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Drug treatment

Lancet. 2013 Jul 18. pii: S0140-6736(13)61501-9. doi: 10.1016/S0140-6736(13)61501-9. [Epub ahead of print]

Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial.

Chakravarthy U, Harding SP, Rogers CA, Downes SM, Lotery AJ, Culliford LA, Reeves BC; on behalf of the IVAN study investigators.

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BACKGROUND: Bevacizumab has been suggested to have similar effectiveness to ranibizumab for treatment of neovascular age-related macular degeneration. The Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial was designed to compare these drugs and different regimens. Here, we report the findings at the prespecified 2-year timepoint.

METHODS: In a multicentre, 2×2 factorial, non-inferiority randomised trial, we enrolled adults aged at least 50 years with active, previously untreated neovascular age-related macular degeneration and a best corrected distance visual acuity (BCVA) of at least 25 letters from 23 hospitals in the UK. Participants were randomly assigned (1:1:1:1) to intravitreal injections of ranibizumab (0·5 mg) or bevacizumab (1·25 mg) in continuous (every month) or discontinuous (as needed) regimens, with monthly review. Study participants and clinical assessors were masked to drug allocation. Allocation to continuous or discontinuous treatment was masked up to 3 months, at which point investigators and participants were unmasked. The primary outcome was BCVA at 2 years, with a prespecified non-inferiority limit of 3·5 letters. The primary safety outcome was arterial thrombotic event or hospital admission for heart failure. Analyses were by modified intention to treat. This trial is registered, number ISRCTN92166560.

FINDINGS: Between March 27, 2008, and Oct 15, 2010, 628 patients underwent randomisation. 18 were withdrawn; 610 received study drugs (314 ranibizumab; 296 bevacizumab) and were included in analyses. 525 participants reached the visit at 2 years: 134 ranibizumab in continuous regimen, 137 ranibizumab in discontinuous regimen, 127 bevacizumab in continuous regimen, and 127 bevacizumab in discontinuous regimen. For BCVA, bevacizumab was neither non-inferior nor inferior to ranibizumab (mean difference -1·37 letters, 95% CI -3·75 to 1·01; p=0·26). Discontinuous treatment was neither non-inferior nor inferior to continuous treatment (-1·63 letters, -4·01 to 0·75; p=0·18). Frequency of arterial thrombotic events or hospital admission for heart failure did not differ between groups given ranibizumab (20 [6%] of 314 participants) and bevacizumab (12 [4%] of 296; odds ratio [OR] 1·69, 95% CI 0·80-3·57; p=0·16), or those given continuous (12 [4%] of 308) and discontinuous treatment (20 [7%] of 302; 0·56, 0·27-1·19; p=0·13).

Mortality was lower with continuous than discontinuous treatment (OR 0·47, 95% CI 0·22-1·03; p=0·05), but did not differ by drug group (0·96, 0·46-2·02; p=0·91).

INTERPRETATION: Ranibizumab and bevacizumab have similar efficacy. Reduction in the frequency of retreatment resulted in a small loss of efficacy irrespective of drug. Safety was worse when treatment was administered discontinuously. These findings highlight that the choice of anti-VEGF treatment strategy is less straightforward than previously thought.

FUNDING: UK National Institute for Health Research Health Technology Assessment programme.

PMID: 23870813 [PubMed - as supplied by publisher]

Drug Des Devel Ther. 2013 Jul 10;7:565-9. doi: 10.2147/DDDT.S46610. Print 2013.

Effect of ranibizumab on serous and vascular pigment epithelial detachments associated with exudative age-related macular degeneration.

Panos GD, Gatzioufas Z, Petropoulos IK, Dardabounis D, Thumann G, Hafezi F.

Department of Ophthalmology, Geneva University Hospitals and Faculty of Medicine of the University of Geneva, Switzerland.

PURPOSE: To report the effect of intravitreal ranibizumab therapy for serous and vascular pigment epithelial detachments (PED) associated with choroidal neovascularisation (CNV) secondary to age-related macular degeneration (AMD).

METHODS: In a prospective study, best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) data were collected for 62 eyes of 62 patients, with serous or vascular PED associated with CNV secondary to AMD. Intravitreal ranibizumab 0.5 mg was administered with a loading phase of three consecutive monthly injections, followed by monthly review with further treatment, as indicated according to the retreatment criteria of the PrONTO study. The change in visual acuity and PED height from baseline to month 12 after the first injection was determined.

RESULTS: Sixty-one eyes of 61 patients (one of the patients developed retinal pigment epithelial tear and was excluded from the study) were assessed at the 12-month follow-up examination. There were two types of PED, including vascular PED in 32 patients (Group A) and serous PED (Group B) in 29 patients. The mean improvement of mean BCVA from baseline to 12 months was 0.09 logMAR (Logarithm of the Minimum Angle of Resolution) in Group A and 0.13 logMAR in Group B. Both groups showed significant improvement of the mean BCVA 12 months after the first injection compared with the baseline value ($P < 0.05$). In relation to the PED height, the mean decrease of mean PED height from baseline to 12 months was 135 µm in Group A and 180 µm in Group B. Both groups showed significant reduction of the PED height during the follow-up period ($P < 0.01$). The PED anatomical response to ranibizumab was not correlated with the BCVA improvement in any of the groups. Apart from one patient who developed pigment epithelial tear no other complications were documented.

CONCLUSION: Ranibizumab is an effective and safe treatment for improving vision in patients with serous and vascular PED, although the anatomical response of the PED to ranibizumab may not correlate directly with the visual outcome.

PMID: 23874084 [PubMed - in process] PMCID: PMC3712738

Clin Ophthalmol. 2013;7:1377-83. doi: 10.2147/OPTH.S46235. Epub 2013 Jul 8.

Comparing bevacizumab and ranibizumab for initial reduction of central macular thickness in patients with retinal vein occlusions.

Singer MA, Cohen SR, Groth SL, Porbandarwalla S.

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PURPOSE: To examine short-term effects of ranibizumab versus bevacizumab on reduction of optical coherence tomography (OCT) central macular thickness (CMT) in patients with macular edema secondary to retinal vein occlusions (RVOs).

METHODS: This is a retrospective analysis in which patients with RVOs were injected with either bevacizumab or ranibizumab. At 2 weeks, all patients were injected with a dexamethasone intravitreal implant (Ozurdex®). CMT on OCT and best-corrected visual acuity were obtained at baseline, at 2 weeks (just prior to the dexamethasone intravitreal implant), and 6 weeks.

RESULTS: Sixty-four patients received injections (32 bevacizumab; 32 ranibizumab). At 2 weeks, bevacizumab group had a mean (±standard error of mean [SEM]) CMT reduction of 26.2% ± 3.4% versus 47% ± 3.5% reduction with ranibizumab ($P < 0.0001$). At 6 weeks, there was a 31.6% ± 3.2% CMT reduction with bevacizumab versus 52% ± 3.2% with ranibizumab ($P < 0.0001$). At 2 weeks, 15 (9%) of bevacizumab patients versus 25 (78.1%) ranibizumab patients achieved OCT CMT < 300 μm ($P = 0.0192$). At 6 weeks, 18 (56.3%) of bevacizumab compared to 30 (93.8%) of ranibizumab patients achieved CMT < 300 μm ($P = 0.0010$). Visual acuity was not significantly different at each time interval between the groups.

CONCLUSION: Ranibizumab appears to have a greater effect in the short-term of decreasing macular edema on OCT when compared to bevacizumab in patients with RVOs.

PMID: 23874079 [PubMed] PMCID: PMC3711954

Ophthalmology. 2013 Jul 16. pii: S0161-6420(13)00489-2. doi: 10.1016/j.ophtha.2013.05.032. [Epub ahead of print]

Influence of the Vitreomacular Interface on Outcomes of Ranibizumab Therapy in Neovascular Age-related Macular Degeneration.

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PURPOSE: To investigate the influence of the vitreomacular interface (VMI) on the functional and anatomic efficacy of ranibizumab therapy in patients with neovascular age-related macular degeneration (AMD).

DESIGN: Subanalysis of a prospective, 12-month, multicenter, phase IIIb trial.

PARTICIPANTS: A total of 353 treatment-naïve patients with subfoveal choroidal neovascularization (CNV) receiving quarterly or monthly ranibizumab therapy.

METHODS: On monthly optical coherence tomography (OCT) scan sets, the VMI configuration was graded by a certified reading center into one of the following conditions: continuous posterior vitreoretinal attachment (PVA), vitreomacular adhesion (VMA), partial vitreous detachment without vitreomacular contact, or complete posterior vitreous detachment (PVD). Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) measurements were performed at monthly intervals. Analysis included patients with a minimum of 10 OCT examinations, including baseline and month 12 (n = 251). After integration of the VMI configuration over 12 months, patients were divided into one of the following categories: PVD (n = 162), release of vitreomacular contact (RELEASE; n = 48), VMA (n = 37), or PVA (n = 4). General estimation equation analyses were applied to test for noninferiority of quarterly versus monthly treatment.

MAIN OUTCOME MEASURES: The BCVA and CRT changes at month 12.

RESULTS: Mean BCVA changes in letters were +4.7 (PVD), +3.2 (RELEASE), and -0.2 (VMA) in the quarterly regimen and +4.9 (PVD), +12.7 (RELEASE), and +7.5 (VMA) in the monthly regimen. No difference in therapeutic efficiency between monthly and quarterly intervention was found in eyes with PVD, and quarterly treatment was noninferior to monthly treatment (P = 0.001). However, monthly treatment was superior to quarterly treatment in the RELEASE (P = 0.008) and VMA (P = 0.043) groups. Mean CRT changes were -98 and -96 µm (PVD), -117 and -136 µm (RELEASE), and -93 and -87 µm (VMA) in the monthly and quarterly regimens, respectively, without statistically significant differences.

CONCLUSIONS: The configuration of the VMI seems to have an important effect on visual outcomes and need for retreatment. In patients with PVD, a lower treatment frequency may be feasible, whereas patients with RELEASE or VMA may benefit from intensive retreatment. These findings may serve as a basis for individualized treatment decisions in anti-angiogenic therapy of neovascular AMD and perhaps other indications.

PMID: 23870300 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2013 Jul 19. doi: 10.1136/bjophthalmol-2013-303417. [Epub ahead of print]

A randomised controlled trial of ranibizumab with and without ketorolac eyedrops for exudative age -related macular degeneration.

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AIMS: To evaluate whether ketorolac eyedrops and ranibizumab intravitreal injections would provide additional benefit over ranibizumab alone in the treatment of choroidal neovascularisation (CNV).

METHODS: This was a pilot study of eyes with new-onset CNV. A total of 56 patients were enrolled consecutively and randomised in a 1:1 ratio to receive combination treatment with intravitreal ranibizumab and topical ketorolac (group 1) or ranibizumab alone (group 2). All patients received monthly 0.5-mg ranibizumab intravitreal injections for 3 months, after which monthly injections were administered in accordance with the standard of care. Group 1 patients also self-administered one drop of ketorolac three times a day for 6 months. All patients were followed up for 6 months.

RESULTS: At 6 months, both groups showed a significant improvement in best-corrected visual acuity (both, p<0.001). The two treatments did not show significant differences in terms of the number of ranibizumab injections required. However, the mean 6-month change in central macular thickness (CMT) in the combination group was -124 µm (-29.7%; p<0.001), while in the ranibizumab-only group, the change was -86.9 µm (-19.5%; p=0.001); thus, the combination treatment resulted in a greater reduction (p=0.003). The combination treatment had no adverse effects.

CONCLUSIONS: This pilot study is the first to prospectively investigate the efficacy and safety of a combination of 0.45% ketorolac eyedrops three times a day and intravitreal ranibizumab injections in patients with CNV, and suggests that topical ketorolac supplements the activity of intravitreal ranibizumab in reducing CMT in CNV.

PMID: 23873901 [PubMed - as supplied by publisher]

Lancet. 2013 Jul 18. pii: S0140-6736(13)61580-9. doi: 10.1016/S0140-6736(13)61580-9. [Epub ahead of print]

Treatment of age-related macular degeneration.

Cheung CM, Wong TY.

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PMID: 23870812 [PubMed - as supplied by publisher]

BMJ. 2013 Jul 23;347:f4678. doi: 10.1136/bmj.f4678.

Avastin is as effective as Lucentis in treating wet age related macular degeneration, study finds.

Torjesen I.

PMID: 23881948 [PubMed - in process]

Other treatment & diagnosis

Graefes Arch Clin Exp Ophthalmol. 2013 Jul 25. [Epub ahead of print]

Repeatability of visual function measures in age-related macular degeneration.

Aslam T, Mahmood S, Balaskas K, Patton N, Tanawade RG, Tan SZ, Roberts SA, Parkes J, Bishop PN.

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PURPOSE: To assess repeatability of visual function measures in patients with early, intermediate or late age-related macular degeneration (AMD) without active neovascular disease in the study eye, but active neovascular AMD in the fellow eye.

METHODS: One hundred subjects from an ongoing trial were screened for this study in which their LogMAR acuity, contrast sensitivity and reading performance were assessed using standardised protocols by trained optometrists. The same measures were repeated one month later and repeatability of the visual functions assessed.

RESULTS: Data from 83 subjects satisfied inclusion criteria for analysis. Coefficient of repeatability was 14.9 letters for LogMAR visual acuity , 7.2 letters for Pelli Robson contrast sensitivity, 0.72 for LogMAR reading acuity, 110.4 words/ min for reading speed and 0.67 for LogMAR critical print size. Intraclass correlation coefficients allowed comparison between measures and were found to be 0.96 for LogMAR visual acuity, 0.93 for contrast sensitivity, 0.75 for LogMAR reading acuity, 0.79 for reading speed and 0.74 for LogMAR critical print size. Coefficients of variation were 9.4 %, 10.7 %, 48.4 %, 28.4 % and 31.8 % respectively.

CONCLUSIONS: We found coefficients of repeatability that concurred with previous studies demonstrating variability of visual functions in patients with AMD. In addition, we found intraclass correlation coefficients to be better with visual acuity and contrast sensitivity than with measures of reading performance.

PMID: 23884391 [PubMed - as supplied by publisher]

Ophthalmic Surg Lasers Imaging Retina. 2013 Jul 1;44(4):366-73. doi: 10.3928/23258160-20130715-08.

Pars plana vitrectomy with multiple transvenous chorioretinotomies for macular edema due to retinal vein occlusion.

Luttrull JK, Spink CJ.

BACKGROUND AND OBJECTIVE: To review results of vitreous surgery for branch and central retinal vein occlusion (BRVO and CRVO).

PATIENTS AND METHODS: All cases of vitrectomy with multiple transvenous chorioretinotomies for retinal vein occlusion at a vitreoretinal subspecialty practice were reviewed.

RESULTS: Twenty eyes of 20 patients (four with BRVO and 16 with CRVO) were included. Mean time from diagnosis to surgery was 15 months, and mean postoperative follow-up was 22 months. Injections of bevacizumab or ranibizumab decreased postoperatively ($P < .0001$; Poisson regression model), while log-MAR visual acuity improved ($P = .0396$; Wilcoxon signed-rank test). Ten eyes required no further injections postoperatively, and three eyes required one postoperative injection. Macular edema expressed as OCT maximum macular thickness was significantly reduced postoperatively at 6 months and 12 months ($P = .0077$ and .0093, respectively).

CONCLUSION: In a pilot study of retinal vein occlusion treatment, multiple transvenous chorioretinotomy surgery significantly improved visual acuity and macular edema and reduced intravitreal drug dependency. Further study is warranted. [Ophthalmic Surg Lasers Imaging Retina. 2013;44:366-373.].

PMID: 23883532 [PubMed - in process]

Ophthalmic Surg Lasers Imaging Retina. 2013 Jul 1;44(4):344-59. doi: 10.3928/23258160-20130715-06.

Predicting the Progression of Geographic Atrophy in Age-Related Macular Degeneration With SD-OCT En Face Imaging of the Outer Retina.

Nunes RP, Gregori G, Yehoshua Z, Stetson PF, Feuer W, Moshfeghi AA, Rosenfeld PJ.

BACKGROUND AND OBJECTIVE:Spectral-domain optical coherence tomography (SD-OCT) en face imaging was used to measure the growth of geographic atrophy (GA) and identify baseline anatomic changes in the outer retina in eyes with nonexudative age-related macular degeneration (AMD).

PATIENTS AND METHODS:In this prospective study, eyes were imaged using 200 × 200 and 512 × 128 A-scan raster patterns. Outer retinal anatomy was visualized using en face imaging of a 20-μm thick slab encompassing the inner segment/outer segment (IS/OS) band.

RESULTS:En face SD-OCT imaging of the IS/OS region revealed a bilaterally symmetrical pattern of outer retinal disruption extending beyond the borders of GA that accurately predicted the progression of GA over 1 year in 13 of 30 eyes (43.3%). In the remaining cases, the area of disruption was much larger than the area of progression.

CONCLUSION:En face imaging of the outer retina can predict the growth of GA in some eyes. Due to the bilateral symmetry of these findings, this imaging strategy may identify a genetic subset of patients in whom photoreceptor loss precedes the progression of GA. These areas with outer retinal disruption should be followed in clinical trials designed to test treatments for dry AMD. [Ophthalmic Surg Lasers Imaging Retina. 2013;44:344-359.].

PMID: 23883530 [PubMed - in process]

Med Image Anal. 2013 Jul 2;17(8):1058-1072. doi: 10.1016/j.media.2013.06.003. [Epub ahead of print]

Automated drusen segmentation and quantification in SD-OCT images.

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Abstract: Spectral domain optical coherence tomography (SD-OCT) is a useful tool for the visualization of drusen, a retinal abnormality seen in patients with age-related macular degeneration (AMD); however, objective assessment of drusen is thwarted by the lack of a method to robustly quantify these lesions on serial OCT images. Here, we describe an automatic drusen segmentation method for SD-OCT retinal images, which leverages a priori knowledge of normal retinal morphology and anatomical features. The highly reflective and locally connected pixels located below the retinal nerve fiber layer (RNFL) are used to generate a segmentation of the retinal pigment epithelium (RPE) layer. The observed and expected contours of the RPE layer are obtained by interpolating and fitting the shape of the segmented RPE layer, respectively. The areas located between the interpolated and fitted RPE shapes (which have nonzero area when drusen occurs) are marked as drusen. To enhance drusen quantification, we also developed a novel method of retinal projection to generate an en face retinal image based on the RPE extraction, which improves the quality of drusen visualization over the current approach to producing retinal projections from SD-OCT images based on a summed-voxel projection (SVP), and it provides a means of obtaining quantitative features of drusen in the en face projection. Visualization of the segmented drusen is refined through several post-processing steps, drusen detection to eliminate false positive detections on consecutive slices, drusen refinement on a projection view of drusen, and drusen smoothing. Experimental evaluation results demonstrate that our method is effective for drusen segmentation. In a preliminary analysis of the potential clinical utility of our methods, quantitative drusen measurements, such as area and volume, can be correlated with the drusen progression in non-exudative AMD, suggesting that our approach may produce useful quantitative imaging biomarkers to follow this disease and predict patient outcome.

PMID: 23880375 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Jul 20. [Epub ahead of print]

The effect of age and cataract surgery on macular pigment optic density: a cross-sectional, comparative study.

Demirel S, Bilici S, Batıoglu F, Ozmert E.

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BACKGROUND: To analyze the effects of age, cataract surgery and postoperative period on macular pigment optical density (MPOD).

METHODS: The study included cases referred to Ankara University Department of Ophthalmology, between April and June 2012, who had a transparent natural lens or had undergone cataract surgery at least a year ago with their best corrected visual acuity of ≥ 0.5 based on Snellen chart. Presence of an ocular disease that might affect lens, retina and optic nerve (cataract, macular degeneration, diabetic retinopathy, glaucoma etc.), cataract surgery within the previous year, light-colored iris, smoking and use of micronutrition supplementation were determined as exclusion criteria. After detailed opthalmologic examination of all patients, they were divided into three groups based on their age and their lens status as: group 1, patients < 50 years of age having a clear lens; group 2, patients > 50 years of age having a clear lens; and group 3, patients > 50 years of age who had cataract surgery. Age, gender, and postoperative period of the patients as well as the MPOD values of the eyes measured with heterochromatic flicker photometric (HFP) method (MacularMetricsTM) were included in the analysis.

RESULTS: Sixty-eight eyes of 37 cases with a mean age of 53.4 ± 15.3 years were enrolled in the study. Group 1 included 20 eyes of 10 cases (mean age 29.4 ± 9.5); group 2 included 32 eyes of 16 cases (mean

age 60.3 ± 6.8); and group 3 included 16 eyes of 11 cases (mean age 65.2 ± 9.7). The mean macular pigment optical density value of all cases was 0.511 ± 0.192 log unit, while the mean MPOD values of groups 1, 2 and 3 were 0.570 ± 170, 0.528 ± 203 and 0.400 ± 180 log units, respectively. The mean MPOD values of the patients with clear lens aged < 50 and aged > 50 years did not reveal a statisticially significant difference (p = 1). However, the mean MPOD value of the cataract surgery group (group 3) was found to be statistically significantly lower than the group 1 and group 2 (p = 0.022, p = 0.039, respectively). The correlations between MPOD values and postoperative periods of the patients in group 3 showed that a decrease in MPOD values in parallel with duration of the postoperative period and this negative correlation was found to be statistically significant (r: -0.66, p = 0.005).

CONCLUSION: Our study has demonstrated that a significant correlation does not exist between age of the patients and MPOD values. MPOD values were lower than age-matched patients who had undergone cataract surgery and finally an inverse correlation existed between duration of the postoperative period after cataract surgery and MPOD values.

PMID: 23873256 [PubMed - as supplied by publisher]

Retina. 2013 Jul 18. [Epub ahead of print]

MULTIMODAL IMAGING OF PIGMENT EPITHELIAL DETACHMENT: A Guide to Evaluation.

Mrejen S, Sarraf D, Mukkamala SK, Freund KB.

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PURPOSE: To describe the spectrum of pigment epithelial detachments (PEDs) occurring mainly in age-related macular degeneration and central serous chorioretinopathy and also in other inflammatory, neoplastic and iatrogenic, retinal, and systemic disorders.

METHODS: Pigment epithelial detachments are divided into drusenoid, serous, vascularized, or mixed categories.

RESULTS: The clinical presentation, classification, and natural history of PEDs are reviewed as illustrated with multimodal imaging combining traditional and novel imaging techniques, including fluorescein angiography, indocyanine green angiography, fundus autofluorescence, and spectral domain optical coherence tomography. Most PEDs occur because of pathophysiologic mechanisms taking place below the retinal pigment epithelium that are difficult to identify with conventional imaging modalities. Enhanced depth imaging optical coherence tomography and indocyanine green angiography allow a better analysis of the subretinal pigment epithelium compartment.

CONCLUSION: The differentiation between various kinds of PEDs is essential because each PED type is a distinct entity that has a specific pathogenesis, natural history, prognosis, and optimal treatment strategy.

PMID: 23873168 [PubMed - as supplied by publisher]

Klin Oczna. 2013;115(1):25-8.

[Vitreomacular adhesion in HD-OCT images in the age-related macular degeneration].[Article in Polish]

Latalska M, Swiech-Zubilewicz A, Mackiewicz J.

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PURPOSE: The aim of this study was to evaluate an incidence of the vitreomacular adhesion in patients with age-related macular degeneration.

MATERIAL AND METHODS: We examined 472 eyes in 241 patients (136 W/ 105 M) in age of 54-92 years (mean 62.6 years +/- 8.5) with dry or wet age-related macular degeneration using Cirrus HD-OCT (Zeiss) macular cube 512x128 program or 5-line pro-gram.

RESULTS: Vitreomacular adhesion was observed in 139 eyes with dry age-related macular degeneration (29.4%, p=0.000*), in 101 eyes with drusen (21.4%, p=0.000*), in 38 eyes with retinal pigment epithelium alterations (8%, p=0.202), in 278 eyes with wet age-related macular degeneration (58.9%, p=0.001*), in 21 eyes with pigment epithelial detachment (4.4%, p=0.303), in 161 eyes with choroidal neovascularzation (34. 1%, p=0.031*/ and in 96 eyes with scar (20.4%, p=0.040*).

CONCLUSIONS: Probably, vitreomacular adhesion alone is not able to induce age-related macular degeneration, but it may be associated with choroidal neovascularization development, it can contribute to exudate formation and choroidal neovascularization, it may induces or sustains a chronic low-grade inflammation in the macula region.

PMID: 23882735 [PubMed - in process]

Front Psychol. 2013 Jul 17;4:428. doi: 10.3389/fpsyg.2013.00428. Print 2013.

Functional and structural brain modifications induced by oculomotor training in patients with age-related macular degeneration.

Rosengarth K, Keck I, Brandl-Rühle S, Frolo J, Hufendiek K, Greenlee MW, Plank T.

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Abstract: Patients with age-related macular degeneration (AMD) are reliant on their peripheral visual field. Oculomotor training can help them to find the best area on intact peripheral retina and to efficiently stabilize eccentric fixation. In this study, nine patients with AMD were trained over a period of 6 months using oculomotor training protocols to improve fixation stability. They were followed over an additional period of 6 months, where they completed an auditory memory training as a sham training. In this cross-over design five patients started with the sham training and four with the oculomotor training. Seven healthy age-matched subjects, who did not take part in any training procedure, served as controls. During the 6 months of training the AMD subjects and the control group took part in three functional and structural magnetic resonance imaging (MRI) sessions to assess training-related changes in the brain function and structure. The sham-training phase was accompanied by two more fMRI measurements, resulting in five MRI sessions at intervals of 3 months for all participants. Despite substantial variability in the training effects, on average, AMD patients benefited from the training measurements as indexed by significant improvements in their fixation stability, visual acuity, and reading speed. The patients showed a significant positive correlation between brain activation changes and improvements in fixation stability in the visual cortex during training. These correlations were less pronounced on the long-term after training had ceased. We also found a significant increase in gray and white matter in the posterior cerebellum after training in the patient group. Our results show that functional and structural brain changes can be associated, at least on the short-term, with benefits of oculomotor and/or reading training in patients with central scotomata resulting from AMD.

PMID: 23882237 [PubMed] PMCID: PMC3713239

Ophthalmologica. 2013 Jul 25. [Epub ahead of print]

Patient-Reported Outcomes in Spanish Patients Diagnosed with Bilateral Age-Related Macular Degeneration.

López-Miguel A, Coco-Martín MB, Martínez-Fernández R, Gómez-Ramírez AM, García-Ayuso D, Sobrado-Calvo P, Maldonado MJ.

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Purpose: To evaluate the patient-reported outcomes (PRO) in age-related macular degeneration (AMD) patients by using instruments for eliciting health status and vision specific issues.

Methods: PRO were assessed using the 25-item National Eye Institute Visual Function Questionnaire (NEIVFQ-25) and the Short-Form General Health Survey (SF-12).

Results: The mean age and corrected distance visual acuity (CDVA) in the better eye of the AMD patients were 82.53 ± 5.17 years and 0.82 ± 0.43 logMAR, respectively. The overall NEIVFQ-25 composite score was 57.89. SF-12 physical and mental component summary scores were 37.28 and 57.25, respectively. There were significant correlations ($p \leq 0.05$) between CDVA and the following NEIVFQ-25 subscales: general ($r = -0.73$), near ($r = -0.40$) and distance vision ($r = -0.60$), role limitations ($r = -0.40$), social function ($r = -0.48$) and mental health ($r = -0.38$).

Conclusions: Visual function is severely affected in AMD patients. It hampers their daily living without, however, deeply disturbing their social function. This may help them retain adequate mental health despite their poor physical status.

PMID: 23886949 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2013 Aug;88(8):307-312. doi: 10.1016/j.oftal.2012.10.009. Epub 2012 Dec 20.

Availability of resources for patients with wet age-related macular degeneration. Optimal study.

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OBJECTIVE:The aim of the study was to assess the availability of resources for patients with wet age-related macular degeneration (wAMD) in current clinical practice.

METHODS:Observational, cross-sectional and multicenter study. Eligible subjects were ≥ 18 years old, with primary/secondary active subfoveal AMD-related choroidal neovascularization diagnosed 12-18 months prior to inclusion in the study.

RESULTS:A total of 266 patients were included (39 centers). The mean age (SD) was 76.1 (8.1) years, of whom 55.6% were female. According to the investigator assessment a median (Q1-Q3) of 20.0 (10.0-50.0) patients were visited weekly. A mean of 100.0 (45.0-250.0) were currently under treatment mainly performed in operating rooms (61.5%). Centers had 1.0 (1.0-2.0) operating rooms available for treatment 2.0 (2.0-5.0) days/week. In 74.4% they were located on different floors/buildings from ophthalmology services. Waiting time until visit was 40.0 (30.0-60.0) min, and duration of treatment was 20.0 (15.0-50.0) min. The time between request until medical visit was 20.0 (15.0-30.0) days, and from diagnosis to treatment was 7.0 (5.0-10.0) days. Clinicians considered there was insufficient staff for examinations (84.6%), and treatment (46.2%). About 30.8% and 20.5% mentioned lack of diagnostic tools, such as optical coherence tomography and fluorescein angiography.

CONCLUSIONS:More resources for diagnosis and treatment of wAMD are required. These results,

together with the current policy of reducing the budget in the Spanish Health System, could lead to possible delays in the diagnosis and treatment of wAMD.

PMID: 23886362 [PubMed - as supplied by publisher]

Pathogenesis

PLoS One. 2013 Jul 11;8(7):e68882. doi: 10.1371/journal.pone.0068882. Print 2013.

Electrical Stimulation of Inner Retinal Neurons in Wild-Type and Retinally Degenerate (rd/rd) Mice.

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Abstract: Electrical stimulation of the retina following photoreceptor degeneration in diseases such as retinitis pigmentosa and age-related macular degeneration has become a promising therapeutic strategy for the restoration of vision. Many retinal neurons remain functional following photoreceptor degeneration; however, the responses of the different classes of cells to electrical stimuli have not been fully investigated. Using whole-cell patch clamp electrophysiology in retinal slices we investigated the response to electrical stimulation of cells of the inner nuclear layer (INL), pre-synaptic to retinal ganglion cells, in wild-type and retinally degenerate (rd/rd) mice. The responses of these cells to electrical stimulation were extremely varied, with both extrinsic and intrinsic evoked responses observed. Further examination of the intrinsically evoked responses revealed direct activation of both voltage-gated Na(+) channels and K(+) channels. The expression of these channels, which is particularly varied between INL cells, and the stimulus intensity, appears to dictate the polarity of the eventual response. Retinally degenerate animals showed similar responses to electrical stimulation of the retina to those of the wild-type, but the relative representation of each response type differed. The most striking difference between genotypes was the existence of a large amplitude oscillation in the majority of INL cells in rd/rd mice (as previously reported) that impacted on the signal to noise ratio following electrical stimulation. This confounding oscillation may significantly reduce the efficacy of electrical stimulation of the degenerate retina, and a greater understanding of its origin will potentially enable it to be dampened or eliminated.

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Concerted inhibition of HIF-1α and -2α expression markedly suppresses angiogenesis in cultured RPE cells.

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Abstract: HIF-1α is known to play an important role in the induction of VEGF by hypoxia in retinal pigment epithelial (RPE) cells. However, the involvement of the other isoform, HIF-2α, in RPE cells remains unclear. Thus, the purpose of present study was to clarify the role of HIF-2α during induction of angiogenic genes in hypoxic RPE cells. When human RPE cells (ARPE-19) were cultured under hypoxic conditions, HIF-1α and HIF-2α proteins increased. This induced an increase in mRNA for VEGF, causing secretion of VEGF protein into the medium. This conditioned medium induced tube formation in human vascular endothelial cells (HUVEC). The increased expression of mRNA for VEGF in hypoxic RPE cells was partially inhibited by HIF-1α siRNA, but not by HIF-2α siRNA. However, co-transfection of HIF-1α siRNA and HIF-2α siRNA augmented downregulation of VEGF mRNA and protein in hypoxic RPE cells and inhibited formation of tube-like structures in HUVEC. GeneChip and PCR array analyses revealed that not only VEGF, but also

expression of other angiogenic genes were synergistically downregulated by co-transfection of hypoxic RPE cells with HIF-1α and HIF-2α siRNAs. These findings suggest an important compensatory role for the HIF-2α isoform in the regulation of angiogenic gene expression. Thus, suppression of angiogenic genes for HIF-1α and HIF-2α may be a possible therapeutic strategy against retinal angiogenesis in Age-related macular degeneration (ARMD).

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Klin Oczna. 2013;115(1):74-8.

[Age-related macular degeneration as a local manifestation of atherosclerosis - a novel insight into pathogenesis].[Article in Polish]

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Abstract: Age-related macular degeneration is the leading cause of irreversible visual impairment and disability among the elderly in developed countries. There is compelling evidence that atherosclerosis and age-related macular degeneration share a similar pathogenic process. The association between atherosclerosis and age-related macular degeneration has been inferred from histological, biochemical and epidemiological studies. Many published data indicate that drusen are similar in molecular composition to plaques in atherosclerosis. Furthermore, a great body of evidence has emerged over the past decade that implicates the chronic inflammatory processes in the pathogenesis and progression of both disorders. We speculate that vascular atherosclerosis and age-related macular degeneration may represent different manifestations of the same disease induced by a pathologic tissue response to the damage caused by oxidative stress and local ischemia. In this review, we characterise in detail a strong association between age-related macular degeneration and atherosclerosis development, and we postulate the hypothesis that age-related macular degeneration is a local manifestation of a systemic disease. This provides a new approach for understanding the aspects of pathogenesis and might improve the prevention and treatment of both diseases which both result from ageing of the human body.

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The eye: A window to the soul of the immune system.

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Abstract: The eye is considered as an immune privileged site, and with good reason. It has evolved a variety of molecular and cellular mechanisms that limit immune responses to preserve vision. For example, the cornea is mainly protected from autoimmunity by the lack of blood and lymphatic vessels, whereas the retina-blood barrier is maintained in an immunosuppressive state by the retinal pigment epithelium. However, there are several scenarios in which immune privilege is altered and the eye becomes susceptible to immune attack. In this review, we highlight the role of the immune system in two clinical conditions that affect the anterior and posterior segments of the eye: corneal transplantation and age-related macular degeneration. Interestingly, crosstalk between the innate and adaptive immune systems is

critical in both acute and chronic inflammatory responses in the eye, with T cells playing a central role in combination with neutrophils and macrophages. In addition, we emphasize the advantage of using the eye as a model for in vivo longitudinal imaging of the immune system in action. Through this technique, it has been possible to identify functionally distinct intra-graft motility patterns of responding T cells, as well as the importance of chemokine signaling in situ for T cell activation. The detailed study of ocular autoimmunity could provide novel therapeutic strategies for blinding diseases while also providing more general information on acute versus chronic inflammation.

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Topical anti-angiogenic SRPK1 inhibitors reduce choroidal neovascularization in rodent models of exudative-AMD.

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PURPOSE: Exudative age related macular degeneration (wet AMD) is treated by monthly injection into the eye of anti-vascular endothelial growth factor (VEGF) proteins. VEGF is alternatively spliced to produce numerous isoforms that differ in angiogenic activity. Serine-rich protein kinase-1 (SRPK1) has been identified as a regulator of pro-angiogenic VEGF splicing by phosphorylating serine-rich splicing factor-1 (SRSF1), which binds to VEGF pre-mRNA. We tested the hypothesis that topical (eye drop) SRPK1 selective inhibitors could be generated that reduce pro-angiogenic isoforms, and prevent choroidal neovascularization in vivo.

METHODS: Novel inhibitors were tested for SRPK inhibition in vitro, pro-angiogenic VEGF production in RPE cells by PCR and ELISA, and for inhibition of choroidal neovascularisation in mice and rats.

RESULTS: A novel disubstituted furan inhibitor was selective for the SRPK family of kinases and reduced expression of pro-angiogenic but not anti-angiogenic VEGF isoforms. This inhibitor and previously identified SRPK inhibitors significantly reduced choroidal neovascularisation in vivo. Topical adminstration of SRPK inhibitors dose dependently blocked CNV with an EC50 of 9µM.

CONCLUSIONS: These results indicate that novel SRPK1 selective inhibitors could be potential novel topical (eye drop) therapeutics for wet AMD.

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Epidemiology

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Regular aspirin use and risk of age-related macular degeneration.

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Pattern of presentation of idiopathic polypoidal choroidal vasculopathy in Ibadan, Sub-Saharan Africa.

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BACKGROUND: Idiopathic polypoidal choroidal vasculopathy is an abnormal choroidal vascular pathology similar to age-related macular degeneration. It may present with sudden visual loss from hemorrhagic retinal pigment epithelial detachment and breakthrough vitreous hemorrhage or with chronic recurrent episodes. The condition is not uncommon in the retina clinic at the University College Hospital, Ibadan, Sub -Saharan Africa. This study presents the pattern of presentation in Ibadan.

METHODS: We review all cases of idiopathic polypoidal choroidal vasculopathy seen from 2007 to 2012 in the retina clinic at the University College Hospital, Ibadan, to determine the major pattern of presentations, available treatment modalities, and visual outcomes.

RESULTS: Ten cases were seen during the study period. Their mean age was 58 years, with a male to female ratio of 1:4. The most common presenting complaint was sudden visual loss. Major examination findings were retinal pigment epithelial detachment, orange subretinal lesions, and breakthrough vitreous hemorrhage. The modalities of treatment available included vitrectomy to clear vitreous hemorrhage. Intravitreal bevacizumab reduced the height of the pigment epithelial detachment and cleared vitreous hemorrhage. Thermal laser was applied for extrafoveal lesions. Two patients with subfoveal lesions were referred abroad for photodynamic therapy. Visual outcome showed significant improvement in vitrectomized patients who presented with vitreous hemorrhage. Presenting vision of hand motion and light perception improved to vision ranging from counting fingers to 6/12 after vitrectomy.

CONCLUSION: Idiopathic polypoidal choroidal vasculopathy may not be uncommon in Sub-Saharan Africa. A high index of suspicion is warranted in the diagnosis so as to provide timely intervention.

PMID: 23874078 [PubMed] PMCID: PMC3711879

JAMA Ophthalmol. 2013 Jul 18. doi: 10.1001/jamaophthalmol.2013.4694. [Epub ahead of print]

Socioeconomic Disparity in Use of Eye Care Services Among US Adults With Age-Related Eye Diseases: National Health Interview Survey, 2002 and 2008.

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IMPORTANCE: Individuals with age-related eye disease (ARED) need to use eye care services for detection, assessment, and care at regular intervals.

OBJECTIVE: To explore the association between socioeconomic position (SEP) and use of eye care services among US adults with self-reported ARED during 2002 and 2008.

DESIGN: Data were from the National Health Interview Survey 2002 and 2008. We used multiple logistic regression to estimate predictive margins, controlling for other factors, and we used the slope index of inequality to measure the relationship between SEP and use of eye care services across the entire distributions of poverty-income ratio (PIR) and educational attainment. SETTING A cross-sectional, nationally representative sample of adults, with prevalence estimates weighted to represent the civilian, noninstitutionalized US population.

PARTICIPANTS: The sample included US participants in the 2002 (n = 3586) and the 2008 (n = 3104) National Health Interview Survey who were at least 40 years old and reported any ARED (age-related macular degeneration, cataract, diabetic retinopathy, or glaucoma).

MAIN OUTCOMES AND MEASURES: Use of eye care services; SEP was measured by the PIR and educational attainment.

RESULTS: In 2002, persons with ARED and a PIR of less than 1.50 were significantly less likely than those with a PIR of at least 5 to report visiting an eye care provider (62.7% vs 80.1%; P < .001) or undergoing a dilated eye examination in the past 12 months (64.3% vs 80.4%; P < .001), after adjustment for other factors. Similarly, persons with less than a high school education were less likely than those with at least a college education to report a visit to an eye care provider (62.9% vs 80.8%; P < .001) or dilated eye examination (64.8% vs 81.4%; P < .001). In 2002, the slope index of inequality showed statistically significant differences for eye care provider visits across the levels of education (24.4; P = .006), and in 2008, it showed a significant difference for eye care provider visits across the levels of educational attainment (25.2; P = .049) and PIR (21.8; P = .01).

CONCLUSIONS AND RELEVANCE: Significant differences in the use of eye care services by SEP persist among US adults with eye diseases.

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Genetics

Hum Mol Genet. 2013 Jul 19. [Epub ahead of print]

Genetic influences on plasma CFH and CFHR1 concentrations and their role in susceptibility to age-related macular degeneration.

Ansari M, McKeigue PM, Skerka C, Hayward C, Rudan I, Vitart V, Polasek O, Armbrecht AM, Yates JR, Vatavuk Z, Bencic G, Kolcic I, Oostra BA, Van Duijn CM, Campbell S, Stanton CM, Huffman J, Shu X, Khan JC, Shahid H, Harding SP, Bishop PN, Deary IJ, Moore AT, Dhillon B, Rudan P, Zipfel PF, Sim RB, Hastie ND, Campbell H, Wright AF.

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Abstract: It is a longstanding puzzle why non-coding variants in the complement factor H (CFH) gene are more strongly associated with age-related macular degeneration (AMD) than functional coding variants that directly influence the alternative complement pathway. The situation is complicated by tight genetic associations across the region, including the adjacent CFH-related genes CFHR3 and CFHR1, which may themselves influence the alternative complement pathway and are contained within a common deletion (CNP147) which is associated with protection against AMD. It is unclear whether this association is mediated through a protective effect of low plasma CFHR1 concentrations, high plasma CFH or both. We examined the triangular relationships of CFH/CFHR3/CFHR1 genotype, plasma CFH or CFHR1 concentrations and AMD susceptibility in combined case-control (1,256 cases, 1,020 controls) and cross-sectional population (N=1,004) studies and carried out genome-wide association studies of plasma CFH and CFHR1 concentrations. A non-coding CFH SNP (rs6677604) and the CNP147 deletion were strongly correlated both with each other and with plasma CFH and CFHR1 concentrations. The plasma CFH-raising rs6677604 allele and raised plasma CFH concentration were each associated with AMD protection. In contrast, the protective association of the CNP147 deletion with AMD was not mediated by low plasma CFHR1, since AMD-free controls showed increased plasma CFHR1 compared with cases, but it may be mediated by the association of CNP147 with raised plasma CFH concentration. The results are most consistent with a regulatory locus within a 32 kb region of the CFH gene with a major effect on plasma CFH concentration and AMD susceptibility.

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RAD51 gene is associated with advanced age-related macular degeneration in Chinese population.

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OBJECTIVES: This study aims to investigate whether variations in RAD51, B3GALTL, TNFRSF10A and REST-C4ORF14-POLR2B-IGFBP7 are associated with advanced forms of age-related macular degeneration (AMD) in Chinese population.

DESIGN AND METHODS: A total of 119 Chinese patients with AMD and 99 control individuals were recruited. Genomic DNA was extracted from peripheral blood leukocytes. Seven single nucleotide polymorphisms (SNPs) from CFH, HTRA1, RAD51, B3GALTL, TNFRSF10A and REST-C4ORF14-POLR2B-IGFBP7 were genotyped by polymerase chain reaction (PCR) followed by allele-specific restriction enzyme digestion or SNaPshot.

RESULTS: Rs10483810 in RAD51 was significantly associated with advanced AMD (P=0.045). Compared with the wild-type genotype GG, the odds ratio for the risk of advanced AMD was 4.92 (95% confidence interval: 1.04-23.36) for the heterozygous TG genotype. Moreover, the GT genotype at rs10483810 confers significantly increased risk of bilateral AMD compared to unilateral AMD (OR=12.04, 95% CI: 2.50-57.69, P=0.002). Rs13278062 in TNFRSF10A, rs1713985 in REST-C4ORF14-POLR2B-IGFBP7 and rs9542236 in B3GALTL were not found to be associated with AMD (all P>0.05).

CONCLUSION: Our data suggested that the risk allele T of rs10483810 in RAD51 gene is associated with an increased risk of advanced AMD, especially bilateral AMD, in Chinese population.

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Association Analysis of CFH and ARMS2 Gene Polymorphisms in a Brazilian Cohort with Age-Related Macular Degeneration.

Almeida LN, Melilo-Carolino R, Veloso CE, Pereira PA, Bastos-Rodrigues L, Sarubi H, Miranda DM, Soubrane G, De Marco L, Nehemy MB.

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Purpose: To investigate the association between the CFH and ARMS2 gene polymorphisms and age-related macular degeneration (AMD) in a Brazilian cohort.

Methods: We examined 163 individuals with AMD and 154 controls recruited at the Department of Ophthalmology of the Universidade Federal de Minas Gerais, at the Instituto da Visão, and at the Centro Especializado em Olhos, in Brazil, between 2007 and 2012. Genotyping for CFH rs1061170 and ARMS2 rs10490924 single-nucleotide polymorphisms was performed. The odds ratios (OR) for all of the studied genotypes (heterozygous and homozygous) of both genes were calculated compared to homozygous ancestral alleles.

Results: Homozygosity for the CFH and ARMS2 at-risk allele was 33.3 and 23.6%, respectively, for AMD individuals and 10.3 and 7.1%, respectively, for controls (p < 0.0001). The OR was 7.2 (95% CI 3.6-14.5; p

< 0.001) for the CFH at-risk genotype (CC) and 5.5 (95% CI 2.6-11.8; p < 0.0001) for ARMS2 (TT). Subjects homozygous for both polymorphisms had a much higher risk of developing AMD (n = 14 patients, OR 33.3, 95% CI 12.8-86.4). The proportion of ancestry in each group indicated that AMD patients had a higher European (Caucasian) component than controls.

Conclusion: CFH and ARMS2 polymorphisms were strongly associated with AMD in this Brazilian cohort.

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Correction: Haplotypes in IL-8 Gene Are Associated to Age-Related Macular Degeneration: A Case-Control Study.

Ricci F, Staurenghi G, Lepre T, Missiroli F, Zampatti S, Cascella R, Borgiani P, Marsella LT, Eandi CM, Cusumano A, Novelli G, Giardina E.

Abstract: [This corrects the article on p. e66978 in vol. 8.].

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