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Drug treatment

Eye (Lond). 2013 Mar 1. doi: 10.1038/eye.2013.8. [Epub ahead of print]

Ranibizumab for the treatment of choroidal neovascularisation secondary to pathological myopia: interim analysis of the REPAIR study.

Tufail A, Patel PJ, Sivaprasad S, Amoaku W, Browning A, Cole M, Gale R, George S, Lotery A, Majid M, McKibbin M, Menon G, Yang Y, Andrews C, Brittain C, Osborne A.

Moorfields Eye Hospital, London, UK.

Aims: To evaluate the efficacy and safety of intravitreal ranibizumab in patients with choroidal neovascularisation secondary to pathological myopia (myopic CNV). Data are from a pre-planned, 6-month interim analysis.

Methods: Phase II, open-label, single arm, multicentre, 12-month study, recruiting patients (aged ≥18 years) with active primary or recurrent subfoveal or juxtafoveal myopic CNV, with a best-corrected visual acuity (BCVA) score of 24-78 Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the study eye and a diagnosis of high myopia of at least -6 dioptres.Patients received 0.5 mg ranibizumab administered intravitreally to the study eye, followed by monthly injections given as needed (based on a predefined algorithm) for up to 11 months.

Results: At 6 months, mean BCVA improved from baseline by 12.2 letters, as did central macular thickness (in this interim analysis defined as a measure of either central subfield macular thickness or centre point macular thickness) from baseline by 108 μm in the 48 study eyes of 48 patients. Fewer patients had centre-involving intraretinal oedema (13.0% vs 91.5%), intraretinal cysts (10.9% vs 57.4%), or subretinal fluid (13.0% vs 66.0%) at 6 months than at baseline. Patients received a mean of 1.9 retreatments, were satisfied with ranibizumab treatment, and well being was maintained. No new safety signals were identified.

Conclusions: Results from the planned interim analysis support the role of ranibizumab in the treatment of myopic CNV, with excellent efficacy achieved with a low number of injections and few serious adverse events.Eye advance online publication, 1 March 2013; doi:10.1038/eye.2013.8.

PMID: 23449508 [PubMed - as supplied by publisher]

Cochrane Database Syst Rev. 2013 Jan 31;1:CD009510. doi: 10.1002/14651858.CD009510.pub2.

Anti-vascular endothelial growth factor for macular oedema secondary to branch retinal vein

occlusion.

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BACKGROUND: Branch retinal vein occlusion (BRVO) is one of the most common occurring retinal vascular abnormalities. The pathogenesis of BRVO is thought to involve both retinal vein compression and damage to the vessel wall, possibly leading to thrombus formation at sites where retinal arterioles cross retinal veins. The most common cause of visual loss in patients with BRVO is macular oedema (MO). Grid or focal laser photocoagulation has been shown to reduce the risk of visual loss and improve visual acuity (VA) in up to two thirds of individuals with MO secondary to BRVO, however, limitations to this treatment exist and newer modalities have suggested equal or improved efficacy. Recently, antiangiogenic therapy with anti-vascular endothelial growth factor (anti-VEGF) has been used successfully to treat MO resulting from a variety of causes. As elevated intraocular levels of VEGF have been demonstrated in patients with retinal vein occlusions there is a strong basis for the hypothesis that anti-VEGF agents may be beneficial in the treatment of vascular leakage and MO.

OBJECTIVES: To investigate the efficacy and safety of intravitreal anti-VEGF agents for preserving or improving vision in the treatment of MO secondary to BRVO.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 7), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non -Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to August 2012), EMBASE (January 1980 to August 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to August 2012, the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 7 August 2012 and the clinical trials registers on 10 September 2012.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) and quasi-RCTS of at least six months duration where anti-VEGF treatment was compared with another treatment, no treatment, or placebo. We excluded trials where combination treatments (anti-VEGF plus other treatments) were used and trials that investigated the dose and duration of treatment without a comparison group (other treatment/ no treatment/sham).

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted the data. The primary outcome was the proportion of participants with an improvement from baseline in best-corrected visual acuity (BCVA) of greater than or equal to 15 letters (3 lines) on the Early Treatment in Diabetic Retinopathy Study (ETDRS) Chart at six months and at 12 months of follow-up. The secondary outcomes we report are the proportion of participants who lost greater than or equal to 15 ETDRS letters (3 lines) and the mean VA change at six months and any additional follow-up intervals as well as the change in central retinal thickness on optical coherence tomography (OCT) from baseline and final reported follow-up, the number and type of complications, the number of additional interventions administered and any adverse outcomes. Where available, the cost benefit and quality of life data reported in the primary studies is presented.

MAIN RESULTS: We found one RCT and one quasi-RCT that met the inclusion criteria after independent and duplicate review of the search results. The studies used different anti-VEGF agents and different study groups which were not directly comparable.One multi-centre RCT (BRAVO) conducted in the USA randomised 397 individuals and compared monthly intravitreal ranibizumab (0.3 mg and 0.5 mg) injections with sham injection. The study only included individuals with non-ischaemic BRVO. Although repeated injections of ranibizumab appeared to have a favourable effect on the primary outcome, approximately 50% of the ranibizumab 0.3 mg group and 45% of the ranibizumab 0.5 mg group received rescue laser treatment which may have an important effect on the primary outcome. In addition, during the six-month observation period 93.5% of individuals in the sham group received intravitreal ranibizumab (0.5 mg). This cross-over

design limits the ability to compare the long-term impact of ranibizumab versus a pure control group.The second trial was a small study (n = 30) from Italy with limitations in study design that reported a benefit of as-required intravitreal bevacizumab (1.25 mg) over laser photocoagulation in MO secondary to BRVO. We present the evidence from these trials and other interventional case series.

AUTHORS' CONCLUSIONS: The available RCT evidence suggests that repeated treatment of non-ischaemic MO secondary to BRVO with the anti-VEGF agent ranibizumab may improve clinical and visual outcomes at six and 12 months. However, the frequency of re-treatment has not yet been determined and the impact of prior or combined treatment with laser photocoagulation on the primary outcome is unclear. Results from ongoing studies should assess not only treatment efficacy but also, the number of injections needed for maintenance and long-term safety and the effect of any prior treatment.

PMID: 23440840 [PubMed - in process]

Cochrane Database Syst Rev. 2013 Jan 31;1:CD005022. doi: 10.1002/14651858.CD005022.pub3.

Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration.

Geltzer A, Turalba A, Vedula SS.

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BACKGROUND: Neovascular age-related macular degeneration (AMD) is associated with rapid vision loss due to choroidal neovascularization (CNV), leakage, and scarring. Steroids have gained attention in their role for the treatment of neovascular AMD for their antiangiogenic and anti-inflammatory properties.

OBJECTIVES: This review aims to examine effects of steroids with antiangiogenic properties in the treatment of neovascular AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 11), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to November 2012), EMBASE (January 1980 to November 2012), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to November 2012), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 21 November 2012.

SELECTION CRITERIA: We included randomized controlled clinical trials of intra- and peri-ocular antiangiogenic steroids in people diagnosed with neovascular AMD.

DATA COLLECTION AND ANALYSIS: Two authors independently screened abstracts and full-text articles, assessed risk of bias in the included trials, and extracted data. We did not conduct a meta-analysis.

MAIN RESULTS: We included three trials after screening a total of 1503 abstracts and 21 full-text articles. The three trials included a total of 809 participants. One trial compared different doses of acetonide anecortave acetate with placebo, a second trial compared triamcinolone acetonide versus placebo, and the third trial compared anecortave acetate against photodynamic therapy (PDT). We did not conduct a meta-analysis owing to heterogeneity of interventions and comparisons. The risk ratio for loss of 3 or more lines of vision at 12 months follow-up was 0.8 (95% confidence interval (CI) 0.45 to 1.45) with 3 mg anecortave acetate, 0.45 (95% CI = 0.21 to 0.97) with 15 mg anecortave acetate, 0.91 (0.52 to 1.58) with 30 mg anecortave acetate, 0.97 (95% CI 0.74 to 1.26) with triamcinolone acetonide, all compared to placebo and 1.08 (95% CI 0.91 to 1.29) with anecortave acetate compared with PDT.

AUTHORS' CONCLUSIONS: Based on the included trials, we found no evidence that antiangiogenic steroids prevent visual loss in patients with neovascular AMD. With the emergence of anti-vascular endothelial growth factor modalities, based on evidence summarized in this review, it is unclear what role steroids have in treating patients with neovascular AMD.

Update of Cochrane Database Syst Rev. 2007;(4):CD005022.

PMID: 23440797 [PubMed - in process]

Retina. 2013 Feb 26. [Epub ahead of print]

VARIABLE RESPONSE OF VASCULARIZED PIGMENT EPITHELIAL DETACHMENTS TO RANIBIZUMAB BASED ON LESION SUBTYPES, INCLUDING POLYPOIDAL CHOROIDAL VASCULOPATHY.

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PURPOSE: The purpose of this study was to evaluate the prognosis and response to intravitreal ranibizumab (IVR) of neovascular age-related macular degeneration, according to the type of pigment epithelial detachment (PED).

METHODS: The authors prospectively studied 57 eyes of 57 consecutive patients with PED associated with exudative age-related macular degeneration, who were treated by IVR. All patients received 3 consecutive monthly injections of 0.5 mg/0.05 mL of ranibizumab as induction treatment. Retreatment was allowed if evidence of clinical deterioration was noted or spectral domain optical coherence tomography at the 1-month follow-up showed intraretinal edema, subretinal fluid, or recurrent PED. The best-corrected visual acuity (BCVA) values measured before and at 3, 6, and 12 months after the first injection were compared according to the type of PED. Changes in the height of PED to treatment with IVR were also investigated.

RESULTS: Fifty-six eyes were assessed at the 12-month follow-up examination. There were 4 types of PED, including serous PED in 11 patients (19.6%), fibrovascular PED in 28 patients (50.0%), mixed PED with serous and fibrovascular component in 7 patients (12.5%), and hemorrhagic PED in 10 patients (17.9%). Eyes with serous PED showed significant improvement of the mean logarithm of the minimum angle of resolution (logMAR) BCVA as compared with the value at the baseline, which was sustained throughout the 12-month period ($P < 0.05$). Regarding the eyes with fibrovascular and mixed PED, significant improvement of the mean logMAR BCVA was observed compared with the value at the baseline at 3 months; however, a slight decrease was observed at 6 and 12 months. In the eyes with hemorrhagic PED, no significant difference in the mean BCVA values compared with the value at the baseline was observed at any follow-up time point. In relation to the height of the PED, all eyes in the serous and mixed PED group, 17 eyes in the fibrovascular PED group (60.7%), and 9 eyes in the hemorrhagic PED group (90.0%) showed reduction of the maximum PED height by 100 μm or more. The PED response to IVR was not correlated with the final BCVA.

CONCLUSION: Intravitreal ranibizumab for the treatment of exudative age-related macular degeneration is effective for stabilizing vision in patients with PED, but it may be better tolerated in patients with serous PED. Although it may be important to consider the type of PED to predict the visual acuity in patients treated by IVR, the anatomical response of the PED may not correlate directly with the visual outcome.

PMID: 23446653 [PubMed - as supplied by publisher]

Semin Ophthalmol. 2013 Mar;28(2):61-7. doi: 10.3109/08820538.2012.754479.

Effect of Dorzolamide/Timolol or Brinzolamide/Timolol Prophylaxis on Intravitreal Anti-VEGF Injection-Induced Intraocular Hypertension.

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Purpose: To evaluate prospectively whether anti-glaucomatic drugs administered prior to intravitreal anti-vascular endothelial growth factor (VEGF) injection bevacizumab (Avastin,® Roche) or ranibizumab (Lucentis,® Novartis) prevents intraocular hypertension after the injection.

Subjects and methods: In total, 166 patients (175 eyes) scheduled for intravitreal anti-VEGF injection treatment were prophylactically treated 1 hour before the procedure with Dorzolamide/Timolol (Cosopt,® MSD) (Group 1, 53 eyes) or Brinzolamide/Timolol (Elazop,® Alcon) (Group 2, 84 eyes) or left untreated (Group 3, 29 eyes). Intraocular pressure was analyzed 5 minutes prior to the injection, every 5 minutes for 30 minutes after the procedure, and 1 hour, 1 day, 7 days, and 1 month after the procedure.

Results: The intraocular pressures 5 minutes before the procedure (baseline) for Groups 1, 2, and 3 were 12.06 ± 1.85, 13.98 ± 2.68, and 13.81 ± 2.24 mmHg, respectively. Five and 30 minutes after the procedure, the intraocular pressures of the three groups were 14.12 ± 4.18, 14.87 ± 3.35, and 28.21 ± 3.16 mmHg, respectively, and 10.87 ± 1.58, 14.25 ± 2.43, and 17.48 ± 2.34 mmHg, respectively. For all three groups, the changes relative to baseline 5 and 30 minutes after injection were significant. When the three groups were divided according to whether they received bevacizumab or ranibizumab and the changes in intraocular pressure relative to baseline were analyzed, all six subgroups exhibited significant changes in intraocular pressure 5 and 30 minutes after the procedure.

Conclusion: The prophylactic administration of anti-glaucomatic drugs prior to intravitreal anti-VEGF injection effectively reduced the early intraocular pressure elevation. This approach was also safe and could be performed accurately.

PMID: 23448557 [PubMed - in process]

Oman J Ophthalmol. 2012 Sep;5(3):184-6. doi: 10.4103/0974-620X.106103.

Intravitreal ranibizumab as salvage therapy in an extremely low-birth-weight infant with rush type retinopathy of prematurity.

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Abstract: We report the effects of intravitreal ranibizumab as salvage therapy in an extremely low-birth-weight (ELBW) infant with rush type retinopathy of prematurity (ROP). This case was a girl of 23 weeks gestational age weighing 480 g at birth. At a postconceptual age of 33 weeks, she presented with zone 1, stage 3 ROP with plus disease. Despite intravitreal bevazucimab and laser photocoagulation, extraretinal fibrovascular proliferation persisted. Intravitreal 0.25 mg (0.025 ml) ranibizumab was injected OU. After treatment, extraretinal fibrovascular proliferation disappeared. Fundus examination showed flat retinas and normal vasculature in both eyes. She has been followed up for 2 years. Intravitreal ranibizumab injection seems effective and well tolerated as salvage therapy in an ELBW infant with rush type ROP. No short-term ocular or systemic side effects were identified. More cases and longer follow-up are mandatory.

PMID: 23440056 [PubMed]

Oman J Ophthalmol. 2012 Sep;5(3):161-5. doi: 10.4103/0974-620X.106099.

Ranibizumab in patients with dense cataract and proliferative diabetic retinopathy with rubeosis.

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BACKGROUND: To evaluate the safety of ranibizumab as a surgical adjunct during cataract surgery in patients with proliferative diabetic retinopathy (PDR) with rubeosis, and to evaluate the efficacy and adverse effects of ranibizumab in treating PDR with rubeosis.

MATERIALS AND METHODS: Three intravitreal injections of 0.5 mg ranibizumab were administered on day-1, months-1 and -2 with cataract surgery 6-16 days after first injection. Retreatments with ranibizumab injections and pan-retinal photocoagulation (PRP) were given if recurrence or persistence of PDR was noted between months-3 and -11. Safety observation visits occurred at months-12, -18 and -24. Primary end points were incidence and severity of adverse events (AEs) that were related to both cataract surgery and treatment of PDR with rubeosis through month -12.

RESULTS: Of six patients screened, four (mean age 61.3 years) were enrolled. No AEs were noted with either cataract surgery or treatment of PDR. Neovascularization of iris (NVI) promptly regressed by 4 days after first ranibizumab injection, prior to cataract surgery in three of four patients (one had significantly regressed NVI by post-injection day-3 visit); NVI was not noted in any patient at 2 weeks after first ranibizumab injection. Recurrence of rubeosis or NVA after 3 monthly injections was not observed in any. At month-12, PDR was not present when assessed clinically and by fluorescein angiogram (FA). Only one patient developed neovascularization of disc and neovascularization elsewhere and required retreatments at months-5 and -9.

CONCLUSIONS: Multiple intravitreal injections of ranibizumab may be a safe, effective treatment adjunct for PDR and diabetes-related rubeosis.

PMID: 23439790 [PubMed]

Ophthalmologe. 2013 Feb 24. [Epub ahead of print]

[Ranibizumab in diabetic macular edema : Evaluation of functional and morphological aspects.] [Article in German]

Reznicek L, Cserhati S, Liegl R, Seidensticker F, Haritoglou C, Wolf A, Kampik A, Ulbig MW, Neubauer A, Kernt M.

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BACKGROUND: Intravitreal anti-VEGF (vascular endothelial growth factor) therapy with ranibizumab has been shown to be an effective therapeutic option for foveal diabetic macular edema (DME). This prospective study evaluated the functional and morphological retinal changes after intravitreal ranibizumab treatment.

MATERIAL AND METHODS: A consecutive prospective series of DME patients treated with intravitreal ranibizumab were examined before and after 3 and 6 months of intravitreal ranibizumab therapy. Best-corrected visual acuity (BCVA) according to the ETDRS protocol, retinal thickness in the macular area and central retinal thickness (CRT) measured with spectral-domain optical coherence tomography (SD-OCT) was determined. In addition, microperimetric functional macular mapping was determined before therapy and 4 weeks after the third injection.

RESULTS: A total of 41 eyes from 33 patients were evaluated. During the 6-month observational period patients received a mean number of 5.2 injections. The mean BCVA increased significantly from 26 ± 14 to 33 ± 13 letters 4 weeks after the third injection and to 34 ± 14 letters 6 months after starting the treatment. The mean CRT decreased significantly from 509 ± 147 µm to 385 ± 121 µm after the third injection and to 383 ± 110 µm after 6 months. After 3 injections, the thickness of the most prominent central retinal area was less than 445 µm in 68.3% of patients and after a further 3 months of treatment in 78.0%.

CONCLUSION: The presented data demonstrate that intravitreal ranibizumab is effective for DME in everyday clinical practice and results are comparable to those of registration trials. After three initial injections significant structural and functional improvements were observed in a considerable number of patients.

PMID: 23436196 [PubMed - as supplied by publisher]

Int J Nanomedicine. 2013;8:495-504. doi: 10.2147/IJN.S30725. Epub 2013 Feb 14.

Liposomes and nanotechnology in drug development: focus on ocular targets.

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Abstract: Poor drug delivery to lesions in patients' eyes is a major obstacle to the treatment of ocular diseases. The accessibility of these areas to drugs is highly restricted by the presence of barriers, including the corneal barrier, aqueous barrier, and the inner and outer blood-retinal barriers. In particular, the posterior segment is difficult to reach for drugs because of its structural peculiarities. This review discusses various barriers to drug delivery and provides comprehensive information for designing nanoparticle-mediated drug delivery systems for the treatment of ocular diseases. Nanoparticles can be designed to improve penetration, controlled release, and drug targeting. As highlighted in this review, the therapeutic efficacy of drugs in ocular diseases has been reported to be enhanced by the use of nanoparticles such as liposomes, micro/nanospheres, microemulsions, and dendrimers. Our recent data show that intravitreal injection of targeted liposomes encapsulating an angiogenesis inhibitor caused significantly greater suppression of choroidal neovascularization than did the injection of free drug. Recent progress in ocular drug delivery systems research has provided new insights into drug development, and the use of nanoparticles for drug delivery is thus a promising approach for advanced therapy of ocular diseases.

PMID: 23439842 [PubMed - in process]

Other treatment & diagnosis

Graefes Arch Clin Exp Ophthalmol. 2013 Feb 26. [Epub ahead of print]

Sensitivity of fluorescein angiography alone or with SD-OCT for the diagnosis of myopic choroidal neovascularization.

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BACKGROUND: Myopic choroidal neovascularization (mCNV) has certain characteristics and features that distinguish it from choroidal neovascularization secondary to age-related macular degeneration. There may be angiographic diagnostic difficulties even when using the scanning laser ophthalmoscope, which gives more contrast and better definition than traditional angiography. The aim of the study is to compare the sensitivity of fluorescein angiography (FA) alone or combined with Spectral Domain Optical Coherence

Tomography (SD-OCT) for assessing the incidence of mCNV.

METHODS: In this retrospective study, two authors reviewed the charts and images of patients with recent (<30 days) vision deterioration, pathologic myopia, axial length >26 mm, documentation or suspicion of mCNV or macular exudative pathologies at FA and OCT. They only examined the images at first presentation obtained by the multi-modal imaging system that combines Infrared reflectance, FA, and SD-OCT, (Spectralis, Heidelberg Engineering, Germany). The images selected were then evaluated by three other investigators in blinded, independent conditions, in order to make their diagnosis, which was noted or rated as doubtful if it could not be decided on the basis of FA alone. SD-OCT images were then shown and compared to IR and FA by each of the three investigators individually to formulate a conclusive diagnosis.

RESULTS: A total of 71 eyes of 69 patients were suitable for the study, mean age 65.97±14.57 years, spherical equivalent refraction -8.82 ± 2.51 diopters. Concordance between the three examiners' interpretations of FA features and FA-guided SD-OCT was 50/71 (70.4 %) and 67/71 (94 %) respectively. Total agreement on diagnosis between the three examiners was achieved in 55 % of cases for FA (κ = 0.53, p < 0.001), and 94 % for FA-guided SD-OCT (k = -0.01, p = 0.5). The final diagnosis with FA and FA-guided SD-OCT differed in 29 cases (40 %; 95 % C.I. 29-42 %), whereas 12 (17 %) mCNV were overlooked at FA, and in 11 (15 %) cases none of the examiners reached a diagnosis based on FA alone.

CONCLUSIONS: On the basis of FA alone, active mCNV can be misdiagnosed. The use of SD-OCT combined with FA should therefore be strongly considered.

PMID: 23436079 [PubMed - as supplied by publisher]

Mol Vis. 2013;19:424-9. Epub 2013 Feb 20.

In vitro effects of verteporfin on ocular cells.

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PURPOSE: Photodynamic therapy (PDT) laser light in conjunction with the benzoporphyrin derivative verteporfin is a current clinical treatment for choroidal vascular diseases such as age-related macular degeneration. The aim of this study was to examine the effects of PDT laser-activated and inactive verteporfin on various cultured ocular cells.

METHODS: Primary human scleral fibroblasts (hFibro), primary human trabecular meshwork (TM) cells (hTMC), primary porcine TM cells (pTMC), and a human retinal pigment epithelial cell line (ARPE-19 cells) were treated with verteporfin with and without activation by PDT laser. Cell viability was determined according to mitochondrial enzyme activity (3-(4,5- dimethyl-2-thiazoyl)-2,5-diphenyl-2H-tetrazolium bromide assay).

RESULTS: PDT laser treatment alone was insufficient to cause significant cell death in any of the cell types tested. Twenty-four-hour exposure to inactive verteporfin (without PDT laser) caused a dose-dependent decrease in cell viability in hFibro and hTMC, and to a lesser extent ARPE-19 cells. Verteporfin (0.5 µg/ml) without PDT laser activation caused a slight but statistically insignificant reduction in cell viability in hFibro (81.5%±19.3%), pTMC (82.9%±6.7%), hTMC (80.3%±7.7%), and ARPE-19 cells (84.5%±14.9%). Verteporfin (0.5 µg/ml) plus 50 µJ/cm(2) PDT laser treatment significantly decreased viability in hFibro (13.5% ± 3.3%), pTMC (7.1%±1.5%), hTMC (11.1%±5.2%), and ARPE-19 (44.5%±7.8%). Similar results were obtained in cells where verteporfin incubation was followed by washout before PDT laser, indicating that verteporfin is internalized by the studied cell lines.

CONCLUSIONS: PDT laser-induced cell death was obtained with coincubation of verteporfin or preincubation followed by washout. These results suggest a potential future use of PDT therapy for

selective in vivo removal of targeted ocular cells beyond the current use for destroying vascular endothelial cells.

PMID: 23441114 [PubMed - in process]

Ophthalmology. 2013 Feb 21. pii: S0161-6420(12)01170-0. doi: 10.1016/j.ophtha.2012.12.002. [Epub ahead of print]

Peripheral Autofluorescence and Clinical Findings in Neovascular and Non-neovascular Age-related Macular Degeneration.

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PURPOSE: To characterize peripheral fundus autofluorescence (FAF) abnormalities in patients with age-related macular degeneration (AMD), correlate these with clinical findings, and identify risk factors associated with these FAF abnormalities.

DESIGN: Clinic-based, cross-sectional study.

PARTICIPANTS: A total of 119 consecutive patients: 100 patients with AMD (200 eyes) and 19 patients without AMD (38 eyes).

METHODS: In a prospective study performed at the Doheny Eye Institute, University of Southern California, widefield 200-degree FAF and color images were obtained by the Optos 200Tx Ultra-Widefield device (Optos, Dunfermline, Scotland) using a standardized imaging protocol. The FAF images were captured centered on the fovea, and additional images were captured after steering the field of view inferiorly and superiorly. All FAF and color images were graded independently by 2 masked ophthalmologists with respect to the presence, location, extent, and type of peripheral (defined as outside the central 30 degrees) FAF abnormality.

MAIN OUTCOME MEASURES: Presence and type of peripheral FAF abnormalities.

RESULTS: Peripheral FAF abnormalities were evident in 164 eyes (68.9%), with several distinct FAF patterns identified: granular (46.2%), mottled (34.0%), and nummular (18.1%). A 90% concordance of FAF patterns was observed between both eyes. Abnormal FAF occurred more frequently in neovascular compared with non-neovascular AMD or normal eyes (86% vs. 72.8% vs. 18.4%, respectively, P<0.001). Significant risk factors for peripheral FAF abnormalities were AMD type (neovascular AMD odds ratio [OR], 12.7 and non-neovascular AMD OR, 6.2 compared with normal eyes, P<0.001), older age (OR, 6.5; 95% confidence interval [CI], 2.4-17.8; P<0.001 for the oldest quartile compared with the youngest), and female sex (OR, 4.1; 95% CI, 1.9-8.9; P<0.001). Clinical features on color photography were detected in 174 eyes (73.1%): peripheral drusen (51.7%), retinal pigment epithelium (RPE) depigmentation (34.9%), RPE hyperpigmentation (branching reticular pigmentation) (22.7%), and atrophic patches (16.8%). There was a high correlation between specific FAF and clinical findings: granular FAF with peripheral drusen (P<0.001) and mottled FAF with RPE depigmentation (P<0.001).

CONCLUSIONS: Several distinct patterns of peripheral FAF abnormalities were observed in 68.9% of patients, with AMD type, female sex, and age being independent risk factors. The peripheral FAF patterns correlate strongly with specific clinical features seen in eyes with AMD.

PMID: 23433790 [PubMed - as supplied by publisher]

Retina. 2013 Feb 26. [Epub ahead of print]

CORRELATION OF SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY CHARACTERISTICS WITH VISUAL ACUITY IN EYES WITH SUBFOVEAL SCARRING AFTER TREATMENT FOR WET AGE-RELATED MACULAR DEGENERATION.

El-Emam S, Chhablani J, Barteselli G, Wang H, Lee SN, Kozak I, Cheng L, Freeman WR.

Department of Ophthalmology, Jacobs Retina Center at Shiley Eye Center, University of California San Diego, La Jolla, California. Dr. Chhablani is now at L V Prasad eye institute, Hyderabad, India.

PURPOSE: Correlating spectral domain optical coherence tomography characteristics with final best-corrected visual acuity (BCVA) in eyes with subfoveal scarring after treatment for wet age-related macular degeneration.

METHODS: Seventy-nine eyes from 64 subjects, who developed subfoveal scarring after treatment of wet age-related macular degeneration, were retrospectively studied. Spectral domain optical coherence tomography characteristics were analyzed, including percentage disruption of inner segment/outer segment junction and external limiting membrane, central macular thickness, subfoveal scar thickness, subretinal scar area, and proximity of retina with intact outer structures to the fovea. A multivariate stepwise regression analysis was performed with the final BCVA logarithm of minimum angle of resolution as a response and the above-identified spectral domain optical coherence tomography variables as predictors.

RESULTS: There was no correlation between the final BCVA and any of the demographic data, treatment modality received, and central macular thickness. The final BCVA was significantly correlated with the percentage of inner segment/outer segment disruption (P = 0.011), external limiting membrane disruption (P = 0.005), and scar area on spectral domain optical coherence tomography (P = 0.018). Multivariate analysis showed that the baseline BCVA and distance between the fovea and nearest retina with intact outer structures are the most predictive of the final BCVA (R = 0.52).

CONCLUSION: Baseline BCVA and integrity of outer retinal structures are good predictors of the final BCVA of wet age-related macular degeneration patients developing scarring after treatment.

PMID: 23446655 [PubMed - as supplied by publisher]

Int J Ophthalmol. 2013;6(1):108-9. doi: 10.3980/j.issn.2222-3959.2013.01.23. Epub 2013 Feb 18.

Surgical treatment for neovascularized retinal pigment epithelial detachment in age-related macular degeneration.

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PMID: 23447804 [PubMed]

Age Ageing. 2013 Feb 25. [Epub ahead of print]

Complex visual hallucinations in a patient with macular degeneration: a case of the Charles Bonnet syndrome.

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Pathogenesis

Int J Mol Sci. 2013 Jan 31;14(2):2996-3010. doi: 10.3390/ijms14022996.

Mitochondrial and nuclear DNA damage and repair in age-related macular degeneration.

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Abstract: Aging and oxidative stress seem to be the most important factors in the pathogenesis of age-related macular degeneration (AMD), a condition affecting many elderly people in the developed world. However, aging is associated with the accumulation of oxidative damage in many biomolecules, including DNA. Furthermore, mitochondria may be especially important in this process because the reactive oxygen species produced in their electron transport chain can damage cellular components. Therefore, the cellular response to DNA damage, expressed mainly through DNA repair, may play an important role in AMD etiology. In several studies the increase in mitochondrial DNA (mtDNA) damage and mutations, and the decrease in the efficacy of DNA repair have been correlated with the occurrence and the stage of AMD. It has also been shown that mitochondrial DNA accumulates more DNA lesions than nuclear DNA in AMD. However, the DNA damage response in mitochondria is executed by nucleus-encoded proteins, and thus mutagenesis in nuclear DNA (nDNA) may affect the ability to respond to mutagenesis in its mitochondrial counterpart. We reported that lymphocytes from AMD patients displayed a higher amount of total endogenous basal and oxidative DNA damage, exhibited a higher sensitivity to hydrogen peroxide and UV radiation, and repaired the lesions induced by these factors less effectively than did cells from control individuals. We postulate that poor efficacy of DNA repair (i.e., is impaired above average for a particular age) when combined with the enhanced sensitivity of retinal pigment epithelium cells to environmental stress factors, contributes to the pathogenesis of AMD. Collectively, these data suggest that the cellular response to both mitochondrial and nuclear DNA damage may play an important role in AMD pathogenesis.

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Cannabinoid receptor 1 blockade protects human retinal pigment epithelial cells from oxidative injury.

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BACKGROUND: Because oxidative stress is assumed to be a key mechanism in the pathological process of age-related macular degeneration (AMD), increasing numbers of studies have focused on discovering new pathways and treatments for reducing oxidative damage. Our work investigates the potential role of the cannabinoid receptor 1 (CB1) in oxidative stress of primary human retinal pigment epithelial (RPE) cells, a cellular model of AMD.

METHODS: Primary human RPE cells were cultured and exposed to hydrogen peroxide for 24 h to induce oxidative damage. The expression of and changes in the CB1 receptor were determined with western blot assay and confocal imaging. The CB1 receptor in the RPE cells was inhibited with small interfering RNA (siRNA) or rimonabant (SR141716). Cell viability, apoptosis, and reactive oxygen species production were measured by using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) and sulforhodamine B assay, annexin V and propidium iodide staining, and the dichlorofluorescein fluorescence assay, respectively. Intracellular superoxide dismutase activity was assayed with a commercially available assay kit. Phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) protein expression and activation of signaling molecules were assessed with western blot analysis.

RESULTS: We showed that human RPE cells express the CB1 receptor. In addition, oxidative stress upregulates the expression of the CB1 receptor. Deleting the CB1 receptor or treating with the CB1 receptor antagonist rimonabant (SR141716) rescued RPE cells from hydrogen peroxide-induced oxidative damage. Rimonabant pretreatment effectively reduced the apoptosis of RPE cells, inhibited the generation of intracellular reactive oxygen species and elevated the activity of superoxide dismutase. In addition, rimonabant significantly strengthened the oxidative stress-induced activation of the PI3K/Akt signaling pathway.

CONCLUSIONS: The results demonstrate the expression and regulation of CB1 receptors in human RPE cells. Inhibiting the CB1 receptor may be an effective therapeutic strategy for AMD by downregulating oxidative stress signaling and facilitating PI3K/Akt activation.

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PLoS One. 2013;8(2):e56556. doi: 10.1371/journal.pone.0056556. Epub 2013 Feb 18.

Neurological basis for eye movements of the blind.

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Abstract: When normal subjects fix their eyes upon a stationary target, their gaze is not perfectly still, due to small movements that prevent visual fading. Visual loss is known to cause greater instability of gaze, but reported comparisons with normal subjects using reliable measurement techniques are few. We measured binocular gaze using the magnetic search coil technique during attempted fixation (monocular or binocular viewing) of 4 individuals with childhood-onset of monocular visual loss, 2 individuals with late-onset monocular visual loss due to age-related macular degeneration, 2 individuals with bilateral visual loss, and 20 healthy control subjects. We also measured saccades to visual or somatosensory cues. We tested the hypothesis that gaze instability following visual impairment is caused by loss of inputs that normally optimize the performance of the neural network (integrator), which ensures both monocular and conjugate gaze stability. During binocular viewing, patients with early-onset monocular loss of vision showed greater instability of vertical gaze in the eye with visual loss and, to a lesser extent, in the normal eye, compared with control subjects. These vertical eye drifts were much more disjunctive than upward saccades. In individuals with late monocular visual loss, gaze stability was more similar to control subjects. Bilateral visual loss caused eye drifts that were larger than following monocular visual loss or in control subjects. Accurate saccades could be made to somatosensory cues by an individual with acquired blindness, but voluntary saccades were absent in an individual with congenital blindness. We conclude that the neural gaze-stabilizing network, which contains neurons with both binocular and monocular discharge preferences, is under adaptive visual control. Whereas monocular visual loss causes disjunctive gaze instability, binocular blindness causes both disjunctive and conjugate gaze instability (drifts and nystagmus). Inputs that bypass this neural network, such as projections to motoneurons for upward saccades, remain conjugate.

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Genetics

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Seven new loci associated with age-related macular degeneration

Abecasis GR and the AMD Gene Consortium

Abstract: Age-related macular degeneration (AMD) is a common cause of blindness in older individuals. To accelerate the understanding of AMD biology and help design new therapies, we executed a collaborative genome-wide association study, including >17,100 advanced AMD cases and >60,000 controls of European and Asian ancestry. We identified 19 loci associated at P < 5 × 10−8. These loci show enrichment for genes involved in the regulation of complement activity, lipid metabolism, extracellular matrix remodeling and angiogenesis. Our results include seven loci with associations reaching P < 5 × 10−8 for the first time, near the genes COL8A1-FILIP1L, IER3-DDR1, SLC16A8, TGFBR1, RAD51B, ADAMTS9 and B3GALTL. A genetic risk score combining SNP genotypes from all loci showed similar ability to distinguish cases and controls in all samples examined. Our findings provide new directions for biological, genetic and therapeutic studies of AMD.

Mol Vis. 2013;19:374-83. Epub 2013 Feb 13.

Complement factor H Val62Ile variant and risk of age-related macular degeneration: A meta-analysis.

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PURPOSE: To evaluate the precise association of complement factor H (CFH) Val62Ile polymorphism with age-related macular degeneration (AMD) susceptibility.

METHODS: We performed a meta-analysis using databases including PubMed, EMBASE, and Web of Science to find relevant studies. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using fixed-effect and random-effects models. The inconsistency index (I(2)) was used to assess heterogeneity. Funnel plots and Egger's test were used to evaluate publication bias. Sensitivity analysis was also performed.

RESULTS: Fourteen studies including 4,438 patients with AMD and 6,099 controls based on the search criteria were involved in the meta-analysis. In overall populations, the pooled OR(1) for genotype GA+GG versus homozygous genotype AA was 2.28 (95% confidence interval (CI): 1.48-3.52), the OR(2) of heterozygous genotype GA versus AA was 1.58 (95% CI: 1.13-2.19), the OR(3) of homozygous genotype GG versus AA was 2.90 (95% CI: 1.95-4.30), and the OR(4) of allele G versus A was 1.77 (95% CI: 1.43-2.21). In Asian populations, our results provided substantial evidence that the Val62Ile variant was significantly associated with AMD (OR(4)=1.85, 95% CI: 1.63-2.09). However, in Caucasian populations, no significant association of Val62Ile with AMD was established in all circumstances.

CONCLUSIONS: Our analysis provides substantial evidence that the Val62Ile variant is significantly associated with AMD in Asian populations. However, our results have demonstrated no link between the Val62Ile polymorphism and AMD in Caucasian populations.

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RNAi in Clinical Studies.

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Abstract: RNA interference (RNAi) is an efficient process of posttranscriptional gene silencing. In recent

years it has been developed into a new technology in biopharmaceutical fields of science. RNAi products include short interference RNA (siRNA) but also short hairpin RNA (shRNA), bifunctional short hairpin RNA (bi-shRNA) and microRNA (miRNA). They combine with homologous fragments of the mRNA and cause its degradation. It results in inhibition of protein synthesis, or in mutation in the gene encoding it. RNAi has been used in analysis of genomes and creation of new animal models to test drugs. From the pharmaceutical point of view, what is the most important is its therapeutic application. So far the basic and clinical research has been focused on the following targets: macular degeneration, cancer and antiviral therapy. But there are also reports on clinical trials in asthma, hypercholesterolemia and genetic diseases such as inherited skin disorders and amyloidosis. Among over 20 therapeutics that reached clinical trials, only few are still investigated. Another few are clinical candidates. The review focuses on RNAi products under clinical evaluation and their most promising new applications.

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Diet

Nutrients. 2013 Feb 15;5(2):543-51. doi: 10.3390/nu5020543.

Effects of lutein and docosahexaenoic Acid supplementation on macular pigment optical density in a randomized controlled trial.

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Abstract: We studied the macular pigment ocular density (MPOD) in patients with early age macular degeneration (AMD) before and 1 year after nutritional supplementation with lutein and docosahexaenoic acid (DHA). Forty-four patients with AMD were randomly divided into two groups that received placebo (n = 21) or a nutritional supplement (n = 23, 12 mg of lutein and 280 mg of DHA daily). Heterochromatic flicker photometry was used to determine the MPOD. At baseline, the MPOD in AMD patients with placebo was 0.286 ± 0.017 meanwhile in AMD patients with supplementation it was 0.291 ± 0.016. One year later, the mean MPOD had increased by 0.059 in the placebo group and by 0.162 in patients receiving lutein and DHA. This difference between groups was significant ($p < 0.05$). Lutein and DHA supplementation is effective in increasing the MPOD and may aid in prevention of age related macular degeneration.

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Ginkgo biloba extract for age-related macular degeneration.

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BACKGROUND: Ginkgo is used in the treatment of peripheral vascular disease and 'cerebral insufficiency'. It is thought to have several potential mechanisms of action including increased blood flow, platelet activating factor antagonism, and prevention of membrane damage caused by free radicals. Vascular factors and oxidative damage are thought to be two potential mechanisms in the pathology of age-related macular degeneration (AMD).

OBJECTIVES: The objective of this review was to determine the effect of Ginkgo biloba extract on the

progression of AMD.

SEARCH METHODS: We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library 2012, Issue 10), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to October 2012), EMBASE (January 1980 to October 2012), Allied and Complementary Medicine Database (AMED) (January 1985 to October 2012), OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu/), the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 5 October 2012. We searched the reference lists of identified reports and the Science Citation Index. We also contacted investigators of included studies for additional information.

SELECTION CRITERIA: All randomised trials in people with AMD where Ginkgo biloba extract had been compared to control were included.

DATA COLLECTION AND ANALYSIS: The review author extracted data using a standardised form. The data were verified with the trial investigators. Trial quality was assessed.

MAIN RESULTS: Two published trials were identified that randomised a total of 119 people. In one study conducted in France, 20 people were randomly allocated to Gingko biloba extract EGb 761 80 mg twice daily or placebo. In the other study conducted in Germany, 99 people were randomly allocated to two different doses of Ginkgo biloba extract EGb 761 (240 mg per day and 60 mg per day). Treatment duration in both studies was six months. Both trials reported some positive effects of Ginkgo biloba on vision however their results could not be pooled. Adverse effects and quality of life for people with AMD were not reported.

AUTHORS' CONCLUSIONS: The question as to whether people with AMD should take Ginkgo biloba extract to prevent progression of the disease has not been answered by research to date. Two small trials have suggested possible benefit of Gingko biloba on vision and further trials are warranted. Ginkgo biloba is widely used in China, Germany, and France. Future trials should be larger, and last longer, in order to provide a more robust measure of the effect of Gingko biloba extract on AMD.

Update of Cochrane Database Syst Rev. 2000;(2):CD001775.

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Oxidative Stress and Anti-oxidative Defence in Patients with Age-Related Macular Degeneration.

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Abstract Purpose: To evaluate the oxidative stress status and anti-oxidative defence in patients with age-related macular degeneration (AMD).

Methods: A total of 22 patients diagnosed with AMD and 23 age-matched healthy controls were included in the present study. Serum levels of total oxidant status (TOS), total antioxidant status (TAS), total thiol status (TTS) and paraoxonase 1 (PON1) activity were investigated from samples.

Results: Significant increase in TOS levels were observed in sera of AMD patients (25.3 ± 12.8) compared to controls (15.0 ± 4.4). TTS (404.3 ± 55.3) and serum PON1 enzyme activities (163.0 ± 65.5) were

significantly lower in AMD patients (594.0 ± 64.2) relative to control groups (252.8 ± 132.7).

Conclusion: The results of the present study show that there is a significant increase in oxidative stress in AMD patients and significant decrease in antioxidant defence, in the total thiol level and in PON1 activity in AMD patients compared with controls. The increased oxidative stress and decreased antioxidant levels may have a synergistic role in AMD development.

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