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# MD Research News

Issue 8

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## Drug treatment

**Ophthalmology. 2010 Dec 9. [Epub ahead of print]**

**Efficacy and Safety of Monthly versus Quarterly Ranibizumab Treatment in Neovascular Age-related Macular Degeneration The EXCITE Study.**

Schmidt-Erfurth U, Eldem B, Guymer R, Korobelnik JF, Schlingemann RO, Axer-Siegel R, Wiedemann P, Simader C, Gekkieva M, Weichselberger A; EXCITE Study Group.

Department of Ophthalmology, University of Vienna, Waehringer Guertel, Vienna, Austria.

OBJECTIVE: To demonstrate noninferiority of a quarterly treatment regimen to a monthly regimen of ranibizumab in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

DESIGN: A 12-month, multicenter, randomized, double-masked, active-controlled, phase IIIb study.

PARTICIPANTS: Patients with primary or recurrent subfoveal CNV secondary to AMD (353 patients), with predominantly classic, minimally classic, or occult (no classic component) lesions.

INTERVENTION: Patients were randomized (1:1:1) to 0.3 mg quarterly, 0.5 mg quarterly, or 0.3 mg monthly doses of ranibizumab. Treatment comprised of a loading phase (3 consecutive monthly injections) followed by a 9-month maintenance phase (either monthly or quarterly injection).

MAIN OUTCOME MEASURES: Mean change in best-corrected visual acuity (BCVA) and central retinal thickness (CRT) from baseline to month 12 and the incidence of adverse events (AEs).

RESULTS: In the per-protocol population (293 patients), BCVA, measured by Early Treatment Diabetic Retinopathy Study-like charts, increased from baseline to month 12 by 4.9, 3.8, and 8.3 letters in the 0.3 mg quarterly (104 patients), 0.5 mg quarterly (88 patients), and 0.3 mg monthly (101 patients) dosing groups, respectively. Similar results were observed in the intent-to-treat (ITT) population (353 patients). The mean decrease in CRT value from baseline to month 12 in the ITT population was -96.0 μm in 0.3 mg quarterly, -105.6 μm in 0.5 mg quarterly, and -105.3 μm in 0.3 mg monthly group. The most frequent ocular

AEs were conjunctival hemorrhage (17.6%, pooled quarterly groups; 10.4%, monthly group) and eye pain (15.1%, pooled quarterly groups; 20.9%, monthly group). There were 9 ocular serious AEs and 3 deaths; 1 death was suspected to be study related (cerebral hemorrhage; 0.5 mg quarterly group). The incidences of key arteriothromboembolic events were low.

CONCLUSIONS: After 3 initial monthly ranibizumab injections, both monthly (0.3 mg) and quarterly (0.3 mg/0.5 mg) ranibizumab treatments maintained BCVA in patients with CNV secondary to AMD. At month 12, BCVA gain in the monthly regimen was higher than that of the quarterly regimens. The noninferiority of

a quarterly regimen was not achieved with reference to 5.0 letters. The safety profile was similar to that reported in prior ranibizumab studies.

PMID: 21146229 [PubMed - as supplied by publisher]

**Clin Ophthalmol. 2010 Nov 10;4:1271-5.**

**Initial clinical experience of ranibizumab therapy for neovascular age-related macular degeneration.**

Rotsos T, Patel PJ, Chen FK, Tufail A.

Medical Retina Service, Moorfields Eye Hospital, London, UK.

PURPOSE: To describe the visual acuity and safety outcomes for the first 50 patients with neovascular age -related macular degeneration (nAMD) treated with ranibizumab at Moorfields Eye Hospital.

METHODS: A retrospective analysis of case notes from the first 50 consecutive patients with Primary Care Trust funding for ranibizumab therapy for nAMD. Visual acuity outcomes and adverse events were noted, as were service delivery-related indicators.

RESULTS: The mean (±standard deviation) age of the 50 patients was 81 ± 17 years. The mean follow-up of patients was 13.6 ± 2 (range 7.7-18) months. The mean change in visual acuity ± standard error was +4.6 ± 2.2 letters at the end of follow-up, with 26% gaining 15 letters or more. The mean (median) number of injections was 4.7 (4.5) per 12-month period. The mean (median) delay in Primary Care Trust funding approval was 35 days (32 days) prior to the final appraisal document from the National Institute of Health and Clinical Excellence.

CONCLUSIONS: The real-world outcomes of ranibizumab therapy in this initial cohort of patients with nAMD are comparable with those reported in the pivotal, randomized, controlled trials using fewer injections and a prn strategy of retreatment to achieve the gain in visual acuity.

PMID: 21151333 [PubMed - in process]PMCID: PMC2993128

**Arch Ophthalmol. 2010 Dec;128(12):1523-7.**

**Effect of prophylactic intraocular pressure-lowering medication on intraocular pressure spikes after intravitreal injections.**

Frenkel MP, Haji SA, Frenkel RE.

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OBJECTIVE: To determine if prophylactic use of intraocular pressure (IOP)-lowering medication is effective in reducing the IOP spikes after intravitreal injections of pegaptanib, bevacizumab, and ranibizumab.

METHODS: Seventy-one patients with exudative age-related macular degeneration received intravitreal injections of 1 of 3 anti-vascular endothelial growth factor medications: 30 patients received pegaptanib (0.09 mL), 47 patients received bevacizumab (0.05 mL), and 42 patients received ranibizumab (0.05 mL). Intraocular pressure-lowering medication, 1 hour prior to the injection, was used 63%, 74%, and 66% of the time in eyes that received pegaptanib, ranibizumab, and bevacizumab, respectively. Intraocular pressure was measured prior to injection, within 1 minute after injection, and every 5 to 10 minutes until the pressure was reduced to a safe level.

RESULTS: All 3 intravitreal injections caused significant initial IOP spikes (mean [SD] IOP of 38.5 [11.56] mm Hg in the pegaptanib group, 37.75 [8.36] mm Hg in the ranibizumab group, and 34.88 [10.45] mm Hg in the bevacizumab group). The IOP reduced to less than 30 mm Hg in all 3 groups within 20 minutes. Prophylactic medication did not prevent postinjection IOP spikes. Patients with and without glaucoma showed a similar rate of IOP normalization over time in all 3 groups.

CONCLUSION: Intraocular pressure spikes after intravitreal injection of pegaptanib, ranibizumab, and bevacizumab are common and in most cases transient. Routine prophylactic use of IOP-lowering medications is essentially ineffective in preventing IOP spikes after intravitreal injection of pegaptanib, ranibizumab, and bevacizumab and therefore not necessary before the injection.

PMID: 21149773 [PubMed - in process]

**Ophthalmology. 2010 Dec 9. [Epub ahead of print]**

**A Phase 1 Study of KH902, a Vascular Endothelial Growth Factor Receptor Decoy, for Exudative Age-Related Macular Degeneration.**

Zhang M, Zhang J, Yan M, Luo D, Zhu W, Kaiser PK, Yu DC; KH902 Phase 1 Study Group.

Department of Ophthalmology, West China Hospital, Chengdu, China.

PURPOSE: To determine the safety, tolerability, and bioactivity of KH902, a fully human fusion protein containing key domains from vascular endothelial growth factor receptors 1 and 2 with human immunoglobulin Fc.

DESIGN: Prospective, single-center, open-label, dose-escalating, interventional case series.

PARTICIPANTS: Twenty-eight patients with choroidal neovascularization (CNV) resulting from exudative age-related macular degeneration (AMD) with lesion size of 12 disc areas or less and best-corrected visual acuity (VA) of 55 letters or worse.

METHODS: A single intravitreal injection of KH902 at 1 of 6 escalating doses if no dose-limiting toxicity (DLT) occurred through postinjection day 14 of the previous dose level. Follow-up examinations were performed on postinjection days 1, 3, 5, 7, 14, 28, and 42. The primary end point was at 42 days, and patients were monitored for an additional 6 weeks (12 weeks total).

MAIN OUTCOME MEASURES: The primary safety measures were changes from baseline in VA, intraocular pressure (IOP), intraocular inflammation, and production of anti-KH902 antibody. Dose-limiting toxicity was defined as intraocular inflammation, elevated IOP, significantly reduced vision, or retinal hemorrhage within 42 days after injection. Bioactivity measures included mean change from baseline in VA, central retinal thickness, and total macular volume on optical coherence tomography and CNV changes on fluorescein angiography.

RESULTS: All patients completed the study with no DLT and no serious or drug-related adverse events. Ocular adverse events were mild to moderate in severity, including transient IOP elevation and injection-site subconjunctival hemorrhage after KH902 injections. No serum anti-KH902 antibodies were detected. On day 42 after injection, the mean change in VA from baseline was +19.6 letters with no subjects losing 1 letter or more and 57% of patients gaining 15 letters or more from baseline. The mean change in center point thickness from baseline was -77.2 μm and the mean decrease in CNV area was 12.6%.

CONCLUSIONS: No safety concerns were detected after a single, intravitreal injection of KH902 up to 3.0 mg in this phase 1 study. Bioactivity of KH902 was suggested with improvements in VA, reduction in central retinal thickness, and a decrease in CVN area in patients with CNV resulting from exudative AMD, indicating that further study is warranted.

PMID: 21146224 [PubMed - as supplied by publisher]

**Clin Ophthalmol. 2010 Oct 28;4:1249-52.**

**Use of nepafenac (Nevanac) in combination with intravitreal anti-VEGF agents in the treatment of recalcitrant exudative macular degeneration requiring monthly injections.**

Chen E, Benz MS, Fish RH, Brown DM, Wong TP, Kim RY, Major JC.

Retina Consultants of Houston, The Methodist Hospital, Houston, TX, USA.

Abstract

PURPOSE: The purpose of this study is to determine the efficacy of combining topical nepafenac with monthly intravitreal injections of ranibizumab or bevacizumab in the treatment of recalcitrant exudative macular degeneration.

METHODS: This was a retrospective, consecutive case series of patients with exudative macular degeneration requiring maintenance therapy of antivascular endothelial growth factor ( anti-VEGF) injections at least every 6 weeks, who were started on topical nepafenac. Despite frequent anti-VEGF dosing, all patients included in the study had persistence of any combination of the following: intraretinal cysts, subretinal fluid, and/or pigment epithelial detachment. Patients underwent pinhole visual acuity, clinical exam, and optical coherence tomography (OCT) at baseline and every follow-up visit. Response to therapy was graded by reviewing quantitative and qualitative OCT data, and statistical analysis was done with paired Student's t-test.

RESULTS: Twenty-five patients (average age 77; 14 male and 11 female) were reviewed; the mean number of previous injections was 17.4 (range 3-31). Baseline mean visual acuity was 20/55, and final mean visual acuity after 3 months of treatment was 20/51 (P = 0.13). Monthly mean central foveal thickness measurements were 248, 250, 257, and 247 μm (P = 0.53) at baseline, 1, 2, and 3 months, respectively. By the end of the 3-month time point, qualitative OCT findings on 13 patients treated with nepafenac were classified as stable, 10 as better, and 2 as worse.

CONCLUSIONS: There was no significant change in visual acuity or quantitative OCT measurements, but there appeared to be a mild trend toward improved anatomy and qualitative OCT findings when topical nepafenac was added to monthly anti-VEGF injections in patients with persistent intraretinal cysts, subretinal fluid, and/or pigment epithelial detachment. Further prospective studies with longer follow-up may be warranted.

PMID: 21151329 [PubMed - in process]PMCID: PMC2993124

**Indian J Ophthalmol. 2011 Jan-Feb;59(1):62-4.**

**Combination photodynamic therapy and bevacizumab for choroidal neovascularization associated with toxoplasmosis.**

Rishi P, Venkataraman A, Rishi E.

Shri Bhagwan Mahavir Vitreoretinal Services, Sankara Nethralaya, 18, College Road, Chennai - 600 006, Tamil Nadu, India.

Abstract

A 14-year-old girl presenting with visual loss in both eyes was diagnosed to have healed toxoplasma retinochoroiditis in the right eye with active choroidal neovascularization (CNV) secondary to toxoplasmosis in the left. She underwent combination photodynamic therapy (PDT) and intravitreal bevacizumab as primary treatment. PDT was performed as per the 'Treatment of Age-related Macular Degeneration by Photodynamic therapy' study protocol and was followed by intravitreal bevacizumab after 2 days. CNV regressed at 8 weeks of follow-up and remained stable at 8 months of follow-up. The initial visual acuity improved from 20/120 to 20/30. Combination therapy with PDT and intravitreal bevacizumab appears to be effective in the treatment of CNV secondary to toxoplasma retinochoroiditis.

PMID: 21157079 [PubMed - in process]

**Recent Pat Drug Deliv Formul. 2010 Dec 14. [Epub ahead of print]**

**Recent Advances in Intraocular Drug Delivery Systems.**

Yasukawa T, Tabata Y, Kimura H, Ogura Y.

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Vitreoretinal diseases are refractory to both topical and systemic pharmacological approaches because of specific environment of the eye. That is, the cornea, the sclera, nasolacrimal drainage of tears, frontward stream of aqueous humor, blood-aqueous barrier, and blood-retinal barrier strictly limit penetration and diffusion of drug into the retina. However, recent advances in intraocular drug delivery systems (DDS) have enabled drug to be delivered effectively into the eye. Clinically successful or promising cases involve non-biodegradable implants and inserts, biodegradable inserts and microparticles, intravitreal or sub-Tenon's injection of triamcinolone acetonide, and a photodynamic therapy (PDT) with verteporfin, a photosensitizer. More recently, a variety of pharmacological challenges to treat exudative age-related macular degeneration and macular edema are proceeding into clinical trials, as soon as anti-vascular endothelial growth factor (anti-VEGF) therapies have been proved to be effective by repeated intravitreal injections. In the near future, DDS must be required not only to develop a new treatment modality but also to improve efficacy and/or reduce injection numbers of currently available drugs. Here we introduce controlled release of drug and discussion of recent patents with biodegradable or non-biodegradable implants and drug targeting by modification of systemically administered drug.

PMID: 21143129 [PubMed - as supplied by publisher]

## Other treatment

**Clin Neuropharmacol. 2010 Dec 14. [Epub ahead of print]**

**Yi-Gan San for Treatment of Charles Bonnet Syndrome (Visual Hallucination Due to Vision Loss): An Open-Label Study.**

Miyaoka T, Furuya M, Kristian L, Wake R, Kawakami K, Nagahama M, Kawano K, Ieda M, Tsuchie K, Horiguchi J.

Department of Psychiatry, Shimane University School of Medicine, Izumo, Japan.

BACKGROUND: Recent studies indicate that the traditional Japanese herbal medicine yi-gan san (YGS, yokukan-san in Japanese) may be safe and useful for treating behavioral and psychological symptoms in dementia, borderline personality disorder, neuroleptic-induced tardive dyskinesia, and treatment-resistant schizophrenia. Visual hallucinations are common and often distressing consequences of vision loss, particularly in age-related macular degeneration. Charles Bonnet syndrome (CBS) is defined by the triad of complex visual hallucinations, ocular pathology causing visual deterioration, and preserved cognitive status. We aimed at evaluating both the efficacy and safety of YGS in patients with CBS.

METHODS: Twenty patients diagnosed with CBS were investigated, according to the diagnostic criteria established by Gold and Rabins and Teunisse. Participants were treated in a 4-week open-label study with YGS at an average daily dose of 5.8 ± 2.6 g (2.5-7.5 g). Psychometric instruments used to assess efficacy included the Neuropsychiatric Inventory, hallucination subscale of the Positive and Negative Syndrome Scale, and Clinical Global Impression. No cases of serious adverse events were attributed to the study's drug therapy.

RESULTS: A significant decrease in visual hallucination was observed at 2 and 4 weeks in the Neuropsychiatric Inventory, hallucination subscale of the Positive and Negative Syndrome Scale, and Clinical Global Impression scores.

CONCLUSIONS: Yi-gan san may be an effective and safe therapy to control visual hallucination in patients

with CBS and should be further tested in double-blind, placebo-controlled trials. Given the design characteristics of this trial, the present findings should be taken cautiously.

PMID: 21164340 [PubMed - as supplied by publisher]

**Ophthalmologica. 2010 Dec 9;225(3):155-160. [Epub ahead of print]**

**Detection of Macular Function Changes in Early (AREDS 2) and Intermediate (AREDS 3) Age-Related Macular Degeneration.**

Vujosevic S, Smolek MK, Lebow KA, Notaroberto N, Pallikaris A, Casciano M. Fondazione G.B. Bietti, IRCCS, Roma, Italy.

Background/Aim: To evaluate if retinal sensitivity values obtained with a dedicated (screening) device can be used to functionally identify early and intermediate age-related macular degeneration (ARMD).

Methods: A fully automatic fundus perimeter combined with an image-stabilized scanning laser ophthalmoscope was used in 200 ARMD patients (319 eyes) in 5 study sites. The age-matched control group consisted of 200 normals. Sensitivity point values (S values), mean retinal sensitivity, number of points below 24 dB (K value, cutoff for normal values) and fixation stability were recorded.

Results: Of 319 eyes, 164 were classified as early (AREDS 2) and 155 as intermediate (AREDS 3) ARMD. Mean retinal sensitivity was significantly reduced in ARMD patients versus normals ($p < 0.001$). K values were different between normals and ARMD patients ($p < 0.001$). Fixation stability did not differ between early and intermediate ARMD patients.

Conclusions: Macular sensitivity is reduced in patients with early and intermediate ARMD when compared to age-matched normals. These changes may be detected with a screening device.

PMID: 21150232 [PubMed - as supplied by publisher]

**Psychol Aging. 2010 Dec 13. [Epub ahead of print]**

**The adaptation dynamics of chronic functional impairment: What we can learn from older adults with vision loss.**

Schilling OK, Wahl HW, Horowitz A, Reinhardt JP, Boerner K.

This study used vision loss due to age-related macular degeneration to learn about adaptation processes related to chronic functional impairment, focusing on Horowitz and Reinhardt's (1998) concept of Adaptation to Age-related Vision Loss (AVL) as the outcome. We hypothesized that impacts of visual acuity on AVL are mediated by perceived functional vision losses and functional abilities, and tested for "adaptive" weakening of this impact with ongoing loss. Longitudinal data covering a one-year interval from samples with age-related macular degeneration gathered in New York (N = 361) and Heidelberg (Germany, N = 90) were used. We analyzed the hypothesized causal structure by modeling latent change scores, and checked if those with low, medium, and high levels of vision loss at baseline differ in the relations between one-year change scores. Results confirmed that impacts of vision loss on AVL are mediated by decline in functional ability. However, under the most severe levels of vision loss at baseline, functional decline showed only a minor impact on AVL change not explained by a lack of further decline in vision. Findings confirm the effectiveness of adaptation in terms of reduced reactivity to functional losses across increasing level of chronic impairment. Thus, adaptation, weakening the impact of chronic functional impairment on psychological outcomes over time with disease progression, deserves consideration in the study of psychological consequences of chronic physical health conditions in old age. (PsycINFO Database Record

PMID: 21142375 [PubMed - as supplied by publisher]

**Retina. 2010 Dec 9. [Epub ahead of print]**

**PATHOLOGIC INSIGHTS FROM INTEGRATED IMAGING OF RETICULAR PSEUDODRUSEN IN AGE-RELATED MACULAR DEGENERATION.**

Querques G, Querques L, Martinelli D, Massamba N, Coscas G, Soubrane G, Souied EH.

From the Department of Ophthalmology, Centre Hospitalier Intercommunal de Creteil University Paris XII, Creteil, France.

PURPOSE: The purpose of this study was to analyze the integrated infrared reflectance, fundus autofluorescence, and fluorescein angiography (integrated confocal scanning laser ophthalmoscopy fundus imaging) features of reticular pseudodrusen and eye-tracked Spectralis high-resolution spectral domain optical coherence tomography (Spectralis SD-OCT; Heidelberg Engineering).

METHODS: Twenty-two consecutive patients with reticular pseudodrusen were prospectively enrolled and evaluated regarding confocal scanning laser ophthalmoscopy fundus imaging and eye-tracked SD-OCT findings.

RESULTS: Integrated fundus imaging revealed a "target" aspect of most reticular pseudodrusen in the 42 included eyes (22 patients; 12 women, 10 men; mean age 81.38 ± 6.47 years). On fundus autofluorescence and infrared reflectance, the center of most reticular pseudodrusen appeared as an area of isoautofluorescence/reflectance surrounded by halos of reduced autofluorescence/reflectance. Similarly, on fluorescein angiography, the center of reticular pseudodrusen appeared as an area of decreased fluorescence surrounded by a faint halo of increased fluorescence. Spectral domain optical coherence tomography showed a well-defined round or triangular hyperreflective deposit localized between, externally, the retinal pigment epithelium layer, and, internally, the external limiting membrane or the outer plexiform layer. Moreover, SD-OCT showed the loss of both outer segment/retinal pigment epithelium interface and inner segment/outer segment interface over the hyperreflective lesions, as well as an abrupt interruption of both these interfaces at the border of the hyperreflective lesions.

CONCLUSION: The peculiar confocal scanning laser ophthalmoscopy fundus imaging and tracked SD-OCT of reticular pseudodrusen suggest the presence of central lipofuscin-like retinal deposits localized above the retinal pigment epithelium. These findings give insights to other possible aspects of age-related retinal changes.

PMID: 21150696 [PubMed - as supplied by publisher]

**J R Coll Physicians Edinb. 2009 Dec;39(4):329-30.**

**Age-related macular degeneration is linked to cardiovascular disease.**

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PMID: 21152474 [PubMed - in process]

**Optom Vis Sci. 2010 Dec 9. [Epub ahead of print]**

**A Test of Face Discrimination Ability in Aging and Vision Loss.**

Barnes CS, De L'aune W, Schuchard RA.

*PhD Atlanta Veterans Affairs Medical Center, Rehabilitation R&D Center of Excellence, Decatur, Georgia. The corresponding author is currently at Veterans Affairs Palo Alto Health Care System, Palo Alto, California.

PURPOSE.: The ability to recognize faces is fundamental to social interactions but has not been studied

extensively in visual disorders such as age-related macular degeneration (AMD). We report here the development of a face discrimination test, in which both response times (RTs) and accuracies are measured. Results are compared for young and older control subjects and older adults with AMD to determine the factors underlying performance on this test.

METHODS.: Subjects were 14 older controls, 11 young adult controls, and 34 individuals with binocular AMD. In the face discrimination test, colored reference photographs of eight people were presented continuously (male faces in the first half of the test, female faces in the second). On each trial, subjects reported which reference face matched the test face (shown with different poses and/or expressions). In addition, the older controls then identified the expression on the test face.

RESULTS.: The older controls showed generally small numbers of errors (0 to 9%) on the face identifications but more errors on expression identifications (up to 22%). They tended to show shorter RTs (but no changes in accuracy) with repeated presentations of the same face. The young controls responded more quickly, and they made almost no mistakes. Although performance varied, as a group, those with AMD were slower and showed more errors in identification than the older controls did. Across all subjects, both visual acuity and contrast sensitivity contributed significantly to the variances in RTs and accuracy.

CONCLUSIONS.: The group of older controls had poorer and more variable RTs and accuracies than the young controls. Difficulties in face matching, in terms of both accuracy and RT, were observed for subjects with AMD. Performance accuracy and RTs for this new test depended on both visual acuity and contrast sensitivity.

PMID: 21150678 [PubMed - as supplied by publisher]

**Curr Eye Res. 2010 Dec 15. [Epub ahead of print]**

**Color Doppler Imaging of Ocular Blood Flow after Combined Photodynamic Therapy with Intravitreal Triamcinolone in Age-Related Macular Degeneration.**

Cekiç O, Bardak Y, Yeşildağ A.

Department of Ophthalmology, Vakıf Gureba Training and Research Hospital, Istanbul, Turkey.

Purpose: To investigate the effect of combined intravitreal triamcinolone and ocular photodynamic therapy on retinal and choroidal hemodynamics in age-related macular degeneration.

Methods: Intravitreal triamcinolone (4 mg, 0.1 cc) and photodynamic therapy with verteporfin were applied to 48 eyes of 33 subjects (25 male and 8 female; mean age: 68.9 years) with subfoveal choroidal neovascular membrane secondary to age-related macular degeneration. Patients were assessed for ocular hemodynamic parameters with color Doppler imaging 24 hr before and 1 week, 1 month, and 3 months after a single-dose administration of combined intravitreal triamcinolone and photodynamic therapy.

Results: Throughout the study period, no significant difference in resistance index, peak systolic velocity, or end diastolic velocity existed in the ophthalmic artery (P = 0.58, P = 0.18, and P = 0.19, respectively), the posterior ciliary arteries (P = 0.73, P = 0.19, and P = 0.34, respectively), or the central retinal artery (P = 0.09, P = 0.32, and P = 0.47, respectively).

Conclusion: Combined intravitreal triamcinolone and photodynamic therapy was not associated with any alteration in ocular blood flow or flow velocity over 3 months in eyes with age-related macular degeneration.

PMID: 21158585 [PubMed - as supplied by publisher]

**Retina. 2010 Dec 13. [Epub ahead of print]**

**LONG-TERM SD-OCT/SLO IMAGING OF NEURORETINA AND RETINAL PIGMENT EPITHELIUM AFTER SUBTHRESHOLD INFRARED LASER TREATMENT OF DRUSEN.**

Mojana F, Brar M, Cheng L, Bartsch DU, Freeman WR.

From the Jacobs Retina Center at Shiley Eye Center, University of California, San Diego, California.

PURPOSE: The purpose of this study was to determine the long-term effect of subthreshold diode laser treatment for drusen in patients with nonexudative age-related macular degeneration with spectral domain optical coherence tomography combined with simultaneous scanning laser ophthalmoscope.

METHODS: Eight eyes of four consecutive age-related macular degeneration patients with bilateral drusen previously treated with subthreshold diode laser were imaged with spectral domain optical coherence tomography/scanning laser ophthalmoscope. Abnormalities in the outer retinal layers' reflectivity as seen with spectral domain optical coherence tomography/scanning laser ophthalmoscope were retrospectively analyzed and compared with color fundus pictures, and autofluorescence images were acquired immediately before and after the laser treatment.

RESULTS: A focal discrete disruption in the reflectivity of the outer retinal layers was noted in 29% of the laser lesions. The junction in between the inner and outer segment of the photoreceptor was more frequently affected, with associated focal damage of the outer nuclear layer. Defects of the retinal pigment epithelium were occasionally detected. These changes did not correspond to threshold burns on color fundus photography but corresponded to focal areas of increased autofluorescence in the majority of the cases.

CONCLUSION: Subthreshold diode laser treatment causes long-term disruption of the retinal photoreceptor layer as analyzed by spectral domain optical coherence tomography/scanning laser ophthalmoscope. The concept that subthreshold laser treatment can achieve a selected retinal pigment epithelium effect without damage to rods and cones may be flawed.

PMID: 21157398 [PubMed - as supplied by publisher]

## Genetics

**Protein Expr Purif. 2010 Dec 9. [Epub ahead of print]**

**Production of biologically active complement factor H in therapeutically useful quantities.**

Schmidt CQ, Slingsby FC, Richards A, Barlow PN.

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Human complement factor H (FH), an abundant 155-kDa plasma glycoprotein with 40 disulfide bonds, regulates the alternative-pathway complement cascade. Mutations and single nucleotide polymorphisms in the FH gene predispose to development of age-related macular degeneration, atypical haemolytic uraemic syndrome and dense deposit disease. Supplementation with FH variants protective against disease is an enticing therapeutic prospect. Current sources of therapeutic FH are restricted to human blood plasma highlighting a need for recombinant material. Previously FH expression in cultured plant, mammalian or insect cells yielded protein amounts inadequate for full characterisation, and orders of magnitude below therapeutic usefulness. Here, the V62,Y402 variant of FH has been produced recombinantly (rFH) in Pichia pastoris cells. Codon-optimisation proved essential whilst exploitation of the yeast mating α-factor peptide ensured secretion. We thereby produced multiple 10s-of-milligram of rFH. Following endoglycosidase H digestion of N-linked glycans, rFH (with eight residual N-acetylglucosamine moieties) was purified on heparin-affinity resin and anion-exchange chromatography. Full-length rFH was verified by mass spectrometry and western blot using monoclonal antibodies to the C-terminus. Recombinant FH is a single non-aggregated species (by dynamic light scattering) and fully functional in biochemical and biological assays. An additional version of rFH was produced in which eight N-glycosylation sequons were ablated by Asn-Gln substitutions resulting in a glycan-devoid product. Successful production of rFH in this potentially very highly expressing system makes production of therapeutically useful quantities economically viable.

Furthermore, ease of genetic manipulation in P. pastoris would allow production of engineered FH versions with enhanced pharmacokinetic and pharmacodynamic properties.

PMID: 21146613 [PubMed - as supplied by publisher]

**Curr Eye Res. 2010 Dec 15. [Epub ahead of print]**

**Serum VEGF and CFH in Exudative Age-Related Macular Degeneration.**

Haas P, Steindl K, Aggermann T, Schmid-Kubista K, Krugluger W, Hageman GS, Binder S.

Ludwig Boltzmann Institute for Retinology and Biomicroscopic Lasersurgery, Rudolf Foundation Clinic, Vienna, Austria.

Purpose: To determine serum vascular endothelial growth factor 165 (VEGF165) levels and the association of the complement factor H gene (CFH) Y402H polymorphism in patients with exudative age-related macular degeneration (AMD) in comparison to unaffected control subjects.

Methods: Sixty-six AMD patients and 66 healthy age- and gender-matched controls were included in this case-control study. The serum VEGF165 was assayed by ELISA (R&D). Genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism analysis. Chi-squared tests were used regarding the polymorphism, a t-test regarding the VEGF-levels.

Results: Levels of serum VEGF165 were similar in both groups (p-value = 0.2112). Genotype frequency differed significantly between patients with exudative AMD and the healthy control group ($p = 0.003136$). The serum VEGF165 levels were similar irrespective of the presence of the CFH Y402H polymorphism ($p = 0.4113$) and independent of the specific genotype ($p = 0.9634$).

Conclusion: In the present study, exudative AMD is not associated to serum VEGF165 levels; furthermore, our data does not establish a statistical link between VEGF165 and the CFH Y402H polymorphism.

PMID: 21158586 [PubMed - as supplied by publisher]

**Mol Vis. 2010 Dec 7;16:2598-604.**

**Involvement of genetic factors in the response to a variable-dosing ranibizumab treatment regimen for age-related macular degeneration.**

Teper SJ, Nowinska A, Pilat J, Palucha A, Wylegala E.

PURPOSE: To determine whether gene polymorphisms of the major genetic risk factor for age-related macular susceptibility 2 (ARMS2 A69S) and the complement factor H Y402H influence the response to a variable-dosing treatment regimen with ranibizumab for age-related macular degeneration.

METHODS: This prospective cohort study included 90 patients (90 eyes) with exudative age related macular degeneration (AMD) treated with ranibizumab. Patients underwent a 1-year treatment as in the Study of Ranibizumab in Patients with Subfoveal Choroidal Neovascularization Secondary to Age-Related Macular Degeneration (Mitchell et al.). Injections were administered monthly when a patient lost five letters on the Early Treatment Diabetic Retinopathy Study chart or gained 100 μm in central subfield retinal thickness (CSRT). Genotypes (rs10490924 and rs1061170) were analyzed using gene sequence analysis. Best-corrected visual acuity (BCVA) and CSRT values were compared between ARMS2 and complement factor H genotypes. Multiple regression analysis was used to assess the statistical significance.

RESULTS: Mean increase in visual acuity was 4.44±8.12 letters with a 103.63±94.7 μm decrease in CSRT. BCVA improvement was statistically significant in all genotype groups except in homozygous 69S in the AMRS2 gene. CSRT and BCVA changes were correlated (r=0.2521; 95% CI: 0.04746-0.4364, p=0.0165). Multiple regression analysis revealed a significant impact of 69S (p=0.015) on the change in BCVA.

CONCLUSIONS: Visual acuity did not improve during the study in patients homozygous for ARMS2 69S, despite a decrease in CSRT. Further investigation is needed to confirm our findings and understand the mechanisms involved.

PMID: 21151600 [PubMed - in process]PMCID: PMC3000236

## Pathogenesis & epidemiology

**BMC Ophthalmol. 2010 Dec 13;10(1):31. [Epub ahead of print]**

**Clinical risk factors for age-related macular degeneration: a systematic review and meta-analysis.**

Chakravarthy U, Wong TY, Fletcher A, Piault E, Evans C, Zlateva G, Buggage R, Pleil A, Mitchell P.

BACKGROUND: Age-related macular degeneration (AMD) is the leading cause of blindness in Western countries. Numerous risk factors have been reported but the evidence and strength of association is variable. We aimed to identify those risk factors with strong levels of evidence which could be easily assessed by physicians or ophthalmologists to implement preventive interventions or address current behaviors.

METHODS: A systematic review identified 18 prospective and cross-sectional studies and 6 case control studies involving 113,780 persons with 17,236 cases of late AMD that included an estimate of the association between late AMD and at least one of 16 pre-selected risk factors. Fixed-effects meta-analyses were conducted for each factor to combine odds ratio (OR) and/or relative risk (RR) outcomes across studies by study design. Overall raw point estimates of each risk factor and associated 95 percent confidence intervals (CI) were calculated.

RESULTS: Increasing age, current cigarette smoking (OR 2.01; 95 percent CI 1.77 - 2.28), previous cataract surgery (OR 1.77; 95 percent CI 1.49 -2.11), and a family history of AMD (3.67; 95 percent CI 2.18 - 6.29) showed strong and consistent associations with late AMD. Risk factors with moderate and consistent associations were higher body mass index, history of cardiovascular disease, hypertension, and higher plasma fibrinogen. Risk factors with weaker and inconsistent associations were gender, ethnicity, diabetes, iris colour, history of cerebrovascular disease, and serum total and HDL cholesterol and triglyceride levels.

CONCLUSIONS: Smoking, previous cataract surgery and a family history of AMD are consistent risk factors for AMD. Cardiovascular risk factors are also associated with AMD. Knowledge of these risk factors that may be easily assessed by physicians and general ophthalmologists may assist in identification and appropriate referral of persons at risk of AMD.

PMID: 21144031 [PubMed - as supplied by publisher]

**Am J Ophthalmol. 2010 Dec;150(6):940-1; author reply 941-2.**

**Submacular choroidal vascular bed watershed zones and their clinical importance.**

Hayreh SS.

Comment on:

Am J Ophthalmol. 2010 Jul;150(1):40-47.e2.

PMID: 21094712 [PubMed - indexed for MEDLINE]

**J Biol Chem. 2010 Dec 14. [Epub ahead of print]**

**C20-D3-vitamin A slows lipofuscin accumulation and electrophysiological retinal degeneration in a mouse model of Stargardt's disease.**

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Abstract

Stargardts disease, also known as juvenile macular degeneration, occurs in approximately one in 10,000 people and results from genetic defects in the ABCA4 gene. The disease is characterized by premature accumulation of lipofuscin in the retinal pigment epithelium (RPE) of the eye and by vision loss. No cure or treatment is available. Although lipofuscin is considered a hallmark of Stargardts disease, its mechanism of formation and its role in disease pathogenesis are poorly understood. In this work we investigated the effects of long-term administration of deuterium enriched vitamin A, C20-D3-vitamin A, on RPE lipofuscin deposition and eye function in a mouse model of Stargardts disease. Results support the notion that lipofuscin forms partly as a result of the aberrant reactivity of vitamin A through the formation of vitamin A dimers, provide evidence that preventing vitamin A dimerization may slow disease related, retinal physiological changes and perhaps vision loss and suggest that administration of C20-D3-vitamin A may be a potential clinical strategy to ameliorate clinical symptoms resulting from ABCA4 genetic defects.

PMID: 21156790 [PubMed - as supplied by publisher]

**Mol Vis. 2010 Dec 6;16:2578-84.**

**Plasma oxidized LDL and thiol-containing molecules in patients with exudative age-related macular degeneration.**

Javadzadeh A, Ghorbanihaghjo A, Bahreini E, Rashtchizadeh N, Argani H, Alizadeh S.

PURPOSE: It was proposed that total thiols (tSH) as powerful reducing agents and oxidized low-density lipoprotein (OX-LDL) may be associated with development of choroidal neovascularization in exudative age -related macular degeneration (E-ARMD).

METHODS: In a case-control study, 45 patients with E-ARMD were compared with 45 sex- and age-matched healthy controls. The levels of plasma homocysteine (Hcy) and OX-LDL as oxidant agents, and of tSH and glutathione (GSH) as antioxidant markers, were estimated in E-ARMD patients and controls.

RESULTS: The levels of Hcy (15.4±7.2 μM versus 10.7±3.7 μM; p=0.001) and OX-LDL (52.2±13.8 U/l versus 37.8±10.8 U/l; p=0.001) were statistically higher, while GSH (1.10±0.97 μM versus 2.09±1.04 μM; p=0.001) and tSH (0.31±0.06 mM versus 0.35±0.05 mM; p=0.001) were statistically lower, in the patients with E-ARMD than in the control group, respectively. The plasma OX-LDL concentration also exhibited a positive and significant correlation with Hcy (r=0.719, p=0.001) in patients with E-ARMD.

CONCLUSIONS: Lower GSH and tSH as antioxidant and higher Hcy levels as oxidant agents in E-ARMD patients may have resulted in an oxidative environment that was associated with OX-LDL. Further studies with more cases are required to confirm the hypothesis.

PMID: 21151596 [PubMed - in process]PMCID: PMC3000232

# Diet & lifestyle

**Arch Ophthalmol. 2010 Dec 13. [Epub ahead of print]**

**Healthy Lifestyles Related to Subsequent Prevalence of Age-Related Macular Degeneration.**

Mares JA, Voland RP, Sondel SA, Millen AE, Larowe T, Moeller SM, Klein ML, Blodi BA, Chappell RJ, Tinker L, Ritenbaugh C, Gehrs KM, Sarto GE, Johnson E, Snodderly DM, Wallace RB.

OBJECTIVE: To investigate the relationships between lifestyle behaviors of diet, smoking, and physical activity and the subsequent prevalence of age-related macular degeneration (AMD).

METHODS: The population included 1313 participants (aged 55-74 years) in the Carotenoids in Age-Related Eye Disease Study, an ancillary study of the Women's Health Initiative Observational Study. Scores on a modified 2005 Healthy Eating Index were assigned using responses to a food frequency questionnaire administered at baseline of the Women's Health Initiative Observational Study (1994-1998). Physical activity and lifetime smoking history were queried. An average of 6 years later, stereoscopic fundus photographs were taken to assess the presence and severity of AMD; it was present in 202 women, 94% of whom had early AMD, the primary outcome.

RESULTS: In multivariate models, women whose diets scored in the highest quintile compared with the lowest quintile on the modified 2005 Healthy Eating Index had 46% lower odds for early AMD. Women in the highest quintile compared with those in the lowest quintile for physical activity (in metabolic energy task hours per week) had 54% lower odds for early AMD. Although smoking was not independently associated with AMD on its own, having a combination of 3 healthy behaviors (healthy diet, physical activity, and not smoking) was associated with 71% lower odds for AMD compared with having high-risk scores ($P < .001$).

CONCLUSION: Modifying lifestyles might reduce risk for early AMD as much as 3-fold, lowering the risk for advanced AMD in a person's lifetime and the social and economic costs of AMD to society.

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**Ophthalmology. 2010 Dec 9. [Epub ahead of print]**

**Relationship of Smoking and Cardiovascular Risk Factors with Polypoidal Choroidal Vasculopathy and Age-Related Macular Degeneration in Chinese Persons.**

Cackett P, Yeo I, Cheung CM, Vithana EN, Wong D, Tay WT, Tai ES, Aung T, Wong TY.

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PURPOSE: Polypoidal choroidal vasculopathy (PCV) has been described as a distinct clinical entity from choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). The present study aimed to determine risk factors for PCV and to compare associations with those for CNV secondary to AMD.

DESIGN: Case-control study.

PARTICIPANTS: Patients of Chinese ethnicity with clinically and angiographically diagnosed PCV (n = 123) or CNV secondary to AMD (n = 128) were recruited from a tertiary eye hospital in Singapore. Controls without signs of PCV, CNV secondary to AMD, or other retinal pathologic features (n = 1489) were selected from a population-based study.

METHODS: Patients underwent an ophthalmologic examination including digital color fundus photography, stereoscopic fluorescein angiography (FA), and indocyanine green angiography (ICGA). Classification into PCV or CNV secondary to AMD was based on FA and ICGA findings. Risk factors were determined from a standardized interview, with blood pressure recorded using a digital automatic blood pressure monitor.

MAIN OUTCOME MEASURES: Polypoidal choroidal vasculopathy or CNV secondary to AMD.

RESULTS: Persons who smoked were more likely to have PCV (39.9% vs. 13.4%) or CNV secondary to AMD (45.0% vs. 12.3%) than those who did not smoke. After controlling for age, gender, diabetes, hypercholesterolemia, and hypertension, persons who smoked were 4 times more likely to have PCV (odds ratio [OR], 4.4; 95% confidence interval [CI], 2.5-7.7; P<0.001) and CNV secondary to AMD (OR, 4.9; 95% CI, 2.7-8.8; P<0.001). A significant, negative association also was found between diastolic blood pressure and CNV secondary to AMD (OR, 0.7; 95% CI, 0.5-0.9; P = 0.017, adjusted for age, gender, smoking, diabetes, and hypercholesterolemia), but diastolic blood pressure was not associated with PCV.

CONCLUSIONS: Smoking but not other vascular risk factors is significantly associated with both PCV and CNV secondary to AMD in Chinese persons. The similarity of associations suggests that there may be common risk factors and pathological mechanisms.

PMID: 21146223 [PubMed - as supplied by publisher]

**Nepal J Ophthalmol. 2009 Jul-Dec;1(2):114-7.**

**The factors associated with age related macular degeneration and quality of life of the patients in a tertiary-level ophthalmic center in kathmandu.**

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INTRODUCTION: age-related macular degeneration (ARMD) is a leading cause of blindness in the elderly population.

OBJECTIVE: to frame a profile of patients withARMD and find out the factors associated with it

MATERIALS AND METHODS: a cross-sectional study was carried out including a total of 75 patients with ARMD presenting to the out-patient department of a tertiary level ophthalmic center in Kathmandu. The data pertaining to their demography, ocular and systemic history and the findings of clinical examination and laboratory investigations were analyzed. The quality of life was assessed based on their dependability on the others for daily activity.

RESULTS: mean age of presentation of ARMD was 73 years +/- 7.93. Of the total, 44 were male and 31 female. Smoking was significantly associated with ARMD (p<0.01). 47 of the subjects had a sedentary lifestyle and 28 a non-sedentary lifestyle. Sedentary life style was significantly associated with ARMD (p=0.028). 48 subjects were hypertensive. Systemic hypertension was significantly associated with ARMD (p = 0.015). 45 had dry ARMD, 21 had wet ARMD and 9 ofthemhad a mixed variety. Thirteen out of the 75 study subjects were leading a normal life while 45 of them had some limitation (self-care only) and 17 of them were dependent on the others for their daily activity. The quality of life was not significantly different between dry and wet ARMD (p = 0.40).

CONCLUSION: sedentary life style, smoking and hypertension are the modifiable factors that are associated with ARMD. A significant number of people with the ARMD have a compromised quality of life.

PMID: 21141003 [PubMed - in process]