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Drug treatment

Retina. 2012 Mar 29. [Epub ahead of print]

COMBINED FLUORESCEIN ANGIOGRAPHY AND SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IMAGING OF CLASSIC CHOROIDAL NEOVASCULARIZATION SECONDARY TO AGE -RELATED MACULAR DEGENERATION BEFORE AND AFTER INTRAVITREAL RANIBIZUMAB INJECTIONS.

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PURPOSE: To evaluate the combined fluorescein angiography and spectral-domain optical coherence tomography features in a consecutive series of exudative age-related macular degeneration eyes with classic choroidal neovascularization before and after anti-vascular endothelial growth factor treatment.

METHODS: Retrospective interventional study. All consecutive patients with exudative age-related macular degeneration because of newly diagnosed classic choroidal neovascularization visited during 3 months and treated by intravitreal ranibizumab injection on "as-needed" basis were analyzed. Combined fluorescein angiography and spectral-domain optical coherence tomography examination (Spectralis Heidelberg Retina Angiograph OCT) was performed at baseline and at the 12-month follow-up visit.

RESULTS: Twenty-nine treatment-naive eyes (29 patients, 10 men and 19 women, mean age 76.28 ± 10.86 years) were included. A mean of 5.3 ± 3.5 injections was administered during 12 months. At Month 12 visit, patients showed an improved best-corrected visual acuity ($P = 0.01$), a reduction of linear dimension of the entire lesion on fluorescein angiography ($P = 0.02$), and a reduction of the entire lesion width on spectral-domain optical coherence tomography ($P < 0.001$). At baseline, in all cases we distinguished on spectral-domain optical coherence tomography scan a highly reflective subretinal lesion, above and separate from the retinal pigment epithelium. The highly reflective subretinal lesion showed a significant reduction of width along the length of a single B-scan, at Month 12 follow-up visit ($P < 0.001$). It is notable that a small "discreet" pigment epithelial detachment associated with the highly reflective subretinal lesions was present in 28 of 29 eyes at baseline and after treatment (at Month 12 follow-up visit).

CONCLUSION: A discreet pigment epithelial detachment represents a common associated finding of classic choroidal neovascularization. Our study demonstrated that anti-vascular endothelial growth factor treatment may not only stop the growth of the highly reflective subretinal lesion that colocalize with the classic choroidal neovascularization but also determine its regression.

PMID: 22466476 [PubMed - as supplied by publisher]

Retina. 2012 Mar 29. [Epub ahead of print]

LONG-TERM RESULTS OF INTRAVITREAL RANIBIZUMAB, INTRAVITREAL RANIBIZUMAB WITH PHOTODYNAMIC THERAPY, AND INTRAVITREAL TRIAMCINOLONE WITH PHOTODYNAMIC THERAPY FOR THE TREATMENT OF RETINAL ANGIOMATOUS PROLIFERATION.

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PURPOSE: To compare intravitreal ranibizumab, intravitreal ranibizumab plus photodynamic therapy (PDT), and intravitreal triamcinolone plus PDT in retinal angiomatous proliferation, presenting the results of a 3-year follow-up.

METHODS: Thirty-seven eyes of 37 patients with retinal angiomatous proliferation were randomized to 1 of the 3 groups. Group 1 (n = 13) received 3 monthly injections of 0.5 mg ranibizumab, Group 2 (n = 13) received 1 session of PDT and 3 monthly injections of ranibizumab, and Group 3 (n = 11) received 1 session of PDT and 1 injection of 4 mg triamcinolone. Retreatment, with the same therapeutic scheme in each group, was considered in case of persistence or recurrence of subretinal/intraretinal fluid.

RESULTS: Twelve patients in Groups 1 and 2 and 9 patients in Group 3 completed the 3-year follow-up. A total of 58% of patients in Group 1, 50% in Group 2, and 88.9% in Group 3 had the same or better visual acuity at the end of the follow-up (P = 0.081). Patients in Group 3 exhibited considerable improvement in visual acuity (P = 0.032) and statistically significant decrease in central retinal thickness (P < 0.0001) than the 2 other groups at the end of the follow-up. Also, the patients in Group 3 received on average the lowest number of injections (P < 0.0001). Of note, geographic atrophy mainly at the place of previous retinal angiomatous proliferation lesion was detected in 0% in Group 1, 25% in Group 2, and 55.6% in Group 3 (P = 0.203), while 33.3% of patients in Group 1 developed retinal scar.

CONCLUSION: Treatment with ranibizumab or ranibizumab plus PDT resulted in stabilization of the disease, while treatment with IVT plus PDT achieved better results in terms of functional and anatomical features compared with the other groups.

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A LACK OF DELAYED INTRAOCULAR PRESSURE ELEVATION IN PATIENTS TREATED WITH INTRAVITREAL INJECTION OF BEVACIZUMAB AND RANIBIZUMAB.

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PURPOSE: The purpose of this study was to report the rate of intraocular pressure (IOP) elevation after intravitreal injections of anti-vascular endothelial growth factor agents for exudative age-related macular degeneration.

METHODS: Retrospective chart review of all patients receiving intravitreal ranibizumab and/or bevacizumab injections for exudative age-related macular degeneration from November 2005 to June 2010. Delayed ocular hypertension (OHT) was defined as either an IOP ≥22 mmHg on 2 consecutive visits (with an increase from baseline >6 mmHg) or an IOP >26 mmHg on a single visit with a concomitant initiation or augmentation of IOP-lowering treatment. Noninjected fellow eyes served as controls. Incidence of delayed OHT was analyzed using survival analyses, with risk assessed by Cox proportional hazards

regression models. Eyes with glaucoma were evaluated separately.

RESULTS: Three hundred and two treated eyes and 226 control eyes met inclusion criteria. In eyes with exudative age-related macular degeneration without glaucoma, 3 of 270 injected eyes (0.51% incidence per eye-year) developed delayed OHT compared with 4 of 195 control eyes (1.00% incidence per eye-year), a difference that was not statistically significant (hazard ratio = 0.48; 95% confidence interval: 0.11-2.23). In eyes with exudative age-related macular degeneration and glaucoma, 2 of 32 injected eyes developed delayed OHT (3.1% incidence per eye-year) compared with 3 of 31 control eyes (5.7% incidence per eye-year), a difference that was not statistically significant (hazard ratio = 0.59; 95% confidence interval: 0.10-3.60).

CONCLUSION: The incidence of delayed OHT after intravitreal anti-vascular endothelial growth factor injections was low and did not differ between injected and control eyes, including eyes with glaucoma. These results argue against a significant risk of IOP elevation because of repeated anti-vascular endothelial growth factor therapy.

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Retina. 2012 Mar 29. [Epub ahead of print]

PATTERN DYSTROPHY WITH HIGH INTRAFAMILIAL VARIABILITY ASSOCIATED WITH Y141C MUTATION IN THE PERIPHERIN/RDS GENE AND SUCCESSFUL TREATMENT OF SUBFOVEAL CNV RELATED TO MULTIFOCAL PATTERN TYPE WITH ANTI-VEGF (RANIBIZUMAB) INTRAVITREAL INJECTIONS.

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OBJECTIVE: To identify disease causing mutation in three generations of a Swiss family with pattern dystrophy and high intrafamilial variability of phenotype. To assess the effect of intravitreal ranibizumab injections in the treatment of subfoveal choroidal neovascularization associated with pattern dystrophy in one patient.

METHODS: Affected family members were ascertained for phenotypic and genotypic characterization. Ophthalmic evaluations included fundus photography, autofluorescence imaging, optical coherence tomography, and International Society for Clinical Electrophysiology of Vision standard full-field electroretinography. When possible family members had genetic testing. The proband presented with choroidal neovascularization and had intravitreal injections as needed according to visual acuity and optical coherence tomography.

RESULTS: Proband had a multifocal type pattern dystrophy, and his choroidal neovascularization regressed after four intravitreal injections. The vision improved from 0.8 to 1.0, and optical coherence tomography showed complete anatomical restoration. A butterfly-shaped pattern was observed in her cousin, whereas a fundus pulverulentus pattern was seen in a second cousin. Aunt had a multifocal atrophic appearance, simulating geographic atrophy in age-related macular degeneration. The Y141C mutation was identified in the peripherin/RDS gene and segregated with disease in the family.

CONCLUSION: This is the first report of marked intrafamilial variation of pattern dystrophy because of peripherin/RDS Y141C mutation. Intravitreal ranibizumab injections might be a valuable treatment for associated subfoveal choroidal neovascularization.

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THE EFFECT OF FELLOW EYE VISUAL ACUITY ON VISUAL ACUITY OF STUDY EYES RECEIVING RANIBIZUMAB FOR AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To investigate whether extremes in visual acuity (very good or very poor) of the fellow eye (FE) influence visual acuity of the study eye in patients receiving intravitreal ranibizumab treatment for neovascular age-related macular degeneration.

METHODS: From 2 randomized, controlled, clinical trials (MARINA and ANCHOR), we performed a retrospective analysis of ranibizumab-treated patients who maintained stable FE visual acuity (±5 letters from baseline at each of Months 1, 4, 6, and 12), comparing patients with untreated FE visual acuity that was either 20/32 or better (very good) or 20/200 or worse (very poor). Visual acuity of the treated study eyes, which received monthly intravitreal ranibizumab (0.3 mg or 0.5 mg), was compared between the 2 FE cohorts at the Month 6 and Month 12 visits.

RESULTS: A total of 145 patients were analyzed. In the cohort with very poor FE visual acuity (n = 55), there were 35 patients in MARINA and 20 patients in ANCHOR; in the cohort with very good FE visual acuity (n = 90), there were 52 patients in MARINA and 38 patients in ANCHOR.The mean (standard deviation) gain of the study eye visual acuity in the very good FE cohort was 10.3 (13.3) and 10.8 (13.7) letters at Months 6 and 12, respectively, compared with a lesser mean visual acuity gain of 4.6 (12.2) and 6.7 (11.7) letters at Months 6 and 12 in the very poor vision FE cohort. There was no statistically significant difference (adjusted) in the study eye visual acuity change between the 2 cohorts at either 6 months (P = 0.11) or 12 months (P = 0.26).

CONCLUSION: This retrospective analysis of the MARINA and ANCHOR study data did not support the hypothesis that FE visual acuity plays a significant role in driving visual acuity of patients receiving monthly intravitreal ranibizumab injections for neovascular age-related macular degeneration. Visual acuity of the FE by itself is, therefore, not a useful parameter in predicting visual acuity in a majority of ranibizumab-treated patients.

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Factors Associated With the Response of Age-Related Macular Degeneration to Intravitreal Ranibizumab Treatment.

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PURPOSE: To investigate factors affecting patient response to intravitreal ranibizumab treatment for age-related macular degeneration (AMD).

DESIGN: Retrospective chart review.

METHODS: We reviewed medical records of 105 consecutive eyes with AMD treated with intravitreal ranibizumab injections and followed for more than 1 year after treatment. Response to ranibizumab treatment was compared between typical neovascular AMD and polypoidal choroidal vasculopathy (PCV).

Furthermore, we investigated associations of age, lesion size, and single nucleotide polymorphisms (SNPs) in CFH and ARMS2 genes with treatment response.

RESULTS: Forty-nine eyes were diagnosed with typical neovascular AMD and 56 eyes with PCV. Serous retinal detachment and retinal edema resolved similarly in both typical neovascular AMD and PCV after treatment. However, visual acuity (VA) significantly improved in eyes with PCV, whereas VA was maintained in typical neovascular AMD. At the third and twelfth months after injection, VA was better in PCV than in typical neovascular AMD (P = .027 and P = .044, respectively), although there were no differences in baseline VA between the 2 groups. Age and size of greatest linear dimension were significantly associated with visual prognosis in typical neovascular AMD but not in PCV. There was no clear association between 3 SNPs and responsiveness to ranibizumab treatment.

CONCLUSIONS: Although exudative changes were equivalent following ranibizumab treatment in both typical neovascular AMD and PCV, there was a significant increase in VA in PCV compared to typical neovascular AMD. Age and greatest linear dimension correlated with visual prognosis only in typical neovascular AMD and not in PCV.

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One-Year Results of Three Monthly Ranibizumab Injections and As-Needed Reinjections for Polypoidal Choroidal Vasculopathy in Japanese Patients.

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PURPOSE: To investigate the 1-year outcomes of monthly intravitreal injections of ranibizumab for 3 months followed by an as-needed reinjection schedule to treat polypoidal choroidal vasculopathy (PCV) in Japanese patients.

DESIGN: Prospective, consecutive case series.

METHODS: Eighty-five eyes of 82 consecutive Japanese patients with naïve symptomatic PCV received monthly intravitreal injections of ranibizumab for 3 months followed by an as-needed reinjection schedule. Eighty-one eyes (95%) followed for 1 year were studied.

RESULTS: A mean of 4.2 ± 1.3 (mean ± standard deviation) injections were administered over 1 year. Twenty-three of 81 eyes (28%) did not require additional injections and 32 eyes (40%) required only 1 injection after the 3 monthly injections. The mean (± standard error) logarithm of minimal angle of resolution (logMAR) visual acuity (VA) at baseline was 0.59 ± 0.37 and improved to 0.37 ± 0.30 (P = .001). Thirty eyes (37%) and 5 eyes (6%), respectively, had improved and decreased VA of 0.3 or more logMAR unit. Indocyanine green angiography showed that the polypoidal lesions resolved in 21 eyes (26%) and 32 eyes (40%) 3 months and 1 year after the first injection, respectively. Abnormal choroidal vessels remained in all eyes.

CONCLUSIONS: Monthly injections of ranibizumab for 3 months to treat PCV improved the VA, and a reinjection schedule based on need maintained the improved VA. The polypoidal lesions tended to improve over 1 year, whereas abnormal choroidal vessels remained in all eyes. Further long-term follow-up is needed to determine the efficacy of ranibizumab therapy for PCV.

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Intravitreal ranibizumab injection for choroidal neovascularization in Strümpell-Lorrain Syndrome.

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Abstract

Strümpell-Lorrain syndrome, or hereditary spastic paraplegia is a genetic disease of the central nervous system affecting the spinal cord and cerebellum. It represents a clinically heterogenous group of neurodegenerative disorders characterized by progressive spasticity and hyperreflexia of the lower limbs. Ocular abnormalities include keratitis, macular pigmentary abnormalities, juxtafoveolar retinal telangiectasis and choroidal neovascularization. We report the first case of choroidal neovascularization associated with Strüpell-Lorrain syndrome treated successfully with intravitreal ranibizumab injection.

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FUNDUS AUTOFLUORESCENCE NOT PREDICTIVE OF TREATMENT RESPONSE TO INTRAVITREAL BEVACIZUMAB IN EXUDATIVE AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: Foveal autofluorescence (AF) has been suggested to be a potential predictor of treatment outcome in choroidal neovascularization (CNV) secondary to age-related macular degeneration and could be a useful marker to help prognosticate for patients and for clinical trials. This retrospective study aims to determine if pretreatment foveal AF can predict treatment response to intravitreal bevacizumab monotherapy in CNV secondary to age-related macular degeneration.

METHODS: Ninety-five eyes (85 patients) with naive CNV secondary to age-related macular degeneration, treated with intravitreal bevacizumab monotherapy were included in this study. Lesion size, CNV type on fluorescein angiography, pretreatment best-corrected visual acuity, and foveal AF pattern (intact/nonintact) were used as predictors. Multivariate linear regression and logistic regression were performed using best-corrected visual acuity change and anatomical response at 6 months as the dependent variables separately.

RESULTS: Pretreatment foveal AF (intact or nonintact) did not predict visual outcome (P = 0.17) nor did lesion size (P = 0.2) or CNV type (P = 0.61). Foveal AF did correlate with the visual acuity but it did not predict any treatment response. Pretreatment best-corrected visual acuity was the only predictive factor for the visual outcome (P = 0.043).

CONCLUSION: Pretreatment AF is not a predictor for the treatment response to intravitreal bevacizumab monotherapy in eyes with CNV secondary to age-related macular degeneration.

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INHIBITORY ACTIVITY OF RANIBIZUMAB, SORAFENIB, AND PAZOPANIB ON LIGHT-INDUCED OVEREXPRESSION OF PLATELET-DERIVED GROWTH FACTOR AND VASCULAR ENDOTHELIAL GROWTH FACTOR A AND THE VASCULAR ENDOTHELIAL GROWTH FACTOR A RECEPTORS 1 AND 2 AND NEUROPILIN 1 AND 2.

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BACKGROUND: Cumulative light exposure is significantly associated with progression of age-related macular degeneration. Growth factors and growth factor receptor signaling are known to have a substantial impact on the development of age-related macular degeneration. This study explored the effects of ranibizumab, sorafenib, and pazopanib on vascular endothelial growth factor A (VEGF) receptors 1 and 2 and neuropilin 1 and 2 expression in human retinal pigment epithelial cells. In addition, their effects on light-induced overexpression of VEGF and platelet-derived growth factor were investigated.

METHODS: Primary human retinal pigment epithelial cells were exposed to white light and then treated with ranibizumab (0.125 mg/mL), sorafenib (1 μg/mL), or pazopanib (1 μg/mL). Viability of cells, expression of VEGF receptors 1 and 2 and neuropilin 1 and 2 and their mRNA, and secretion of VEGF and platelet-derived growth factor were investigated by reverse transcription-polymerase chain reactions, immunohistochemistry, and enzyme-linked immunosorbent assays.

RESULTS: Treatment with sorafenib or pazopanib reduced the expression of VEGF receptors 1 and 2 and neuropilin 1, and sorafenib also reduced neuropilin 2. Light exposure decreased cell viability and increased expression and secretion of VEGF and platelet-derived growth factor. Sorafenib and pazopanib significantly reduced light-induced overexpression and secretion of VEGF and platelet-derived growth factor. Ranibizumab reduced secreted VEGF in cell culture supernatants only.

CONCLUSION: Our in vitro results suggest that multikinase inhibitors have promising properties as a potential antiangiogenic treatment for age-related macular degeneration.

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Combination therapy with focal laser photocoagulation and intravitreal ranibizumab for polypoidal choroidal vasculopathy: a case series.

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Purpose: The study aim is to describe the clinical outcomes of patients with polypoidal choroidal vasculopathy (PCV) treated with focal argon laser photocoagulation and ranibizumab combination therapy.

Methods: This study is a retrospective case series of 6 patients (6 eyes) diagnosed with PCV who received combination therapy with argon laser photocoagulation and ranibizumab and have at least 12 months follow-up. Argon laser photocoagulation was applied directly to the polypoidal lesions as identified on indocyanine green angiography and followed by a course of intravitreal ranibizumab injections. The primary outcome measures were the mean change in logMAR visual acuity and the mean change in central macular thickness (CMT) at final follow-up.

Results: The mean (SD) duration of follow-up was 1.09 (0.22) years. At the final follow-up the difference (95% confidence interval [CI]) in logMAR acuity was 0.48 (0.10-0.74) (p=0.01) and the difference (95% CI) in CMT was 207 μm (35-490) (p=0.02) on optical coherence tomography. The mean (SD) number of

ranibizumab injections per eye was 4.83 (3.6). The mean (SD) number of laser treatments per eye was 1.16 (0.4).

Conclusions: In this study, combination therapy with focal argon laser photocoagulation and intravitreal ranibizumab resulted in improved visual acuity and clinical outcomes for patients with PCV for up to 1 year.

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Ophthalmology. 2012 Apr 3. [Epub ahead of print]

Incidence of Endophthalmitis and Use of Antibiotic Prophylaxis after Intravitreal Injections.

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PURPOSE: To report the incidence of endophthalmitis in association with different antibiotic prophylaxis strategies after intravitreal injections of anti-vascular endothelial growth factors and triamcinolone acetonide.

DESIGN: Retrospective, comparative case series.

PARTICIPANTS: Fifteen thousand eight hundred ninety-five intravitreal injections (9453 ranibizumab, 5386 bevacizumab, 935 triamcinolone acetonide, 121 pegaptanib sodium) were reviewed for 2465 patients between January 5, 2005, and August 31, 2010. The number of injections was determined from billing code and patient records.

METHODS: The indications for injection included age-related macular degeneration, diabetic macular edema, central and branch retinal vein occlusion, and miscellaneous causes. Three strategies of topical antibiotic prophylaxis were used by the respective surgeons: (1) antibiotics given for 5 days after each injection, (2) antibiotics given immediately after each injection, and (3) no antibiotics given.

MAIN OUTCOME MEASURES: The primary outcome measures were the incidence of culture-positive endophthalmitis and culture-negative cases of suspected endophthalmitis.

RESULTS: Nine eyes of 9 patients with suspected endophthalmitis after injection were identified. Three of the 9 cases had culture-positive results. The overall incidence of endophthalmitis was 9 in 15 895. The incidence of culture-negative cases of suspected endophthalmitis and culture-proven endophthalmitis after injection was 6 in 15 895 and 3 in 15 895, respectively. Taking into account both culture-positive endophthalmitis and culture-negative cases of suspected endophthalmitis, the incidence per injection was 5 in 8259 for patients who were given antibiotics for 5 days after injection, 2 in 2370 for those who received antibiotics immediately after each injection, and 2 in 5266 who received no antibiotics. However, if considering culture-proven endophthalmitis alone, the use of topical antibiotics, given immediately or for 5 days after injection, showed lower rates of endophthalmitis compared with those without postinjection antibiotics. The risk of endophthalmitis after intravitreal injection varied among agents that were used. Among the 9 cases of clinically suspected endophthalmitis, regardless of prophylactic strategies used, the incidence of endophthalmitis per injection was 2 in 935 for triamcinolone acetonide, 3 in 9453 for ranibizumab, and 4 in 5386 for bevacizumab.

CONCLUSIONS: The overall rate of intravitreal injection-related endophthalmitis is greater with the use of topical antibiotics, given immediately or for 5 days after the injection, compared with no antibiotics.

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Other treatment & diagnosis

Retina. 2012 Mar 29. [Epub ahead of print]

SUBRETINAL DRUSENOID DEPOSITS ASSOCIATED WITH PIGMENT EPITHELIUM DETACHMENT IN AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To characterize retrospectively subretinal drusenoid deposits (SDD) in patients with pigment epithelium detachment (PED) secondary to age-related macular degeneration.

METHODS: Confocal scanning laser ophthalmoscopy near-infrared reflectance images (820 nm) were recorded in 208 eyes of 104 patients with serous, drusenoid, or vascularized PED because of age-related macular degeneration in at least 1 eye. The digital images were evaluated by two independent readers with subsequent senior reader arbitration for prevalence of SDD.

RESULTS: Serous PED was present in only two patients and was therefore not included in the statistical analysis. Subretinal drusenoid deposits were detected in 55 of 102 (53.9%) patients in at least 1 eye. Forty-six of those 55 patients showed SDD bilaterally (83.6%). Subretinal drusenoid deposits were present in 51 (50%) right eyes and 50 (49.0%) left eyes. One hundred and forty-six of 204 eyes showed a PED secondary to age-related macular degeneration of which 111 (76%) were vascularized and 35 (24%) drusenoid. Prevalence of SDD was correlated with age ($P < 0.0001$) and female gender ($P = 0.014$), but not with the type of PED ($P = 0.174$). Cohen kappa statistics showed good interobserver agreement for infrared imaging (0.78 for right eyes, 0.74 for left eyes).

CONCLUSION: Subretinal drusenoid deposits represent a common phenotypic characteristic in eyes with PED because of age-related macular degeneration . As described in previous studies, SDD are readily identified using confocal scanning laser ophthalmoscopy imaging technology. Future studies should pursue the pathophysiologic role and the predictive value of the presence of SDD in the development of PED and a subsequent rip of the retinal pigment epithelium.

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EN FACE SPECTRAL-DOMAIN OPTICAL COHERENCE TOMOGRAPHY OUTER RETINAL ANALYSIS AND RELATION TO VISUAL ACUITY.

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PURPOSE: To describe a method of en face visualization and quantification of the photoreceptor inner segment/outer segment junction area, using spectral-domain optical coherence tomography, and association with visual acuity.

METHODS: Case series of 74 eyes in 53 patients. Central 1-mm and 400-μm en face areas were analyzed with a computer algorithm.

RESULTS: The presence or absence of inner segment/outer segment junction was visible on both spectral-domain optical coherence tomography en face and retinal cross sections. Thirty eyes (40.6%) had no

retinal pathology and an average logMAR visual acuity of 0.116. Twenty-five eyes (33.8%) had intraretinal edema, with visual acuity of 0.494. Nineteen eyes had nonneovascular age-related macular degeneration (dry age-related macular degeneration, 25.6%), with visual acuity of 0.392. In all eyes, central 1-mm and 400-µm en face areas were 58.3 ± 25.0% and 56.4 ± 26.0%, which showed significant correlation with visual acuity (Pearson correlation, r = -0.66 and -0.56, both P < 0.001). This correlation was greater than correlation of visual acuity with central subfield thickness (r = 0.39, P < 0.001), macular volume (r = 0.36, P = 0.002), and average macular thickness (r = 0.37, P = 0.001). However, no variables were significantly correlated with dry age-related macular degeneration eyes.

CONCLUSION: Central en face inner segment/outer segment junction areas are significantly correlated with visual acuity in most eyes. This may correlate better with visual acuity than other spectral-domain optical coherence tomography values, as a reflection of photoreceptor integrity. Dry age-related macular degeneration may disrupt the plane used to formulate the en face display. Advancements in spectral-domain optical coherence tomography may provide routine en face visualization analysis.

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Foveal Localization in Non-Exudative AMD Using Scanning Laser Polarimetry.

Vannasdale DA, Elsner AE, Kohne KD, Peabody TD, Malinovsky VE, Haggerty BP, Weber A, Clark CA.

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PURPOSE: To determine whether custom scanning laser polarimetry (SLP) images, differing in polarization content, can be used to accurately localize the fovea in the presence of non-exudative age-related macular degeneration (AMD). To determine whether alterations to the foveal structure in non-exudative AMD significantly disrupts the birefringent Henle fiber layer, responsible for the macular cross pattern in some SLP images. To determine whether phase retardation information, specifically color-coded information representing its magnitude and axis, allow better foveal localization than images including retardation amplitude only.

METHODS: SLP images were acquired in 25 AMD subjects and 25 age-matched controls. Raw data were used to generate five custom image types differing in polarization content. The foveal location was marked by three graders in each image type for each subject. The difference in variability was compared between the AMD subjects and matched controls. We further determined whether the orientation of Henle fiber layer phase retardation improved localization in 10 subjects with the highest variability in images including only phase retardation amplitude.

RESULTS: Images that differed in polarization content led to strikingly different visualizations of AMD pathology. The Henle fiber layer remained sufficiently intact to assist in fovea localization in all subjects but with more variability in the AMD group. For both the AMD and matched control group, images containing birefringence amplitude and orientation information reduced the amount of intragrader, intergrader, and interimage variability for estimating foveal location.

CONCLUSIONS: The disruption in Henle fiber birefringence was evident in the eyes with AMD but nevertheless was sufficient to help in foveal localization despite macular pathology. Phase retardation amplitude and axis of orientation can be a useful tool in foveal localization in patients with AMD.

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Macular Epiretinal Brachytherapy in Treated Age-Related Macular Degeneration: MERITAGE Study: Twelve-Month Safety and Efficacy Results.

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PURPOSE: To evaluate the safety and efficacy of epimacular brachytherapy (EMB) for the treatment of chronic, active, neovascular age-related macular degeneration (AMD).

DESIGN: Prospective, multicenter, interventional, noncontrolled clinical trial.

PARTICIPANTS: Fifty-three eyes of 53 participants with neovascular AMD requiring frequent anti-vascular endothelial growth factor (VEGF) retreatment.

METHODS: Participants underwent pars plana vitrectomy with a single 24-Gy dose of EMB delivered using an intraocular, handheld cannula containing a strontium 90/yttrium 90 source positioned over the active lesion. Participants were retreated with ranibizumab administered monthly as needed, using predefined retreatment criteria. Optical coherence tomography (OCT) was undertaken monthly, with images assessed by an independent reading center.

MAIN OUTCOME MEASURES: Coprimary outcomes at 12 months were proportion of participants with stable vision (losing <15 Early Treatment Diabetic Retinopathy Study [ETDRS] letters) and mean number of anti-VEGF retreatments.

RESULTS: Before enrollment, participants had received an average of 12.5 anti-VEGF injections. After a single treatment with EMB, 81% maintained stable vision, with a mean of 3.49 anti-VEGF retreatments in 12 months. Mean ± standard deviation change in visual acuity was -4.0±15.1 ETDRS letters. Mean ± standard deviation OCT central retinal thickness increased by 50±179 μm. Common adverse events included conjunctival hemorrhage (n = 38), cataract (n = 16), resolving vitreous hemorrhage (n = 6), and eye pain (n = 5).

CONCLUSIONS: Epimacular brachytherapy produces stable visual acuity in most participants with previously treated, active disease. Epimacular brachytherapy may reduce the need for frequent anti-VEGF retreatment.

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SUBRETINAL DRUSENOID DEPOSITS ASSOCIATED WITH PIGMENT EPITHELIUM DETACHMENT IN AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To characterize retrospectively subretinal drusenoid deposits (SDD) in patients with pigment epithelium detachment (PED) secondary to age-related macular degeneration.

METHODS: Confocal scanning laser ophthalmoscopy near-infrared reflectance images (820 nm) were recorded in 208 eyes of 104 patients with serous, drusenoid, or vascularized PED because of age-related macular degeneration in at least 1 eye. The digital images were evaluated by two independent readers with subsequent senior reader arbitration for prevalence of SDD.

RESULTS: Serous PED was present in only two patients and was therefore not included in the statistical

analysis. Subretinal drusenoid deposits were detected in 55 of 102 (53.9%) patients in at least 1 eye. Forty-six of those 55 patients showed SDD bilaterally (83.6%). Subretinal drusenoid deposits were present in 51 (50%) right eyes and 50 (49.0%) left eyes. One hundred and forty-six of 204 eyes showed a PED secondary to age-related macular degeneration of which 111 (76%) were vascularized and 35 (24%) drusenoid. Prevalence of SDD was correlated with age ($P < 0.0001$) and female gender ($P = 0.014$), but not with the type of PED ($P = 0.174$). Cohen kappa statistics showed good interobserver agreement for infrared imaging (0.78 for right eyes, 0.74 for left eyes).

CONCLUSION: Subretinal drusenoid deposits represent a common phenotypic characteristic in eyes with PED because of age-related macular degeneration . As described in previous studies, SDD are readily identified using confocal scanning laser ophthalmoscopy imaging technology. Future studies should pursue the pathophysiologic role and the predictive value of the presence of SDD in the development of PED and a subsequent rip of the retinal pigment epithelium.

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EFFECT OF CHANGE IN DRUSEN EVOLUTION ON PHOTORECEPTOR INNER SEGMENT/OUTER SEGMENT JUNCTION.

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PURPOSE: To evaluate the integrity of photoreceptor inner segment/outer segment (IS/OS) junction after change of drusen size in age-related macular degeneration using spectral-domain optical coherence tomography.

METHODS: Drusen volume raster scans were performed with the Spectralis spectral-domain optical coherence tomography (Heidelberg Engineering) through 2,624 drusen in 14 eyes with clinically dry age-related macular degeneration, which had been longitudinally followed-up between 23 and 28 months without intervention (mean, 26.3 months). All eyes had Early Treatment Diabetic Retinopathy Study visual acuity. A total of 416 of 2,624 drusen were analyzed.

RESULTS: Of 416 drusen, 83 (20%) were found to have regressed spontaneously (Group A), 212 (51%) showed no change in size (Group B), and 121 (29%) progressed (Group C). Mean drusen size of all drusen was 63.7 ± 25.7 μm. Cross-sectional analysis of drusen morphology showed a correlation between drusen size and disrupted IS/OS junction/photoreceptor integrity ($r = -0.48$, $P < 0.001$). Of the drusen that regressed over time, there was intact IS/OS junction integrity. Even drusen that caused a major disruption showed IS/OS restoration in 74% of the drusen ($P < 0.001$).

CONCLUSION: Progression of drusen shows structural disruption of the IS/OS junction. After drusen regression, the IS/OS junction is either able to restore as drusen regress or was artifactitiously compressed and not initially visible because of the initial drusen compression of the IS/OS junctional line. Therefore, drusen evolution may play an important role in affecting the photoreceptor IS/OS junction integrity.

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Assessment of macular pigment optical density (MPOD) in patients with unilateral wet age-related macular degeneration (AMD).

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Pathogenesis

Acta Biochim Pol. 2012;59(1):91-6. Epub 2012 Mar 17.

Light distributions on the retina: relevance to macular pigment photoprotection.

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Abstract

Light exposure has been implicated in age-related macular degeneration (AMD). This study was designed to measure cumulative light distribution on the retina to determine whether it peaked in the macula. An eye-tracker recorded the subject's field of view and pupil size, and superimposed the gaze position. Fifteen naïve subjects formed a test group; 5 formed a control group. In phase 1, all subjects viewed a sequence of photographic images. In phase 2, the naïve subjects observed a video; in phase 3, they performed computer tasks; in phase 4, the subjects walked around freely. In phase 1, control subjects were instructed to gaze at bright features in the field of view and, in a second test, at dark features. Test group subjects were allowed to gaze freely for all phases. Using the subject's gaze coordinates, we calculated the cumulative light distribution on the retina. As expected for control subjects, cumulative retinal light distributions peaked and dipped in the fovea when they gazed at bright or dark features respectively in the field of view. The light distribution maps obtained from the test group showed a consistent tendency to peak in the macula in phase 3, a variable tendency in phase 4, but little tendency in phases 1 and 2. We conclude that a tendency for light to peak in the macula is a characteristic of some individuals and of certain tasks. In these situations, risk of AMD could be increased but, at the same time, mitigated by the presence of macular carotenoids.

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Invest Ophthalmol Vis Sci. 2012 Apr 2;53(4):1742-51. Print 2012.

Is Drusen Area Really So Important? An Assessment of Risk of Conversion to Neovascular AMD Based on Computerized Measurements of Drusen.

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the UPMC Eye Center.

Purpose: To assess the relative risk of an eye's conversion to wet age-related macular degeneration (AMD) based primarily on drusen measurements obtained from analysis of digitized images.

Methods: Four hundred forty-four subjects (820 eyes) enrolled in the Age-Related Eye Disease Study (AREDS I) and 78 subjects (129 eyes) from the Prophylactic Treatment of AMD trial (PTAMD) were studied retrospectively. Drusen size, distribution, drusen area, and hyperpigmentation in two central macular regions on baseline fundus images were determined using an image analysis algorithm. The relative risk for choroidal neovascularization (CNV) based on drusen area, presence of one or five large drusen, hyperpigmentation, and fellow eye status was calculated.

Results: Odds ratios (ORs) for measured drusen area within the 1000- and 3000-μm regions were 1.644* (1.251-2.162) and 1.278 (0.927-1.762) for AREDS eyes and 0.832 (0.345-2.005) and 1.094 (0.524-2.283) for PTAMD eyes (*P < 0.05). In the 1000-μm region, respective ORs for the presence of a large druse, hyperpigmentation, and fellow eye affected were 2.60, 1.71, and 6.44* for AREDS eyes and 8.24, 1.37, and 17.56* for PTAMD eyes; for the 3000-μm region, ORs were 3.45*, 3.40*, and 4.59* for AREDS and nonsignificant, 6.58, and 11.62* for PTAMD eyes, respectively.

Conclusions: Total drusen area, presence of large drusen, and the presence of hyperpigmentation were not consistent risk factors for an eye's development of CNV. Risk depended on study cohort as well as location. Having an affected fellow eye was the strongest and most consistent risk factor across all models. A larger drusen area does not necessarily increase an eye's risk of conversion to CNV.

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Identification of anti-retinal antibodies in patients with age-related macular degeneration.

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Abstract

Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in industrial counties. Recent findings indicate that the autoimmunity is involved in the pathogenesis of the disease. However, there is no autoantibody biomarker applied in a clinical setting for diagnosis and prognosis of AMD. In order to reveal retinal antigens targeted by serum IgG from AMD patients, mouse retinal tissue proteins were separated by 2-dimensional electrophoresis and the proteins in the immunoblots that were specific for dry and wet AMD patients IgG were identified by LC-MS/MS. Retinol-binding protein 3 and aldolase C (ALDOC) were mainly recognized by IgG form wet AMD patients. Pyruvate kinase M2 (PKM2) was targeted by both dry and wet AMD and level of anti-PKM2 IgG antibody was correlated best with the stage of AMD. Expression of ALDOC and PKM2 was decreased in mouse retina from aging whereas PKM2 deposit on RPE was increased in aged mice. Our data demonstrate that sera of AMD patients contain autoantibodies against retinal proteins and anti-PKM2 IgG serves as a biomarker for diagnosis and prognosis of AMD. Further investigation of the association of anti-retinal antibody level with expression level of antigens in retina will be needed to reveal the disease pathogenesis.

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Genetics

Exp Eye Res. 2012 Mar 21. [Epub ahead of print]

Characterization of the 10q26-orthologue in rhesus monkeys corroborates a functional connection between ARMS2 and HTRA1.

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Abstract

Age-related macular degeneration, which is the leading cause of blindness in industrialized countries, is a multifactorial, degenerative disorder of the macula with strong heritability. For age-related macular degeneration in humans, the genes ARMS2 and HTRA1 in the region 10q26 are both promising candidates for being involved in pathogenesis. However, the associated variants are located in a region of strong linkage disequilibrium and so far, the identification of the causative gene in humans was not yet possible. This dilemma might be solved using an appropriate model organism. Rhesus monkeys suffer from drusen, a major hallmark of age-related macular degeneration, and the drusen-phenotype shares susceptibility factors with human macular degeneration. Thus, the rhesus monkey represents a natural animal model to uncover genetic factors leading to macular degeneration. Moreover, the existence of genetically homogenous cohorts offers an excellent opportunity to determine risk factors. However, the 10q26-orthologue genomic region in rhesus monkeys is not characterized in detail so far. Therefore, the aim of this study is to analyze the rhesus linkage disequilibrium structure and to investigate whether variants in ARMS2 or HTRA1 are associated with the drusen-phenotype as well. We sequenced parts of a 20 kb region around ARMS2 and HTRA1 in a genetically homogeneous cohort of 91 rhesus monkeys descending from the CPRC rhesus cohort on Cayo Santiago and currently housed in the German Primate Centre in Göttingen. Within this group, ophthalmoscopic examinations revealed a naturally high drusen prevalence of about 47% in monkeys >5 years. We detected 56 genetic variants within and around ARMS2 and HTRA1 and, as one deviates from Hardy-Weinberg-Equilibrium, 55 polymorphisms were used to generate a linkage disequilibrium-Plot and to perform association studies. We observed strong linkage disequilibrium between the markers and were able to define two haplotype blocks. One of these blocks spanned the whole ARMS2 locus and the 5' part of HTRA1 - almost perfectly resembling the situation found in humans. Tests for association revealed a variant in the promoter region of HTRA1 and two variants in the 5'-UTR of ARMS2 to be associated with drusen. The strong linkage disequilibrium inhibits - as in humans - a determination of the risk gene using statistical methods only. However, the conserved linkage disequilibrium structure in humans and macaques goes in line with the recently emerged dual causality model proposing that ARMS2 and HTRA1 are functionally connected and that both genes contribute to the disease pathology. Moreover, the characterization of the 10q26-orthologue genomic region of the rhesus monkey provides a basis for now needed functional investigations in a well-characterized model organism.

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THE ARMS2 A69S VARIANT AND BILATERAL ADVANCED AGE-RELATED MACULAR DEGENERATION.

Schwartz SG, Agarwal A, Kovach JL, Gallins PJ, Cade W, Postel EA, Wang G, Ayala-Haedo J, Spencer KM, Haines JL, Pericak-Vance MA, Scott WK.

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PURPOSE: To identify genetic associations between specific risk genes and bilateral advanced age-related macular degeneration (AMD) in a retrospective, observational case series of 1,003 patients: 173 patients with geographic atrophy in at least 1 eye and 830 patients with choroidal neovascularization in at least 1 eye.

METHODS: Patients underwent clinical examination and fundus photography. The images were subsequently graded using a modified grading system adapted from the Age-Related Eye Disease Study.

Genetic analysis was performed to identify genotypes at 4 AMD-associated variants (ARMS2 A69S, CFH Y402H, C3 R102G, and CFB R32Q) in these patients.

RESULTS: There were no statistically significant relationships between clinical findings and genotypes at CFH, C3, and CFB. The genotype at ARMS2 correlated with bilateral advanced AMD using a variety of comparisons: unilateral geographic atrophy versus bilateral geographic atrophy (P = 0.08), unilateral choroidal neovascularization versus bilateral choroidal neovascularization (P = 9.0 × 10), and unilateral late AMD versus bilateral late AMD (P = 5.9 × 10).

CONCLUSION: In this series, in patients with geographic atrophy or choroidal neovascularization in at least 1 eye, the ARMS2 A69S substitution strongly associated with geographic atrophy or choroidal neovascularization in the fellow eye. The ARMS2 A69S substitution may serve as a marker for bilateral advanced AMD.

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Association between polymorphisms of the DNA base excision repair genes MUTYH and hOGG1 and age-related macular degeneration.

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Abstract

Age-Related Macular Degeneration (AMD) is an eye disease that results in progressive and irreversible loss of central vision and is considered as the primary cause of visual impairment, including blindness, in the elderly in industrialized countries. Oxidative stress has been implicated in the pathogenesis of AMD. The hOGG1 and the MUTYH genes play an important role in the repair of oxidatively damaged DNA in the base excision repair pathway. The DNA glycosylases encoded by the hOGG1 and MUTYH genes initiate this pathway by recognizing and removing 8-oxoguanine and adenine paired with 8-oxoguanine, respectively. Our study was designed to examine the association between the c.977 C > G polymorphism (rs1052133) of the hOGG1 gene and the c.972 G > C polymorphism (rs3219489) of the MUTYH gene and AMD as well as the modulation of this association by some clinical and lifestyle factors. Genotypes were determined in DNA from blood of 271 AMD patients, including 101 with wet and 170 with dry form of the disease and 105 sex- and age-matched individuals without AMD. We observed an association between AMD, dry and wet forms of AMD and the C/G genotype and the G allele of the c.977 C > G-hOGG1 polymorphism (p 0.006; 0.009; 0.021 and 0.004; 0.005; 0.016 respectively). On the other hand, the C/C genotype and the C allele reduced the risk of AMD as well as of its dry form or wet form (p 0.002; 0.003; 0.010 and 0.004; 0.005; 0.016, respectively). Therefore, the associations we detected were driven by the dry AMD. We observed some statistically significant association between the occurrence of AMD and its dry and wet forms and genotypes of the other polymorphism, the c.972 G > C-MUTYH polymorphism, but due to borderline character of all this association we do not consider them as medically relevant. Our findings suggest that the c.977 C > G-hOGG1 polymorphism may be associated with dry AMD. Further studies are needed to determine possible association between AMD and the c.972 G > C-MUTYH polymorphism.

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Diet

Prog Retin Eye Res. 2012 Mar 21. [Epub ahead of print]

Lutein: More than just a filter for blue light.

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Abstract

Lutein is concentrated in the primate retina, where together with zeaxanthin it forms the macular pigment. Traditionally lutein is characterized by its blue light filtering and anti-oxidant properties. Eliminating lutein from the diet of experimental animals results in early degenerative signs in the retina while patients with an acquired condition of macular pigment loss (Macular Telangiectasia) show serious visual handicap indicating the importance of macular pigment. Whether lutein intake reduces the risk of age related macular degeneration (AMD) or cataract formation is currently a strong matter of debate and abundant research is carried out to unravel the biological properties of the lutein molecule. SR-B1 has recently been identified as a lutein binding protein in the retina and this same receptor plays a role in the selective uptake in the gut. In the blood lutein is transported via high-density lipoproteins (HDL). Genes controlling SR-B1 and HDL levels predispose to AMD which supports the involvement of cholesterol/lutein transport pathways. Apart from beneficial effects of lutein intake on various visual function tests, recent findings show that lutein can affect immune responses and inflammation. Lutein diminishes the expression of various ocular inflammation models including endotoxin induced uveitis, laser induced choroidal neovascularization, streptozotocin induced diabetes and experimental retinal ischemia and reperfusion. In vitro studies show that lutein suppresses NF kappa-B activation as well as the expression of iNOS and COX-2. Since AMD has features of a chronic low-grade systemic inflammatory response, attention to the exact role of lutein in this disease has shifted from a local effect in the eye towards a possible systemic anti-inflammatory function.

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