and do not suggest that a pharmacogenetic basis of drug development in ophthalmology is a concept that can yield immediate results, but can become a reality in the future. In this article an attempt has been made to summarize some of the recent small-scale pharmacogenetic studies on two major eye disorders, age-related macular degeneration (AMD) and glaucoma.

PMID:21878193[PubMed - in process]

Retina. 2011 Aug 11. [Epub ahead of print]

ASSOCIATION BETWEEN HIGH-RISK DISEASE LOCI AND RESPONSE TO ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT FOR WET AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To investigate whether there is an association between known age-related macular degeneration genetic risk variants in the CFH, ARMS2, and HTRA1 genes and response to anti-vascular endothelial growth factor (VEGF) (ranibizumab or bevacizumab) treatment for wet age-related macular degeneration.

METHODS: A retrospective review of 150 patients with documented wet age-related macular degeneration based on clinical examination and fluorescein angiogram was performed. Patients received anti-VEGF therapy with ranibizumab and/or bevacizumab. Patients were genotyped for the single-nucleotide polymorphism rs1061170, rs10490924, rs3750848, rs3793917, rs11200638, and rs932275 and for the indel del443ins54 spanning the CFH, ARMS2, and HTRA1 genes.

RESULTS: There were 57 patients who were characterized as negative responders to anti-VEGF therapy, and 93 patients who were characterized as positive responders. There was no significant difference in mean baseline visual acuity between the groups. Negative responders were followed for a mean duration of 24.0 months, while positive responders were followed for a mean duration of 22.0 months. Although the frequency of the at-risk alleles was higher in the positive responders when compared with the negative responder, this did not reach statistical significance. Additionally, there was no significant association between genotype and the number of injections or absolute change in visual acuity in both groups of responders.

CONCLUSION: In our patient cohort, there was no statistically significant association between response to anti-VEGF therapy and the genotype in both positive-responder and negative-responder groups. Larger studies with more power are necessary to further determine whether a pharmacogenetic association exists between wet age-related macular degeneration and anti-VEGF therapy.

PMID:21878851 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2011;5:1127-33. Epub 2011 Aug 15.

Update on the role of genetics in the onset of age-related macular degeneration.

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Abstract

Age-related macular degeneration (AMD), akin to other common age-related diseases, has a complex pathogenesis and arises from the interplay of genes, environmental factors, and personal characteristics. The past decade has seen very significant strides towards identification of those precise genetic variants associated with disease. That genes encoding proteins of the (alternative) complement pathway (CFH, C2, CFB, C3, CFI) are major players in etiology came as a surprise to many but has already lead to the development of therapies entering human clinical trials. Other genes replicated in many populations ARMS2, APOE, variants near TIMP3, and genes involved in lipid metabolism have also been implicated in disease pathogenesis. The genes discovered to date can be estimated to account for approximately 50% of the genetic variance of AMD and have been discovered by candidate gene approaches, pathway analysis, and latterly genome-wide association studies. Next generation sequencing modalities and meta-analysis techniques are being employed with the aim of identifying the remaining rarer but, perhaps, individually more significant sequence variations, linked to disease status. Complementary studies have also begun to utilize this genetic information to develop clinically useful algorithms to predict AMD risk and evaluate pharmacogenetics. In this article, contemporary commentary is provided on rapidly progressing efforts to elucidate the genetic pathogenesis of AMD as the field stands at the end of the first decade of the 21st century.

PMID:21887094 [PubMed - in process]

Graefes Arch Clin Exp Ophthalmol. 2011 Sep 1. [Epub ahead of print]

Homozygosity for the +674C>T polymorphism on VEGF gene is associated with age-related macular degeneration in a Brazilian cohort.

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PURPOSE: To investigate the association between VEGF gene polymorphism and age-related macular degeneration (AMD) in a Brazilian cohort.

METHODS: We examined 160 affected individuals and 140 sex- and age-matched controls recruited at the Vision Institute and the Retina Department, São Geraldo Hospital, Minas Gerais Federal University, Brazil, between 2007 and 2011. Genotyping for the VEGF rs1413711 single nucleotide polymorphism (SNP) (+674C>T) was performed. The incidence rate ratios and 95% confidence interval (CI) for AMD for this genotype was calculated. The odds ratio (OR) was also assessed by using logistic regression, controlling for CFH and LOC387715 risk genotype.

RESULTS: We observed a prevalence of homozygosity (TT genotype) of 18.1% for rs1413711 among AMD cases compared with 5.8% among controls ($P < 0.002$). The ORs for this polymorphism were 3.6 (95%CI 1.6-8.2) for homozygous subjects and 1.5 (95%CI 1.1-2.1, $P < 0.01$) if the subject had at least one risk allele. When we studied separately exudative and dry AMD groups, this polymorphism was statistically significant for both groups. Controlling for CFH and LOC387715 risk genotype the OR was 3.0 for VEGF

homozygous, and the OR increases if the patient is homozygous for the three genes.

CONCLUSION: The present data suggests that VEGF TT genotype is associated with AMD among Brazilian patients.

PMID:21881842 [PubMed - as supplied by publisher]

Kidney Int. 2011 Aug 31. doi: 10.1038/ki.2011.291. [Epub ahead of print]

Complement factor H variants I890 and L1007 while commonly associated with atypical hemolytic uremic syndrome are polymorphisms with no functional significance.

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Abstract

Mutations and polymorphisms in the gene-encoding factor H (CFH) are associated with atypical hemolytic uremic syndrome, dense deposit disease, and age-related macular degeneration. Many of these CFH genetic variations disrupt the regulatory role of factor H, supporting the concept that dysregulation of complement is a unifying pathogenic feature of these disorders. Evidence of a causal relationship with the disease is, however, not available for all CFH genetic variations found in patients, which is a potential cause of misinterpretations with important consequences for the patients and their relatives. CFH I890 and L1007 are two genetic variations repeatedly associated with atypical hemolytic uremic syndrome and also found in patients with dense deposit disease and age-related macular degeneration. Here we report an extensive genetic and functional analysis of these CFH variants. Our results indicate that I890 and L1007 segregate together as part of a distinct and relatively infrequent CFH haplotype in Caucasians. Extensive analysis of the S890/V1007 (control) and I890/L1007 (disease-associated) factor H protein variants failed to provide evidence that these amino acid changes have functional implications. Thus, the presence of the I890 and L1007 variants in healthy individuals and their high frequency in sub-Saharan African and African-American populations strongly suggest that I890 and L1007 are rare factor H polymorphisms unrelated to disease.Kidney International advance online publication, 31 August 2011; doi:10.1038/ki.2011.291.

PMID:21881555 [PubMed - as supplied by publisher]

Diet

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

Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration.

Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, Werkmeister RM, Dragostinoff N, Simader C, Garhöfer G, Schmidt-Erfurth U, Schmetterer L.

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Purpose: There is evidence from several large scale clinical trials that reduced intake of lutein, a major component of the macular pigment, is a risk factor for the development of AMD. In the present study (LISA = Lutein Intervention Study Austria) we hypothesized that lutein supplementation increases macular pigment optical density (MPOD). In addition, we investigated whether lutein supplementation improves visual acuity (VA) and macular function (mean differential light threshold, MDLT) as assessed with

microperimetry.

Methods: Onehundredtwentysix patients with AMD (AREDS stages 2, 3 and 4) were included in this randomized (2:1), placebo-controlled, double masked parallel group study. Lutein or placebo was administered for 6 months. MPOD was measured using a custom-built reflectometer. VA was assessed with ETDRS charts and MDLT was assessed using a microperimeter.

Results: Lutein significantly increased MPOD by 27.9 ± 2.9% ($p < 0.001$ versus placebo). No significant effect of lutein supplementation on MDLT or VA was seen although a tendency towards an increase was seen for both parameters (MDLT: $p = 0.096$ versus placebo, VA: $p = 0.070$ versus placebo). A significant correlation was, however, found between the increase in MPOD after 6 months and the increase in MDLT after 6 months ($r = 0.25$, $P = 0.027$) as well as between the increase in MPOD after 6 months and the increase in VA after 6 months ($r = 0.27$, $P = 0.013$)

Conclusion: The present study demonstrates that lutein supplementation increases MPOD as assessed with an objective METHOD: The correlation between the change in MPOD and the change in VA and MDLT indicates that patients who show a pronounced increase in MPOD also benefit in terms of visual function.

PMID:21873668 [PubMed - as supplied by publisher]

Food Chem Toxicol. 2011 Aug 22. [Epub ahead of print]

Safety assessment of lutein and zeaxanthin (Lutemax™ 2020): Subchronic toxicity and mutagenicity studies.

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Abstract

Lutein and zeaxanthin, naturally occurring carotenoids, have shown to reduce the risk of cataracts and age-related macular degeneration. Lutemax™ 2020 is a lutein and zeaxanthin (including meso-isomer) enriched product obtained from Marigold flowers (Tagetes erecta L). The objective of the present study was to investigate adverse effects, if any, of Lutemax 2020™ in acute and subchronic toxicity, and mutagenicity studies. In acute toxicity study in rats no lethality was noted at 2000mg Lutemax 2020™/kg body weight (bw). In the subchronic study, Wistar rats (10/sex/group) were administered (gavage) lutein/zeaxanthin concentrate at dose levels of 0, 4, 40 and 400mg/kg bw/day for 90-days. Compared with the control group, administration of lutein/zeaxanthin concentrate did not result in any toxicologically significant treatment-related changes in clinical observations, ophthalmic examinations, body weights, body weight gains, feed consumption, and organ weights. No toxicologically relevant findings were noted in urinalysis, hematology or clinical biochemistry parameters at the end of the treatment or recovery period. Terminal necropsy did not reveal any treatment-related gross or histopathology findings. The results of mutagenicity testing in Salmonella typhimurium did not reveal any genotoxicity. The no observed-adverse-effect level (NOAEL) for lutein/zeaxanthin concentrate was determined as 400mg/kg bw/day, the highest dose tested.

PMID:21872637 [PubMed - as supplied by publisher]