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MD Research News

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Drug treatment

Eye (Lond). 2012 May 11. doi: 10.1038/eye.2012.90. [Epub ahead of print]

High-dose ranibizumab therapy for vascularized pigment epithelial detachment.

Chan CK, Abraham P, Sarraf D.

1] Southern California Desert Retina Consultants, Medical Group, Palm Desert, CA, USA [2] Department of Ophthalmology, Loma Linda University, Loma Linda, CA, USA.

Purpose: The conventional dose of anti-vascular endothelial growth factor treatment may slowly reduce the subretinal fluid and height of a vascularized pigment epithelial detachment (vPED), but rarely leads to its complete resolution. We report a dramatic outcome involving a high dose (2 mg) of ranibizumab for treating vPED.

Methods: This report describes three eyes with vPED that received 2 mg in 0.05 ml of ranibizumab injections on a monthly basis and were followed prospectively. Each patient received a complete ocular examination, including best-corrected standardized ETDRS testing, fundus photography (FP), fluorescein angiography (FA), optical coherent tomography (OCT), and indocyanine-green angiography at baseline. ETDRS and OCT testing were repeated monthly, while FP and FA were performed every 3 months.

Results: Following a single intravitreal injection of 2 mg ranibizumab, there was rapid resolution of the subretinal fluid, haemorrhage, exudates, and flattening of the vPED within 10 days for Case 1, and within 1 month for Case 2 and Case 3.

Conclusion: Rapid and dramatic decrease in the exudative changes and collapse of the vPED may develop after a single injection of high-dose (2 mg) ranibizumab in certain eyes with a vPED. The improvement was maintained with additional monthly injections to 12 months.Eye advance online publication, 11 May 2012; doi:10.1038/eye.2012.90.

PMID: 22576827 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 May 12. [Epub ahead of print]

Recovery of photoreceptor outer segments after anti-VEGF therapy for age-related macular degeneration.

Oishi A, Shimozono M, Mandai M, Hata M, Nishida A, Kurimoto Y.

Department of Ophthalmology, Kobe City Medical Center General Hospital, 4-6 Minatojima-minamimachi, Chuo-ku, Kobe, 650-0046, Japan, aquio@kuhp.kyoto-u.ac.jp.

PURPOSE: To evaluate whether the status of the external limiting membrane (ELM) or inner segment/outer segment junction (IS/OS) improves after intravitreal injection of ranibizumab for age-related macular degeneration (AMD). We also evaluated whether the pre-operative values of these parameters are associated with the visual prognosis.

METHODS: This was a hospital-based, cross-sectional study. Seventy-six eyes of 76 treatment-naive AMD patients who received three monthly intravitreal injections of ranibizumab followed for more than 6 months with additional as-needed injections were investigated. Spectral domain OCT was used to evaluate the length of ELM, IS/OS, and foveal thickness pre- and post-operatively. Changes of ELM and IS/OS length were evaluated postoperatively. Correlation coefficients between pre-operative parameters and post-operative visual acuity were also analyzed.

RESULTS: Significant changes were noted in mean logMAR (0.66 to 0.53), foveal thickness (231.1 to 151.1 μm), and IS/OS length (514.9 to 832.3 μm) after the treatment. ELM length did not improve significantly (1,312.4 to 1,376.7 μm). Restoration of IS/OS occured where ELM is retained. Although pre-operative ELM length, IS/OS length, and foveal thickness showed correlation with post-operative logMAR (R = -0.51, -0.39, and 0.46, respectively), the most powerful predictive factor for visual prognosis was pre-operative logMAR (R = 0.77, $p < 0.001$).

CONCLUSIONS: IS/OS status improves in response to anti-VEGF therapy but ELM seems to have less plasticity. The status of IS/OS and ELM can be used as prognostic factors but the predictive power is inferior to that of baseline visual acuity.

PMID: 22576370 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2012 May 11. [Epub ahead of print]

Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration.

Muether PS, Hoerster R, Hermann MM, Kirchhof B, Fauser S.

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BACKGROUND: Intravitreal injections of ranibizumab are the standard of care for neovascular age-related macular degeneration (AMD). In clinical trials, comparable efficacy has been shown for either monthly injections or as needed injections upon monthly controls. Unlike in trial settings, treatment in clinical routine is often delayed by complex approval procedures of health insurance and limited short-term surgical capacities.

METHODS: Eighty-nine patients with neovascular AMD were followed for 12 months. Early treatment diabetic retinopathy study (ETDRS) visual acuity (VA), Radner reading VA and spectral domain optical coherence tomography were performed monthly, with additional fluorescein angiography if needed. After an initial loading phase of three consecutive monthly intravitreal injections with ranibizumab, re-injections were performed when recurrent activity of choroidal neovascularization (CNV) was detected.

RESULTS: After an initial increase to a value of +5.0 ± 11.87 ETDRS letters from baseline, VA constantly decreased over 12 months to a value of -0.66 ± 16.82 ETDRS letters below baseline. Central retinal thickness (CRT) decreased from a value of 438.1 ± 191.4 μm at baseline to a value of 289.9 ± 138.6 μm after initial therapy and stabilized at a value of 322.4 ± 199.5 μm. Loss of VA during latency between indication to treat and treatment was significantly greater than re-gain of VA after re-initiation of therapy (-2.2 ± 5.0 versus 0.4 ± 7.4 letters; $p = 0.046$).

CONCLUSIONS: Latency between indication to treat and treatment is responsible for irreversible VA deterioration. A successful PRN treatment regimen for neovascular AMD requires immediate access to therapy after indication.

PMID: 22573410 [PubMed - as supplied by publisher]

Ophthalmologica. 2012 May 9. [Epub ahead of print]

Intravitreal Ranibizumab versus Thermal Laser Photocoagulation in the Treatment of Extrafoveal Classic Choroidal Neovascularization Secondary to Age-Related Macular Degeneration.

Ladas ID, Chatziralli IP, Kotsolis AI, Douvali M, Georgalas I, Theodossiadis PG, Rouvas AA.

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Background: To compare the efficacy of thermal laser photocoagulation versus intravitreal ranibizumab for the treatment of extrafoveal classic choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Methods: We conducted a retrospective study on 24 eyes with extrafoveal classic CNV secondary to AMD, treated either with thermal laser photocoagulation (group 1) or with intravitreal ranibizumab (group 2). Visual acuity, number of injections/sessions and recurrence rate were assessed.

Results: The mean follow-up time was 23.6 ± 2.26 and 19.1 ± 9.74 months for group 1 and 2, respectively. Mean best corrected visual acuity (BCVA) of groups 1 and 2 was 0.59 ± 0.32 and 0.46 ± 0.30 logMAR, respectively ($p = 0.343$). At the end of the follow-up, mean BCVA of group 1 was 0.92 ± 0.35 and of group 2 0.16 ± 0.12 logMAR and differed statistically compared to baseline ($p = 0.02$ and $p = 0.006$, respectively). There was a statistically significant difference between the two groups as far as BCVA at the end of the follow-up was concerned ($p < 0.0001$). The patients in group 1 received on average 1.38 sessions of thermal laser photocoagulation, while patients in group 2 received on average 4 injections of ranibizumab. The recurrence rate in the laser group was 84.6%, while in the ranibizumab group it was 18.2% ($p < 0.001$). Specifically, the mean time of recurrence in the laser group was 11.5 months, whereas in the ranibizumab group it was 18 months ($p = 0.048$).

Conclusion: Intravitreal ranibizumab showed promising results in BCVA improvement and decrease in macular thickness in patients with extrafoveal classic CNV due to AMD, with a small number of injections. Laser photocoagulation treatment presented worsening in BCVA and high recurrence rate in our study with long-term follow-up.

PMID: 22571933 [PubMed - as supplied by publisher]

Eur J Ophthalmol. 2012 Apr 24:0. doi: 10.5301/ejo.5000147. [Epub ahead of print]

Shortening ocular pain duration following intravitreal injections.

Rifkin L, Schaal S.

Department of Ophthalmology and Visual Sciences, University of Louisville, Louisville, Kentucky - USA.

Purpose: To determine ocular pain duration after routine in-office intravitreal injection and to determine whether topical eyedrops are beneficial in increasing patient comfort.

Methods: Forty injection-naïve patients receiving routine intravitreal injections of bevacizumab for age-related macular degeneration were randomized into 3 groups: group 1 (control, no drops), group 2 (generic artificial tears), and group 3 (ketorolac tromethamine 0.4% eyedrops). Those who received topical

medications were given a Visual Analog Pain score survey and asked to record their pain on a scale from 0 (no distress) to 10 (unbearable distress) daily until a score of 0 was achieved, at which point they were instructed to discontinue use of their given drops. Self-reported pain scores were assessed.

Results: Pain after routine intravitreal injection lasts on average between 3 and 7 days. Patients receiving topical ketorolac eyedrops reported the fewest average number of pain days (2.25±1.22) vs patients receiving artificial tears (3.54±1.13) or those who received no postprocedure eyedrops (5.13±1.25); p<0.05. At most, patients receiving ketorolac eyedrops reported 3 days of recordable pain. Those who received artificial tears reported at most 5 days of recordable pain, and patients who did not receive any postprocedure eyedrops reported at most 7 days of recordable pain.

Conclusions: Pain after intravitreal injection is generally mild, may be reduced by postinjection topical ketorolac eyedrops, and lasts less than 1 week.

PMID: 22562296 [PubMed - as supplied by publisher]

Eye (Lond). 2012 May 4. doi: 10.1038/eye.2012.72. [Epub ahead of print]

Retinal vascular changes following intravitreal ranibizumab injections for neovascular AMD over a 1 -year period.

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Purpose: To assess retinal vascular calibre changes in eyes with neovascular age-related macular degeneration (AMD), treated with intravitreal anti-vascular endothelial growth factor agents, over a 1-year period and compare any such changes to untreated fellow eyes.

Methods: Treatment naïve patients with neovascular AMD received three consecutive intravitreal injections of ranibizumab, followed by a pro re nata dosing regimen up to 1 year, with the aim of maintaining a 'fluid-free' macula. Retinal arteriolar and venular calibre was measured from digital fundus photographs at baseline and at three monthly intervals to 1 year, and summarised as central retinal artery equivalent (CRAE) and central retinal venular equivalent (CRVE), respectively.

Results: A total of 53 injected eyes and 41 fellow, non-injected eyes were analysed. At baseline, there were no differences in retinal vascular calibre between injected and non-injected eyes (mean CRAE (SD) 144.93 (14.07) vs 145.74 (13.10) μm, P=0.80 and mean CRVE (SD) 216.23 (25.93) vs 219.91 (22.82) μm, P=0.53). Over a 12-month period, retinal venular calibre dilatation occurred in injected eyes (mean CRVE change +5.71 (14.71) μm, P=0.007), with no change in retinal arterioles, +0.69 (14.71) μm, P=0.68. In non-injected eyes, arteriolar narrowing occurred as a whole, mean CRAE change -4.20 (7.00) μm, P=0.001, over 12 months, with a trend for narrowing in venules, -2.16 (11.56) μm, P=0.28. In injected eyes, after controlling for covariates, the changes in CRVE over 12 months mirrored improvements in macular thickness, -0.06 (-0.005, -0.11) μm, P=0.04, and visual acuity, +9.66 (-0.30, +19.32) μm, P=0.06.

Conclusion: Intravitreal ranibizumab significantly dilated retinal venules after a 1-year period.

PMID: 22562186 [PubMed - as supplied by publisher]

Can J Ophthalmol. 2012 Apr;47(2):170-5. Epub 2012 Mar 13.

Hemorrhagic complications after intravitreal ranibizumab injection for polypoidal choroidal vasculopathy.

Cho HJ, Lee DW, Cho SW, Kim CG, Kim JW.

Department of Ophthalmology, Kim's Eye Hospital, Konyang University College of Medicine, Seoul, Korea.

OBJECTIVE: To evaluate clinical features and risk factors for hemorrhagic complications in eyes with polypoidal choroidal vasculopathy (PCV) after intravitreal ranibizumab injection.

DESIGN: Retrospective case series.

PARTICIPANTS: The charts of 54 patients with PCV who had received intravitreal ranibizumab 0.5 mg.

METHODS: The study was conducted as a retrospective chart review of 54 patients with PCV who had received intravitreal ranibizumab 0.5 mg. Analysis of 2 groups was based on mean PCV lesion size: < 15mm(2) (n = 24); or ≥ 15mm(2) (n = 32). The occurrence of fresh postoperative subretinal hemorrhage, best corrected visual acuity, systemic disease, and medication history were documented and analyzed.

RESULTS: The mean injection number was 3.3 ± 0.7 (range, 1 to 6), with a mean follow-up of 7.4 ± 2.8 months (range, 4 to 14 months). During the follow-up period, postoperative subretinal hemorrhage was observed in 5 (8.9%) of 56 eyes. Occurrence of postoperative hemorrhage was significantly increased in the group with large PCV size (p = 0.01). Pars plana vitrectomy was performed for postoperative bleeding that resulted in vitreous hemorrhage in 1 eye (1.8%). Various systemic diseases and medication with an anticoagulant had no correlation with occurrence of hemorrhagic complications.

CONCLUSIONS: Subretinal hemorrhage after ranibizumab injection can occur in patients with PCV. When considering ranibizumab injection for treatment of a large PCV lesion, the risk for hemorrhagic complications should be considered.

PMID: 22560424 [PubMed - in process]

Can J Ophthalmol. 2012 Apr;47(2):165-9.

Bevacizumab and ranibizumab for neovascular age-related macular degeneration: a treatment approach based on individual patient needs.

Bellerive C, Cinq-Mars B, Lalonde G, Malenfant M, Tourville E, Tardif Y, Giasson M, Hébert M.

Department of Ophthalmology, Saint-Sacrement Hospital, Laval University, Qué

OBJECTIVE: To compare the efficacy of intravitreal bevacizumab and ranibizumab for the treatment of neovascular age-related macular degeneration using an as-needed treatment regimen.

DESIGN: Retrospective chart review.

PARTICIPANTS: One hundred and ninety two eyes of 184 patients.

METHODS: Patients received an initial treatment of 3 monthly intravitreal injections of ranibizumab or bevacizumab and retreatment is individually considered for each patient on the basis of optical coherence tomography, angiography, and clinical examination.

RESULTS: Fifty eyes treated with ranibizumab and 142 eyes treated with bevacizumab were included. The average age of the patients at baseline was 76.9 ± 8 years and 76.4 ± 8 years in the ranibizumab and bevacizumab group respectively. Mean visual acuity improved from 0.69 to 0.55 logMAR at 12 months in the ranibizumab group and from 0.70 to 0.67 logMAR in the bevacizumab group. At 12 months, 92% of eyes treated with ranibizumab had lost fewer than 0.3 logMAR, as compared with 83% in the bevacizumab group. The ranibizumab group received a mean of 4.92 injections, compared to 4.75 injections in the bevacizumab group over 12 months. After the first 3 injections, 20% of patients in the ranibizumab group and 26% in the bevacizumab group never needed another injection.

CONCLUSIONS: An approach based on clinical onset and choroidal neovascularization progression at angiography may provide benefit by reducing the number of intravitreal injections required.

PMID: 22560423 [PubMed - in process]

Can J Ophthalmol. 2012 Apr;47(2):159-64.

Comparison of outcomes after switching treatment from intravitreal bevacizumab to ranibizumab in neovascular age-related macular degeneration.

Kent JS, Iordanous Y, Mao A, Powell AM, Kent SS, Sheidow TG.

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OBJECTIVE: To compare visual acuity and central retinal thickness in patients initially treated with bevacizumab (Avastin) and switched to ranibizumab (Lucentis) for neovascular age-related macular degeneration (AMD).

DESIGN: A retrospective chart review.

PARTICIPANTS: This study included 87 eyes from 80 patients over the age of 65 with neovascular AMD.

METHODS: Patients were initially treated with bevacizumab injections every 6 weeks and then switched to ranibizumab every 4 weeks when it became publicly funded by the Ontario government. Outcomes include comparison of visual acuity and central retinal thickness after bevacizumab treatment, and after switching to ranibizumab.

RESULTS: Visual acuity improved significantly versus initial baseline values following a treatment course of 3 or more injections of bevacizumab (0.58 logMar, SD = 0.30 vs 0.73 logMar, SD = 0.41; p = 0.0007). Patients then showed a further significant improvement in visual acuity after switching and receiving a course of ranibizumab (0.51 logMar, SD = 0.32) (p = 0.0122). Mean central retinal thickness as measured by optical coherence tomography significantly decreased after a course of bevacizumab (p = 0.0158), and a further decrease was noted after a subsequent course of ranibizumab (p < 0.0001).

CONCLUSIONS: There was a significant improvement in visual acuity and central retinal thickness in patients with neovascular AMD initially treated with bevacizumab. When these patients were uniformly switched to ranibizumab there was a further significant improvement in visual acuity and a reduction of retinal thickness. It appears that ranibizumab can maintain, or improve the effect achieved after an initial course of bevacizumab.

PMID: 22560422 [PubMed - in process]

Lancet. 2012 May 5;379(9827):1728-38.

Age-related macular degeneration.

Lim LS, Mitchell P, Seddon JM, Holz FG, Wong TY.

Singapore Eye Research Institute, Singapore National Eye Centre, Singapore.

Abstract

Age-related macular degeneration is a major cause of blindness worldwide. With ageing populations in many countries, more than 20% might have the disorder. Advanced age-related macular degeneration, including neovascular age-related macular degeneration (wet) and geographic atrophy (late dry), is associated with substantial, progressive visual impairment. Major risk factors include cigarette smoking,

nutritional factors, cardiovascular diseases, and genetic markers, including genes regulating complement, lipid, angiogenic, and extracellular matrix pathways. Some studies have suggested a declining prevalence of age-related macular degeneration, perhaps due to reduced exposure to modifiable risk factors. Accurate diagnosis combines clinical examination and investigations, including retinal photography, angiography, and optical coherence tomography. Dietary anti-oxidant supplementation slows progression of the disease. Treatment for neovascular age-related macular degeneration incorporates intraocular injections of anti-VEGF agents, occasionally combined with other modalities. Evidence suggests that two commonly used anti-VEGF therapies, ranibizumab and bevacizumab, have similar efficacy, but possible differences in systemic safety are difficult to assess. Future treatments include inhibition of other angiogenic factors, and regenerative and topical therapies.

PMID: 22559899 [PubMed - in process]

Indian J Ophthalmol. 2012 May;60(3):207-9.

Ranibizumab for choroidal neovascular membrane in a rare case of Bietti's crystalline dystrophy: A case report.

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Abstract

We report a rare case of Bietti's crystalline dystrophy presenting with choroidal neovascular membrane (CNVM) which was treated with three injections of intravitreal ranibizumab. The CNVM underwent scarring after the injections with stabilization of visual acuity at a follow-up period of 12 months suggesting that intravitreal ranibizumab may have a role in the management of CNVM in these rare cases.

PMID: 22569382 [PubMed - in process]

BMJ. 2012 May 9;344:e3275. doi: 10.1136/bmj.e3275.

Avastin is as effective as Lucentis for wet AMD and could save NHS {pound}84m a year, study shows.

Hawkes N.

PMID: 22573655 [PubMed - in process]

Other treatment & diagnosis

Biomed Opt Express. 2012 May 1;3(5):927-42. Epub 2012 Apr 12.

Sparsity based denoising of spectral domain optical coherence tomography images.

Fang L, Li S, Nie Q, Izatt JA, Toth CA, Farsiu S.

Abstract

In this paper, we make contact with the field of compressive sensing and present a development and generalization of tools and results for reconstructing irregularly sampled tomographic data. In particular, we focus on denoising Spectral-Domain Optical Coherence Tomography (SDOCT) volumetric data. We take advantage of customized scanning patterns, in which, a selected number of B-scans are imaged at higher

signal-to-noise ratio (SNR). We learn a sparse representation dictionary for each of these high-SNR images, and utilize such dictionaries to denoise the low-SNR B-scans. We name this method multiscale sparsity based tomographic denoising (MSBTD). We show the qualitative and quantitative superiority of the MSBTD algorithm compared to popular denoising algorithms on images from normal and age-related macular degeneration eyes of a multi-center clinical trial. We have made the corresponding data set and software freely available online.

PMID: 22567586 [PubMed - in process] PMCID: PMC3342198

Pathogenesis

Nihon Ganka Gakkai Zasshi. 2012 Mar;116(3):200-31; discussion 232.

[Polypoidal choroidal vasculopathy].

[Article in Japanese]

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Abstract

Polypoidal choroidal vasculopathy (PCV) is characterized by a branching vascular network with polypoidal lesions under the retinal pigment epithelium (RPE). In Japan, it is classified as a specific form of exudative age-related macular degeneration. However, several issues which we investigated regarding the pathogenesis and treatment of PCV remain unresolved. We investigated the pathogenesis, clinical findings and treatment of PCV. 1. Indocyanine green angiographic findings. There were two different patterns on indocyanine green angiograms. In the first pattern, both feeder and draining vessels were visible and network vessels showed characteristic findings of choroidal neovascularization (CNV). Points of focal dilatation on marginal vessels were comprised of polypoidal lesions. In the second pattern, neither feeder nor draining vessels were visible and there were few network vessels. The points of deformation of network vessels appeared to be polypoidal lesions. The former represents a deformation of CNV, i.e. polypoidal CNV; the latter is thought to result from abnormalities of the choroidal vessels, i.e. PCV in the strict sense. 2. Pathological findings of PCV in the strict sense. The histopathological characteristics of PCV in the strict sense, which had been eliminated by vitrectomy, were dilatation and hyalinization of vessels, massive exudative changes in blood plasma, basement membrane-like deposits and scant granulomatous tissue. These vessels were located beneath Bruch's membrane. The findings indicate that PCV in the strict sense arises from hyalinized arteriolosclerosis of choroidal vessels. 3. Optical coherence tomographic findings. A break was found in the high reflective line which revealed Bruch's membrane. Low reflective tissue was observed at the break corresponding to a feeder vessel. The high reflective line which corresponded to the retinal pigment epithelium was uneven, and highly elevated portions of the RPE corresponded to thick network vessels and polypoidal lesions. Feeder vessels are thought to invade via Bruch's membrane to form network vessels and polypoidal lesions at the termini of the network vessels, both of which push the RPE upward. Therefore, polypoidal CNV is thought to represent a deformation of the CNV under the RPE. In PCV in the strict sense, an irregular thickened line with highly reflective substances adhering to the lower portion of it, curved downward corresponding to the site at which the network vessel filling began. A dimple in the RPE was observed which paralleled the curve of the line. The RPE was pushed upward, corresponding to the network vessels. Judging from the results of histopathological studies, abnormal vessels may be pushed up the RPE secondary to an increase in intravascular pressure due to the presence of several dilated vessels and by massive exudation from these vessels within the choroid at network vessels. The dimple in the RPE might be attributable to intra-choroidal pressure being decreased at the point at which network vessel filling began. 4. Genetic findings. There were significant differences in all

distributions of ARMS 2 (A69S) between the polypoidal CNV and control groups. In contrast, the distribution of ARMS 2 (A69S) did not differ between the PCV in the strict sense group and the control group. The ARMS 2 (A69S) gene is closely related to age-related macular degeneration. Polypoidal CNV was thought to be associated with age-related macular degeneration. 5. Treatment of subfoveal PCV. Mean visual acuity improved 1 year after photodynamic therapy (PDT). Good visual acuity, small lesion size of the network of vessels with polypoidal lesions, and the absence of subfoveal polypoidal lesions were pre-PDT predictors that corresponded to the improvement in vision. However, mean visual acuity had decreased to a level similar to that prior to PDT at 2 and 3 years after treatment. In PCV in the strict sense, the branching vascular network persisted after PDT, and polypoidal lesions frequently recurred at the termini. The branching vascular network sometimes expanded and was accompanied by polypoidal CNV or classic CNV. These results indicate that repeated PDT, as monotherapy, has limitations as a long-term treatment for PCV in the strict sense. Intravitreal injection of ranibizumab for eyes with a visual acuity of 0.6 or more, which is not a good indication for PDT, achieved improvement in mean visual acuity 1 year after the treatment, though the frequency of polypoidal lesion regression was low. This procedure seems to be useful for eyes with good visual acuity for a period of at least one year. 6. Conclusion. Using indocyanine green angiography, optical coherence tomography and genetic testing, PCV was classified into 2 groups, polypoidal CNV and PCV in the strict sense. PCV in the strict sense was characterized by arteriolsclerosis histopathologically. Polypoidal CNV is thought to represent deformation of CNV under the RPE in age-related macular degeneration, while PCV in the strict sense is thought to be due to choroidal vessel abnormalities. The long-term efficacy of repeated PDT as monotherapy, for subfoveal PCV was limited. Further evaluation is necessary to establish a treatment algorithm for PCV.

PMID: 22568102 [PubMed - in process]

PLoS Pathog. 2012 Apr;8(4):e1002671. Epub 2012 Apr 26.

Macrophage activation associated with chronic murine cytomegalovirus infection results in more severe experimental choroidal neovascularization.

Cousins SW, Espinosa-Heidmann DG, Miller DM, Pereira-Simon S, Hernandez EP, Chien H, Meier-Jewett C, Dix RD.

Duke University Eye Center, Duke Center for Macular Diseases, Department of Ophthalmology, Duke University, Durham, North Carolina, United States of America.

Abstract

The neovascular (wet) form of age-related macular degeneration (AMD) leads to vision loss due to choroidal neovascularization (CNV). Since macrophages are important in CNV development, and cytomegalovirus (CMV)-specific IgG serum titers in patients with wet AMD are elevated, we hypothesized that chronic CMV infection contributes to wet AMD, possibly by pro-angiogenic macrophage activation. This hypothesis was tested using an established mouse model of experimental CNV. At 6 days, 6 weeks, or 12 weeks after infection with murine CMV (MCMV), laser-induced CNV was performed, and CNV severity was determined 4 weeks later by analysis of choroidal flatmounts. Although all MCMV-infected mice exhibited more severe CNV when compared with control mice, the most severe CNV developed in mice with chronic infection, a time when MCMV-specific gene sequences could not be detected within choroidal tissues. Splenic macrophages collected from mice with chronic MCMV infection, however, expressed significantly greater levels of TNF-α, COX-2, MMP-9, and, most significantly, VEGF transcripts by quantitative RT-PCR assay when compared to splenic macrophages from control mice. Direct MCMV infection of monolayers of IC-21 mouse macrophages confirmed significant stimulation of VEGF mRNA and VEGF protein as determined by quantitative RT-PCR assay, ELISA, and immunostaining. Stimulation of VEGF production in vivo and in vitro was sensitive to the antiviral ganciclovir. These studies suggest that chronic CMV infection may serve as a heretofore unrecognized risk factor in the pathogenesis of wet AMD. One mechanism by which chronic CMV infection might promote increased CNV severity is via stimulation of macrophages to

make pro-angiogenic factors (VEGF), an outcome that requires active virus replication.

PMID: 22570607 [PubMed - in process]

J Biol Chem. 2012 May 8. [Epub ahead of print]

Lipofuscin and N-retinylidene-N-retinylethanolamine (A2E) Accumulate in the Retinal Pigment Epithelium in the Absence of Light Exposure: Their Origin is 11-Cis Retinal.

Boyer NP, Higbee D, Currin MB, Blakeley LR, Chen C, Ablonczy Z, Crouch RK, Koutalos Y.

Medical University of South Carolina, United States;

Abstract

The age-dependent accumulation of lipofuscin in the retinal pigment epithelium (RPE) has been associated with the development of retinal diseases, particularly age-related macular degeneration and Stargardt disease. A major component of lipofuscin is the bis-retinoid N-retinylidene-N-retinylethanolamine (A2E). The current model for the formation of A2E requires photoactivation of rhodopsin and subsequent release of all-trans retinal. To understand the role of light exposure in the accumulation of lipofuscin and A2E, we analyzed RPEs and isolated rod photoreceptors from mice of different ages and strains, reared either in darkness or cyclic light. Lipofuscin levels were determined by fluorescence imaging, while A2E levels were quantified by HPLC and UV/VIS absorption spectroscopy. The identity of A2E was confirmed by tandem mass spectrometry. Lipofuscin and A2E levels in the RPE increased with age, and more so in the Stargardt model Abca4-/- than in the wild-type strains 129/sv and C57Bl/6. For each strain, the levels of lipofuscin precursor fluorophores in dark-adapted rods, and the levels and rates of increase of RPE lipofuscin and A2E were not different between dark-reared and cyclic-light-reared animals. Both 11-cis and all-trans retinal generated lipofuscin-like fluorophores when added to metabolically compromised rod outer segments; however, it was only 11-cis retinal that generated such fluorophores when added to metabolically intact rods. The results suggest that lipofuscin originates from the free 11-cis retinal that is continuously supplied to the rod for rhodopsin regeneration and outer segment renewal. The physiological role of Abca4 may include the translocation of 11-cis retinal complexes across the disk membrane.

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Invest Ophthalmol Vis Sci. 2012 May 8. [Epub ahead of print]

Choroidal Thickness, Vascular Hyperpermeability, and Complement Factor H in Age-related Macular Degeneration and Polypoidal Choroidal Vasculopathy.

Jirarattanasopa P, Ooto S, Nakata I, Tsujikawa A, Yamashiro K, Oishi A, Yoshimura N.

Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, 606-8507, Japan.

Purpose: To investigate the relationship between subfoveal choroidal thickness, choroidal vascular hyperpermeability, and complement factor H (CFH) gene polymorphism in typical age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV).

Methods: Fifty-eight patients with typical AMD and 63 patients with PCV underwent fluorescein angiography, indocyanine green angiography (IA), and spectral-domain optical coherence tomography (OCT) using enhanced depth imaging (EDI). Subfoveal choroidal thickness was measured using EDI-OCT images, and choroidal hyperpermeability was evaluated using late-phase IA images. The major AMD-associated single-nucleotide polymorphisms were genotyped in 86 patients.

Results: Mean subfoveal choroidal thickness was significantly lower in eyes with typical AMD than in eyes with PCV (P = 0.025). Subfoveal choroidal thickness was greater in eyes with choroidal hyperpermeability than in eyes without it in typical AMD (P < 0.001) and PCV (P = 0.020), and in the fellow eyes of typical AMD (P < 0.001) and PCV (P = 0.027). In eyes without choroidal hyperpermeability, the mean subfoveal choroidal thickness was greater in PCV than in typical AMD (P = 0.001). Choroidal thickness decreased after photodynamic therapy combined with intravitreal ranibizumab in typical AMD (P = 0.016) and PCV (P = 0.036). In eyes with PCV, the I62V polymorphism in the CFH gene contributed to choroidal thickness (P = 0.043).

Conclusions: Choroidal thickness is related to the AMD subtypes, choroidal hyperpermeability, and I62V CFH gene polymorphism. In eyes without choroidal hyperpermeability, EDI-OCT is useful as an auxiliary measure for differentiating typical AMD and PCV.

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Retinal pigment epithelium response to oxidant injury in the pathogenesis of early age-related macular degeneration.

Mettu PS, Wielgus AR, Ong S, Cousins SW.

Abstract

Age-related macular degeneration (AMD) represents the leading cause of vision loss in the elderly. Accumulation of lipid- and protein-rich deposits under the retinal pigment epithelium (RPE) heralds the onset of early AMD, but the pathogenesis of subretinal deposit formation is poorly understood. Numerous hypothetical models of deposit formation have been proposed, including hypotheses for a genetic basis, choroidal hypoperfusion, abnormal barrier formation, and lysosomal failure. This review explore the RPE injury hypothesis, characterized by three distinct stages (1) Initial RPE oxidant injury, caused by any number of endogenous or exogenous oxidants, results in extrusion of cell membrane "blebs," together with decreased activity of matrix metalloproteinases (MMPs), promoting bleb accumulation under the RPE as basal laminar deposits (BLD). (2) RPE cells are subsequently stimulated to increase synthesis of MMPs and other molecules responsible for extracellular matrix turnover (i.e., producing decreased collagen), affecting both RPE basement membrane and Bruchs membrane (BrM). This process leads to progression of BLD into basal linear deposits (BLinD) and drusen by admixture of blebs into BrM, followed by the formation of new basement membrane under the RPE to trap these deposits within BrM. We postulate that various hormones and other plasma-derived molecules related to systemic health cofactors are implicated in this second stage. (3) Finally, macrophages are recruited to sites of RPE injury and deposit formation. The recruitment of nonactivated or scavenging macrophages may remove deposits without further injury, while the recruitment of activated or reparative macrophages, through the release of inflammatory mediators, growth factors, or other substances, may promote complications and progression to the late forms of the disease.

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Indian J Ophthalmol. 2012 May;60(3):189-93.

Effects of hydroquinone on retinal and vascular cells in vitro.

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Aim: To explore the molecular pathophysiology that might explain the epidemiologic association between cigarette smoke and age-related macular degeneration (AMD) by examining the effects of hydroquinone (HQ), a toxic compound present in high concentration in cigarette smoke-related tar, on human retinal pigment epithelial cells (ARPE-19), rat retinal neurosensory cells (R-28), and human microvascular endothelial cells (HMVEC).

Materials and Methods: ARPE-19, R-28, and HMVEC were treated for 24 h with four different concentrations of HQ (500 μM, 200 μM, 100 μM, 50 μM). Cell viability, caspase-3/7 activation, DNA laddering patterns, and lactate dehydrogenase (LDH) levels were analyzed.

Results: At 50 μM HQ, R-28 cells showed a significant decrease in cell viability compared with the dimethyl sulfoxide (DMSO)-treated controls. At the 100-500 μM concentrations, all three cell lines showed significant cell death ($P < 0.001$). In the ARPE-19, R-28, and HMVEC cultures, the caspase-3/7 activities were not increased at any of the HQ concentration.

Conclusion: Our findings suggest that the mechanism of cell death in all three cell lines was through non-apoptotic pathway. In addition, neuroretinal R-28 cells were more sensitive to HQ than the ARPE-19 and HMVEC cultures.

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Loss of thioredoxin function in retinas of mice overexpressing amyloid β

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Abstract

Amyloid β peptides (Aβ) have been implicated in the pathogenesis of age-related macular degeneration (ARMD) and glaucoma. In this study, retinas of mice overexpressing Aβ (Tg) were compared to those of wild-type mice (Wt) and analyzed for oxidative stress parameters. We observed a progressive decrease in all retinal cell layers, which was significantly greater in Tg mice at 14 months and culminated in loss of the outer retina at 18 months of age. We also observed higher levels of reactive oxygen species, glial fibrillary acidic protein, and hydroperoxide in Tg versus Wt mice (14 months). These effects were associated with phosphorylation/activation of the apoptosis signal kinase 1 and the p38 mitogen-activated kinase. Western blotting analysis revealed progressive increases in the levels of thioredoxin 1 and thioredoxin inhibitory protein in Tg compared to Wt mice. No changes were observed in the levels of thioredoxin reductase 1 (TrxR1); however, measurements of TrxR1 activity showed a 42.7±8% reduction in Tg mice versus Wt at 14 months of age. Our data suggest that Aβ-mediated retinal neurotoxicity involves impairment of the thioredoxin system and enhanced oxidative stress, potentially implicating this mechanism in the pathogenesis of ARMD and glaucoma.

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Epidemiology

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Prevalence and risk factors of early-stage age-related macular degeneration in patients examined at a health promotion center in Korea.

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Abstract

We evaluated the prevalence and risk factors for early age-related macular degeneration (AMD) in Koreans 50 yr of age or older who were examined at a single health promotion center. We retrospectively reviewed the records of 10,449 subjects who visited the center over a 6-month period. Fundus photography was performed on all subjects, and systematic risk factor analysis was conducted using a structured questionnaire. All patients (n = 322) were initially diagnosed with drusen or early AMD using fundoscopy; the control group (n = 10,127) were those yielding normal fundoscopy findings. The age- and gender-adjusted prevalence of early AMD was 3.08%. Advanced age, male gender, smoking status, hyperlipidemia, working outdoors, and residence in rural areas were all significantly associated with an increased risk for development of early AMD. Higher-level ingestion of fruit or herbal medication and an increased amount of exercise were associated with a lower risk of early AMD development. In our Korean cohort, consisting principally of relatively healthy, middle-class urban adults, the prevalence of early AMD was 3.08% that is similar to that reported in earlier epidemiological studies. Several modifiable risk factors such as smoking and hyperlipidemia are associated with the prevalence of early AMD in our cohort.

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Association of macular pigment optical density with risk factors for wet age-related macular degeneration in the Indian population.

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Purpose: To investigate macular pigment optical density (MPOD) in patients with and without wet age-related macular degeneration (AMD) and to elucidate the association between MPOD and the risk factors for AMD in an Indian population.

Methods: Thirty-three subjects with wet AMD and 29 controls above 50 years old underwent MPOD measurement with the 'Macular Densitometer'. The subjects were also tested for their smoking history, lifetime ultraviolet (UV) exposure, dietary intake of carotenoids, and body mass index (BMI).

Results: Smokers had a higher risk for AMD than the non-smokers (P=0.032) and a lower MPOD level than non-smokers (mean (95% CI)) (0.16 (0.09-0.23) vs 0.28 (0.22-0.34), adjusted P=0.026). Subjects with lowest UV exposure had higher MPOD than those with the highest (0.46 (0.38-0.54) vs 0.17 (0.01-0.33), P=0.01). MPOD was significantly lower among those with the lowest quartile of dietary intake of carotenoids (0.14 (0.08-0.21) vs 0.25 (0.13-0.36), P=0.012). Smoking, obesity, and UV index showed an inverse association with the MPOD. Low MPOD, smoking, and UV exposure had 5.11 (1.73-15.08), 3.54 (1.08-11.57), and 5.24 (1.06-25.96) odds for AMD, respectively, whereas higher dietary intake of carotenoids showed a protective effect for AMD.

Conclusion: We found an inverse association between wet AMD and MPOD. Among the established risk factors of wet AMD, we found an inverse association of smoking, UV index, and obesity with MPOD, whereas a positive association was found between dietary intake of carotenoids and MPOD.

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Genetics

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Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics.

Gorin MB.

Abstract

Age-related macular degeneration (AMD) is a common condition among the elderly population that leads to the progressive central vision loss and serious compromise of quality of life for its sufferers. It is also one of the few disorders for whom the investigation of its genetics has yielded rich insights into its diversity and causality and holds the promise of enabling clinicians to provide better risk assessments for individuals as well as to develop and selectively deploy new therapeutics to either prevent or slow the development of disease and lessen the threat of vision loss. The genetics of AMD began initially with the appreciation of familial aggregation and increase risk and expanded with the initial association of APOE variants with the disease. The first major breakthroughs came with family-based linkage studies of affected (and discordant) sibs, which identified a number of genetic loci and led to the targeted search of the 1q31 and 10q26 loci for associated variants. Three of the initial four reports for the CFH variant, Y402H, were based on regional candidate searches, as were the two initial reports of the ARMS2/HTRA1 locus variants. Case-control association studies initially also played a role in discovering the major genetic variants for AMD, and the success of those early studies have been used to fuel enthusiasm for the methodology for a number of diseases. Until 2010, all of the subsequent genetic variants associated with AMD came from candidate gene testing based on the complement factor pathway. In 2010, several large-scale genome-wide association studies (GWAS) identified genes that had not been previously identified. Much of this historical information is available in a number of recent reviews (Chen et al., 2010b; Deangelis et al., 2011; Fafowora and Gorin, 2012b; Francis and Klein, 2011; Kokotas et al., 2011). Large meta analysis of AMD GWAS has added new loci and variants to this collection (Chen et al., 2010a; Kopplin et al., 2010; Yu et al., 2011). This paper will focus on the ongoing controversies that are confronting AMD genetics at this time, rather than attempting to summarize this field, which has exploded in the past 5years.

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Diet

Tidsskr Nor Laegeforen. 2012 Apr 30;132(8):956-9.

[Ginkgo biloba - effect, adverse events and drug interaction].

[Article in Norwegian]

Roland PD, Nergård CS.

Abstract

Ginkgo is probably one of the most widely used medicinal herbs in Europe. In Norway products of ginkgo leaf extract have been approved by the Norwegian Medicines Agency for the following indication: traditionally used to improve blood circulation, for example, cold hands and feet. Elsewhere, ginkgo is used for cognitive impairment and dementia, acute ischaemic stroke, intermittent claudication, tinnitus and age-related macular degeneration. Evidence of the efficacy of ginkgo for these indications has previously been studied by the Cochrane Collaboration. In this update we have repeated all the searches in Medline and EMBASE exactly as described in the five Cochrane Systematic Reviews (last search date: 16.02.2011). We identified two new randomised and placebo-controlled studies on cognitive impairment and dementia (3187

patients) and one study on acute ischaemic stroke (3069 patients). The results of these studies gave no reason to change the conclusions of earlier reviews by the Cochrane Collaboration. There is no convincing evidence that ginkgo is effective for cognitive impairment or dementia, acute ischaemic stroke, intermittent claudication or tinnitus. There is still a lack of conclusive evidence for the effect on age-related macular degeneration. Ginkgo leaf extract appears to be safe to use, with no excess side effects compared with placebo. It can cause some minor side effects such as stomach upset, headache, dizziness, constipation, forceful heartbeat, and allergic skin reactions. There is some concern that ginkgo leaf extract might increase the risk of bruising and bleeding, and interactions with anticoagulants/antiplatelet drugs cannot be ruled out. As a general precaution, it is recommended withdrawing ginkgo two weeks before elective surgery.

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Health tips. Who needs vitamins?

[No authors listed]

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