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MD Research News

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Drug treatment

Br J Ophthalmol. 2013 Jun 13. [Epub ahead of print]

Aflibercept for exudative AMD with persistent fluid on ranibizumab and/or bevacizumab.

Cho H, Shah CP, Weber M, Heier JS.

Collaborators (4)

Department of Retina, Ophthalmic Consultants of Boston, Boston, Massachusetts, USA.

OBJECTIVE: To investigate the effect of aflibercept 2.0 mg in cases resistant to ranibizumab 0.5 mg and/or bevacizumab 1.25 mg treatment.

PURPOSE: To evaluate the anatomic and visual effect of intravitreal aflibercept 2.0 mg in cases of exudative age-related macular degeneration (AMD) with persistent fluid on optical coherence tomography (OCT) despite regular ranibizumab 0.5 mg and/or bevacizumab 1.25 mg treatment at 1 and 6 months.

METHODS: Retrospective review at Ophthalmic Consultants of Boston, Boston, Massachusetts, USA of exudative AMD cases with persistent fluid on regular ranibizumab 0.5 mg and/or bevacizumab 1.25 mg treatment switched to intravitreal aflibercept 2.0 mg treatment and followed for 6 months. Tabulated data included details of prior treatments, best available visual acuity, central subfoveal thickness on registered spectral domain OCT before and after aflibercept injection centred on the anatomic fovea and macular description before and after aflibercept injection.

RESULTS: A total of 353 eyes with exudative AMD were switched to aflibercept during the study period. Of these, 28 eyes in 28 patients had persistent fluid after an average of 20 regular ranibizumab/bevacizumab injections (range 7-37). At 1 month, 89% (25 eyes) showed anatomic improvement and 18% (five eyes) were dry after a single aflibercept injection. Central subfoveal thickness improved from 295 to 272 microns ($p<0.001$) after one aflibercept injection. After an average of 4.4 aflibercept injections (range 3-6) over 6 months, the central subfoveal thickness remained improved (274 microns, $p=0.008$); 64% (18 eyes) showed anatomic improvement and a quarter of eyes (25%, seven eyes) were dry. Visual acuity did not improve at 1 month (logarithm of minimum angle of resolution (logMAR) 0.54, Snellen 20/69, $p=0.64$) or 6 months (logMAR 0.57, Snellen 20/76, $p=0.49$). Treatment was well tolerated with no adverse events reported.

CONCLUSIONS: A significant proportion of exudative AMD cases with persistent fluid on OCT despite regular ranibizumab 0.5 mg and/or bevacizumab 1.25 mg treatment respond anatomically to aflibercept 2.0 mg. Visual acuity did not improve. Aflibercept may be beneficial anatomically in cases of exudative AMD treated with persistent fluid on ranibizumab and/or bevacizumab.

PMID: 23766432 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2013;7:1089-92. doi: 10.2147/OPTH.S45155. Epub 2013 Jun 7.

Bimonthly half-dose ranibizumab in large pigment epithelial detachment and retinal angiomatous proliferation with high risk of retinal pigment epithelium tear: a case report.

Monés J, Biarnés M, Badal J.

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INTRODUCTION: The management of large pigment epithelial detachments (PEDs) associated with retinal angiomatous proliferation (RAP) remains a challenge due to the high risk of retinal pigment epithelial (RPE) tear. We describe the successful progressive anatomical result and the maintenance of visual acuity to bimonthly, half-dose ranibizumab in a patient with this condition.

PURPOSE: To describe the management of a large PED secondary to RAP with bimonthly, half-dose ranibizumab.

METHOD: Case report.

PATIENT: A 71-year-old woman presented with visual symptoms due to an enlarged PED, compared with previous visits, secondary to a RAP lesion, with a visual acuity of 20/32. To reduce the risk of an RPE tear and a significant decrease in vision, we discussed with the patient the possibility of treating the lesion in a progressive manner, with more frequent but smaller doses of ranibizumab. The patient was treated biweekly with 0.25 mg of ranibizumab until fattening of the PED.

RESULTS: The large PED fattened progressively, and visual acuity was preserved with no adverse events.

DISCUSSION: The use of half-dose antiangiogenic therapy may be useful in managing large vascularized PED associated with RAP, in an attempt to reduce the risk of RPE tear.

PMID: 23766633 [PubMed - in process]

Clin Interv Aging. 2013;8:467-83. doi: 10.2147/CIA.S36811. Epub 2013 Apr 29.

Long-term effectiveness of ranibizumab for age-related macular degeneration and diabetic macular edema.

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Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, Kowloon, Hong Kong.

Abstract: Neovascular age-related macular degeneration (AMD) and diabetic macular edema (DME) are major causes of visual impairment in the elderly population worldwide. With the aging population, the prevalence of neovascular AMD and DME has increased substantially over the recent years. Vascular endothelial growth factor (VEGF) has been implicated as playing an important role in the pathogenesis of both neovascular AMD and DME. Since its introduction in 2006, ranibizumab, a recombinant, humanized, monoclonal antibody fragment against all isoforms of VEGF-A, has revolutionized the treatment of neovascular AMD and DME. The efficacy and safety of ranibizumab in neovascular AMD has been demonstrated in the ANCHOR and MARINA trials. Further studies including the PIER, PrONTO, and SUSTAIN trials have also evaluated the optimal dosing regimen of ranibizumab in neovascular AMD. The CATT and IVAN trials compared the safety and efficacy of ranibizumab with off-label use of bevacizumab. Studies such as SUSTAIN and HORIZON have shown that ranibizumab has a good safety profile and is well tolerated for over 4 years with very few serious ocular and systemic adverse events. For DME, Phase II RESOLVE study and Phase III RISE and RIDE studies have demonstrated superiority of ranibizumab treatment in improving vision over placebo controls. Phase II READ and Phase III RESOLVE and REVEAL studies have shown that ranibizumab is more effective both as monotherapy and in combination with laser

compared with laser monotherapy. The 3-year results from the DRCRnet protocol I study found that ranibizumab with deferred laser resulted in better long-term visual outcome compared with ranibizumab with prompt laser. This review summarizes various important clinical trials on the long-term efficacy and safety of ranibizumab in the treatment of neovascular AMD and DME. The pharmacological properties of ranibizumab, its cost effectiveness, and impact on quality of life will also be discussed.

PMID: 23766636 [PubMed - in process]

Retina. 2013 Jun 6. [Epub ahead of print]

ROLE OF POSTERIOR VITREOUS DETACHMENT ON OUTCOME OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR TREATMENT IN AGE-RELATED MACULAR DEGENERATION.

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Ministry of Health Ankara Training and Research Hospital, Ophthalmology Clinic, Altindag, Ankara, Turkey.

PURPOSE: The aim of this study was to determine the effect of posterior vitreous detachment on outcome of anti-vascular endothelial growth factor injection.

METHODS: Sixty-one eyes with age-related macular degeneration that had received intravitreal bevacizumab or ranibizumab injections were retrospectively reviewed. The vitreomacular interface was evaluated, and eyes were grouped according to the presence of posterior vitreous detachment (Group 1, n = 25) or vitreomacular adhesion (Group 2, n = 36). All patients received three loading doses of intravitreal anti-vascular endothelial growth factor injections at monthly intervals, and subsequently, pro re nata regimen was performed. Best-corrected visual acuity and central foveal thickness measurement at follow-up were evaluated. The development of posterior vitreous detachment during the follow-up was also reported.

RESULTS: The best-corrected visual acuity changes at each visit compared with baseline were significantly better in Group 1 (P = 0.01, 0.02, 0.02, 0.009, 0.009, respectively at third, sixth, ninth, 12th month, and last visit). When best-corrected visual acuity was classified according to the change in visual acuity of 10 letters or more, the rate of improved or stable best-corrected visual acuity was greater in Group 1 (P = 0.02). During the follow-up, 5 eyes (14.3%) developed posterior vitreous detachment.

CONCLUSION: Vitreomacular adhesion seems to have an adverse effect on the visual prognosis of anti-vascular endothelial growth factor treatment for age-related macular degeneration.

PMID: 23751943 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2013 Jun 13. [Epub ahead of print]

Ranibizumab efficiently blocks migration but not proliferation induced by growth factor combinations including VEGF in retinal endothelial cells.

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BACKGROUND: Proliferation and migration of retinal endothelial cells (REC) are associated with the development of proliferative diabetic retinopathy. REC proliferation is stimulated by isoforms of vascular endothelial growth factor-A (i.e., VEGF121 and VEGF165), basic fibroblast growth factor (bFGF), and insulin-like growth factor (IGF-1) of which VEGF165 also enhances migration of REC. Effects induced by VEGF-A can be blocked with ranibizumab, a VEGF-binding Fab fragment used in therapy of diabetic

macular edema. In this study, we investigated potential angiogenic effects of placental growth factors (PlGF -1, PlGF-2) as other members of the VEGF family and whether the primary action of VEGF165 is modulated in the presence of bFGF, IGF-1 and PlGF-1/-2. We also studied how effects of growth factor combinations can be attenuated with ranibizumab.

METHODS: Effects of single growth factors or their combinations on proliferation and migration of immortalized bovine retinal endothelial cells (iBREC) were studied with or without ranibizumab or the inhibitor of VEGF receptors KRN951.

RESULTS: Proliferation of iBREC was significantly stimulated by 1-100 ng/ml PlGF-1 or PlGF-2, but additive effects were not observed with various combinations of the tested growth factors. Ranibizumab neutralized VEGF's effect on proliferation but was not effective when the other growth factors were used in combination with VEGF. bFGF and IGF-1 but not PlGF-1 or PlGF-2 stimulated iBREC migration as single agents, and they further enhanced VEGF-induced migration. The effects of such growth factor combinations including VEGF on migration were efficiently blocked by targeting only VEGF with ranibizumab. Migration induced by VEGF plus bFGF and IGF-1 was also almost completely inhibited by KRN951 interfering with VEGF receptor signalling.

CONCLUSIONS: Migration but not proliferation of iBREC induced by combinations of bFGF, IGF-1, PlGF-1 or PlGF-2 together with VEGF is efficiently suppressed by ranibizumab. VEGF-mediated signalling through VEGFR2 seems to control REC migration dominantly in the presence of other growth factors.

PMID: 23760670 [PubMed - as supplied by publisher]

Int J Biol Macromol. 2013 Jun 5. pii: S0141-8130(13)00323-1. doi: 10.1016/j.ijbiomac.2013.05.034. [Epub ahead of print]

Sustained release of Avastin® from polysaccharides cross-linked hydrogels for ocular drug delivery.

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Abstract: Avastin® was the first choice drug for the treatment of age related macular degeneration (AMD) and proliferative diabetic retinopathy in clinic. Due to its short half-time in intraocular, it was required repeat administration. In this paper, an in-situ injectable polysaccharides cross-linked hydrogel was developed for potential ocular drug delivery of avastin. The polysaccharide cross-linked hydrogel was first synthesized by simple mixing of glycol chitosan and oxidized alginate aqueous solution, and then characterized by scanning electron microscopy (SEM) and rheometer. In vitro degradation test indicated that the degradation rate of hydrogels could be controlled by the varying the concentration of oxidized alginate in hydrogels. In vitro release study showed that the encapsulated avastin had an initial burst release at early stage (within 4h) followed by the sustained release in period of 3 days. With the increase of oxidized alginate concentration in the hydrogel, the release rate of avastin from hydrogels declined, accordingly. Meanwhile, the structure stability of avastin released from hydrogels at specific time intervals did not show apparent changes as compared with native avastin based on the analysis of SDS-polyacrylamide gel electrophoresis (SDS-PAEG). As a result, the developed in-situ injectable polysaccharides cross-linked hydrogel with controllable degradation rate and drug release might be a versatile carrier for avastin to apply in ocular drug delivery.

PMID: 23748006 [PubMed - as supplied by publisher]

Ophthalmologica. 2013 Jun 6:34-42. [Epub ahead of print]

Cost and Effectiveness of Therapy for Wet Age-Related Macular Degeneration in Routine Clinical Practice.

Studnička J, Ríhová B, Rencová E, Rozsíval P, Dubská Z, Chrapek O, Kolář P, Kandrnal V, Demlová R, Pitrová S, Rehák J.

Department of Ophthalmology, Faculty of Medicine in Hradec Králové, Charles University in Prague, and University Hospital, Hradec Králové, Czech Republic.

Purpose: Evaluation of the cost and effectiveness of therapy for patients with the wet form of age-related macular degeneration (AMD) in routine clinical practice.

Methods: A retrospective multicentre evaluation of changes in the best-corrected visual acuity in applied kinds of therapy and a comparison with the cost of individual therapeutic procedures.

Results: An overall total of 788 eyes of 763 patients with an average age of 73.2 ± 8.6 years was evaluated for a 1-year minimum period. In the ranibizumab and pegaptanib therapy groups, a reduction of 1.3 letters ($p = 0.303$) and 1.4 letters ($p = 0.197$) was found, respectively. In the group of photodynamic therapy (PDT) with verteporfin, a reduction of 5.2 letters was achieved ($p < 0.001$). Under the conditions of routine practice in the Czech Republic, the annual cost is highest (EUR 5,467.63/patient) in patients with pegaptanib therapy. The annual cost in patients with ranibizumab therapy is lower by EUR 1,220.16. The cost is nearly half (EUR 2,783.65) in the group treated with PDT with verteporfin.

Conclusion: An initiation of AMD therapy by ranibizumab is cost-effective as compared to pegaptanib. Both ranibizumab and pegaptanib are significantly more efficient as compared to PDT with verteporfin. Therapy with ranibizumab and pegaptanib, as compared to PDT with verteporfin, prevents the loss of 1 line of vision on the ETDRS chart for EUR 1,225.98 and 2,286.18, respectively.

PMID: 23751929 [PubMed - as supplied by publisher]

Arch Ophthalmol. 2012 Jun 1;130(6):806-7. doi: 10.1001/archophthalmol.2012.100.

Systemic and Ocular Risks Associated With Therapies for Macular Degeneration: Clarification vs Confusion-Reply.

Curtis LH, Hammill BG, Schulman KA, Cousins SW.

PMID: 23753704 [PubMed]

Eye (Lond). 2013 Jun;27(6):786. doi: 10.1038/eye.2013.84.

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 AC, Cole M, Gale R, George S, Lotery AJ, Majid M, McKibbin M, Menon G, Yang Y, Andrews C, Brittain C, Osborne A.

PMID: 23759680 [PubMed - in process]

Johns Hopkins Med Lett Health After 50. 2012 Winter;24(12):1-4.

Sight-saving treatments for age-related macular degeneration. New drugs offer new hope for

managing a leading cause of blindness.

[No authors listed]

PMID: 23757782 [PubMed - in process]

Other treatment & diagnosis

Eye (Lond). 2013 Jun 14. doi: 10.1038/eye.2013.106. [Epub ahead of print]

Ocular perfusion pressure and choroidal thickness in eyes with polypoidal choroidal vasculopathy, wet-age-related macular degeneration, and normals.

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PurposeTo measure the choroidal thickness and ocular perfusion pressure in eyes with polypoidal choroidal vasculopathy (PCV), wet-age-related macular degeneration (AMD), and age-matched normal subjects, and look for a possible association between the two.MethodsThis was a prospective study including 22 eyes with PCV, 33 eyes with wet-AMD, and 35 age-matched normal eyes. Choroidal thickness was measured using enhanced depth imaging (EDI) with spectral-domain optical coherence tomography (SD OCT). Mean ocular perfusion pressure (MOPP) was calculated using the mathematical formula 2/3 [DBP+1/3{SBP × DBP}]-IOP (DBP-diastolic blood pressure, SBP-systolic blood pressure, IOP-intraocular pressure). Analyses were carried out using SPSS 14 software and comparisons of mean made using't' tests.ResultsEyes with PCV showed increased (285.9 μm; subfoveal) choroidal thickness, whereas eyes with wet-AMD (119.4 μm; subfoveal) showed reduced choroidal thickness in comparison with normal eyes (186.77 μm; subfoveal). MOPP in the PCV group was 57.85 mm Hg (P value 0.00), in the wet-AMD group was 52.1 mm Hg (P-value 0.12), and in the normal group was 49.79 mm Hg.ConclusionIt is postulated that higher MOPP in eyes with PCV could have an etiologic implication in disease manifestation and progression. Larger studies with longer follow-up may help validate these findings.Eye advance online publication, 14 June 2013; doi:10.1038/eye.2013.106.

PMID: 23764988 [PubMed - as supplied by publisher]

Retina. 2013 Jun 12. [Epub ahead of print]

OUTER RETINAL ATROPHY AFTER REGRESSION OF SUBRETINAL DRUSENOID DEPOSITS AS A NEWLY RECOGNIZED FORM OF LATE AGE-RELATED MACULAR DEGENERATION.

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PURPOSE: To investigate the long-term clinical course of eyes with pseudodrusen appearance caused by subretinal drusenoid deposits.

METHODS: Eyes from the original study identifying subretinal deposits of material as the cause of pseudodrusen appearance were evaluated in a retrospective study of outer retinal morphology. The distance between the inner plexiform layer and the retinal pigment epithelium, termed the photoreceptor length, was measured from optical coherence tomography approximately 2 mm superior to the fovea at baseline and at follow-up visits. The choroidal thickness was measured directly under this retinal area.

RESULTS: Of the 21 eyes available for follow-up, 9 (42.9%) eventually developed choroidal neovascularization over a mean 2.9-year follow-up period. Regression of subretinal drusenoid deposits was

seen in 9 eyes (42.9%) as well. Those with regression of subretinal drusenoid deposits had a decrease in the photoreceptor length with the final photoreceptor length being 74.4% of the initial length (P < 0.001). In eyes with regression, the underlying choroid was 81.4% of its initial value (P = 0.01) at the final follow-up. Eyes with regression also showed loss of the ellipsoid band. Eyes without regression had no change in photoreceptor length, choroidal thickness, or outer retinal architecture.

CONCLUSION: Eyes with regression of subretinal drusenoid deposits develop outer retinal atrophy and loss of the underlying choroidal thickness. This finding seems common in eyes having pseudodrusen and represents a late form of age-related macular degeneration that is not in current classification systems. Further study is needed to determine both the true prevalence and the effects on visual function.

PMID: 23764969 [PubMed - as supplied by publisher]

Retina. 2013 Jun 12. [Epub ahead of print]

CHOROIDAL THICKNESS IN RETINAL PIGMENT EPITHELIAL TEAR AS MEASURED BY SPECTRAL DOMAIN OPTICAL COHERENCE TOMOGRAPHY.

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PURPOSE: To evaluate the choroidal thickness with spectral domain optical coherence tomography in subjects with retinal pigment epithelial (RPE) tear compared with the choroidal thickness of their fellow eye.

METHODS: For this cross-sectional investigation, seven eyes of seven patients with neovascular age-related macular degeneration and RPE tear in one eye imaged with spectral domain optical coherence tomography were identified. Choroidal thickness was measured from the posterior edge of the retinal pigment epithelium to the choroid/sclera junction at 500 μm intervals up to 2,500 μm temporal and nasal to the fovea in both the eye with the RPE tear and the eye with intact RPE. All measurements were performed by two independent observers and averaged for the purpose of the analysis. Measurements were compared using paired t-test.

RESULTS: The average age of patients was 79 years (range, 66-88 years). All subjects had dome-shaped pigment epithelial detachments before RPE tear and no dome-shaped pigment epithelial detachments in the unaffected eye. Average subfoveal choroidal thickness in the eye with the RPE tear was 154.9 ± 10.1 μm. Average subfoveal choroidal thickness in the eye with intact RPE was 212.9 ± 10.6 μm (P = 0.035).

CONCLUSION: There is a significant decrease in subfoveal choroidal thickness in the subjects with RPE tear compared with their fellow eye with intact RPE. It is unclear if this thinning is a consequence of or precedes the RPE tear. Further studies are necessary to prospectively follow choroidal thickness in subjects with dome-shaped pigment epithelial detachments.

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Retina. 2013 Jun 12. [Epub ahead of print]

COMPARISON OF SPECTRAL-DOMAIN AND TIME-DOMAIN OPTICAL COHERENCE TOMOGRAPHY IN THE DETECTION OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION ACTIVITY.

Major JC Jr, Wykoff CC, Mariani AF, Chen E, Croft DE, Brown DM.

Retina Consultants of Houston, Weill Cornell Medical College and The Methodist Hospital, Houston, Texas.

PURPOSE: To compare the sensitivity of commonly used time-domain (TD-OCT) and spectral-domain optical coherence tomography platforms and scanning modalities in the management of neovascular age-related macular degeneration in a population with a high prevalence of exudative disease activity.

METHODS: Fifty consecutive patients within the prospective SAVE (Super-dose Anti-Vascular Endothelial growth factor) trial, which analyzed the utility of 2.0 mg intravitreal ranibizumab for the treatment of recalcitrant neovascular age-related macular degeneration, were enrolled in a comparison trial of 3 different optical coherence tomography (OCT) platforms. Stratus TD-OCT radial scan (Carl Zeiss Meditec, Inc) was compared with 3 Heidelberg Spectralis Heidelberg Retinal Angiograph+OCT (Heidelberg Engineering) acquisition settings (radial, 7-line raster, volumetric) and 2 Cirrus high definition (HD)-OCT (Carl Zeiss Meditec, Inc) acquisition settings (5-line raster, volumetric).

RESULTS: Using every imaging platform and acquisition setting, evidence of exudative disease activity was positively identified in 163 of 191 patient visits (85.3%). Intraretinal cysts were identified in 83 of 191 visits (43.5%), and subretinal fluid was identified in 116 of 191 visits (60.7%). Of these positive visits, the Stratus TD-OCT radial scanning technology demonstrated a significantly lower rate of detection (71.8%) when compared with the Spectralis HRA+OCT spectral domain scanning modalities (radial 87.1%, $P < 0.001$; 7-line raster 92.0%, $P < 0.001$; volumetric 94.5%, $P < 0.001$) or the Cirrus HD-OCT spectral domain scanning modalities (5-line raster 81.6%, $P = 0.001$; volumetric 92.0%, $P < 0.001$). Intraretinal cysts and subretinal fluid were identified in 83 visits (43.5%) and 116 visits (60.7%), respectively, with 36 eyes (18.8%) having fluid in both locations. No individual imaging modality demonstrated a diagnostic advantage for detecting subretinal fluid versus intraretinal cysts (e.g., Cirrus volume detected 86.7% of intraretinal cysts and 88.8% of subretinal fluid, $P = 0.33$).

CONCLUSION: In this neovascular age-related macular degeneration patient population, spectral-domain ocular coherence tomography was a superior diagnostic tool when compared with TD-OCT, with each spectral domain platform and acquisition setting identifying significantly more exudative disease activity. The two spectral domain platforms (Cirrus and Spectralis) were not directly compared because identical image acquisition parameters were not used. No individual imaging modality demonstrated a diagnostic advantage for detecting subretinal fluid versus intraretinal cysts.

PMID: 23764967 [PubMed - as supplied by publisher]

J Glaucoma. 2013 Jun-Jul;22 Suppl 5:S42-5. doi: 10.1097/IJG.0b013e3182934b45.

Cell-based therapies for retinal degenerative diseases: a thousand strategies.

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Abstract: Retinal neuronal death causes a severe and irreversible loss of visual function in the patients of retinitis pigmentosa, age-related macular degeneration and glaucoma, but these degenerative diseases currently still lack effective medical treatments. The restorative properties of stem cells hold the promise in the treatment of these retinal degenerative diseases. The exciting progress has been made on stem cell research in the last decade. Many different stem cell types have been explored for their potential in treating the retinal degenerative diseases, including embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells and retinal stem cells. This review will summarize the recent progress in this exciting area.

PMID: 23733127 [PubMed - in process]

Restor Neurol Neurosci. 2013 Jun 12. [Epub ahead of print]

Transpalpebral electrotherapy for dry age-related macular degeneration (AMD): An exploratory trial.

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Purpose: To evaluate the effect of transpalpebral electrotherapy on patients with dry age-related macular degeneration (AMD).

Methods: 22 patients were randomized in two groups to either receive therapy (n = 12) or placebo (n = 10). There was no statistically significant difference for age and initial visual acuity (VA) between the two groups (p = 0.6; ANOVA). Treatment was performed on 5 consecutive days. On each day two sessions were applied. Every session included 8 spots (40 sec/spot) around the eye globe. The current applied (changing frequency 5-80 Hz) varied individually between 150 and 220 μA. Patients were examined before treatment, at the end of the 5-day treatment period, after 4 weeks and at 6 months. Examinations included a standardized VA testing, using ETDRS letters, contrast sensitivity, macular sensitivity and fixation stability using microperimetry and measurements with SD-OCT.

Results: At the end of week 1, mean VA improved markedly (p = 0.001; T test), with 7 out of 12 patients showing an improvement of more than 5 letters. After 4 weeks, there was an improvement of more than 10 letters in 3 patients (mean + 5.7 letters; p = 0.001; T test) whereas at 6 months a loss of 1.6 letters was observed. Only 4 (33%) of our patients did not show any improvement at all. Contrast sensitivity displayed a similar pattern. Within one week after treatment, there was a rapid improvement (+4.4 optotypes; p = 0.006; T test). After 6 months, contrast sensitivity declined again (+1.5 optotypes; p = 0.2; T test). Compared to the placebo group changes on VA failed statistical significance (p = 0.1 at 4 week; T test) whereas changes on contrast sensitivity were statistically significant (p = 0.01 at week 4; T test). No adverse events were seen or reported during the study period.

Conclusions: To the best of our knowledge, this is the first report of a transpalpebral electrostimulation in patients with dry AMD that demonstrates a temporary increase in visual function in some of these patients; results that seem to justify further research on this potential treatment option for dry AMD.

PMID: 23760223 [PubMed - as supplied by publisher]

J Ophthalmol. 2013;2013:385915. doi: 10.1155/2013/385915. Epub 2013 May 8.

Grading of Age-Related Macular Degeneration: Comparison between Color Fundus Photography, Fluorescein Angiography, and Spectral Domain Optical Coherence Tomography.

Mokwa NF, Ristau T, Keane PA, Kirchhof B, Sadda SR, Liakopoulos S.

Cologne Image Reading Center and Laboratory, Department of Ophthalmology, University of Cologne, 50924 Cologne, Germany.

Purpose: To compare color fundus photography (FP), fluorescein angiography (FA), and spectral domain optical coherence tomography (SDOCT) for the detection of age-related macular degeneration (AMD), choroidal neovascularisation (CNV), and CNV activity.

Methods: FPs, FAs, and SDOCT volume scans from 120 eyes of 66 AMD and control patients were randomly collected. Control eyes were required to show no AMD, but other retinal pathology was allowed. The presence of drusen, pigmentary changes, CNV, and signs for CNV activity was independently analyzed for all imaging modalities.

Results: AMD was diagnosed based on FP in 75 eyes. SDOCT and FA showed sensitivity (specificity) of

89% (76%) and 92% (82%), respectively. CNV was present on FA in 68 eyes. Sensitivity (specificity) was 78% (100%) for FP and 94% (98%) for SDOCT. CNV activity was detected by SDOCT or FA in 60 eyes with an agreement in 46 eyes. Sensitivity was 88% for SDOCT and 88% for FA. FP showed sensitivity of 38% and specificity of 98%.

Conclusions: CNV lesions and activity may be missed by FP alone, but FP may help identifying drusen and pigmentary changes. SDOCT is highly sensitive for the detection of AMD, CNV, and CNV activity; however, it cannot fully replace FA.

PMID: 23762528 [PubMed]

Br J Ophthalmol. 2013 Jun 12. [Epub ahead of print]

Imaging characteristics of neovascular pigment epithelial detachments and their response to anti-vascular endothelial growth factor therapy.

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PURPOSE: To evaluate the imaging characteristics of macular neovascular pigment epithelial detachments (PEDs) and their response to anti-vascular endothelial growth factor (VEGF) therapy.

METHODS: Patients with exudative age-related macular degeneration (AMD), idiopathic polypoidal choroidal vasculopathy, presumed ocular histoplasmosis syndrome (POHS) and central serous retinopathy (CSR) with choroidal neovascularisation (CNV) were included in the study. A retrospective chart review of 72 eyes of 64 patients was performed.

RESULTS: Three types of PEDs were identified based on reflectivity of the material under the retinal pigment epithelium on optical coherence tomography: hollow (26 eyes with primarily hyporeflectivity under the PED), solid (30 eyes with primarily hyperreflective signal under the PED) and mixed (8 eyes with mixed reflectivity). The average number of anti-VEGF injections was 7 per eye and the average duration of follow-up was 16 months. Among eyes with exudative AMD, 7/21 hollow PEDs flattened, 1/19 solid PEDs flattened and 2/6 mixed PEDs flattened after anti-VEGF therapy. POHS and CSR with CNV were associated with subfoveal solid PEDs and were unchanged after therapy. Overall, 46% (12/26) with hollow PEDs, 25% (2/8) with mixed PEDs and 3% (1/30) with solid PEDs had flattening after anti-VEGF therapy.

CONCLUSIONS: The likelihood of PED flattening was inversely related to the reflectivity of the PED. The more reflective the PED, the less likely resolution with anti-VEGF therapy occurred.

PMID: 23759437 [PubMed - as supplied by publisher]

Retina. 2013 Jun 6. [Epub ahead of print]

PACHYCHOROID PIGMENT EPITHELIOPATHY.

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PURPOSE: To report nine cases of pachychoroid pigment epitheliopathy.

METHODS: An observational case series of nine patients who underwent comprehensive ophthalmic examination, fundus photography, fundus autofluorescence, spectral-domain optical coherence tomography, and enhanced depth imaging optical coherence tomography.

RESULTS: Eighteen eyes of 9 patients, aged 27 years to 89 years, were diagnosed with pachychoroid pigment epitheliopathy based on the characteristic funduscopic appearance of reduced fundus tessellation with overlying retinal pigment epithelial changes in one or both eyes, fundus autofluorescence abnormalities, and increased subfoveal choroidal thickness confirmed by enhanced depth imaging optical coherence tomography (mean, 460.2 μm). The five older patients had been previously diagnosed with age-related macular degeneration, while the four younger subjects were referred for possible inflammatory chorioretinitis, pattern dystrophy, or nonspecific drusen. No subjects had a history of or subsequently developed subretinal fluid.

CONCLUSION: Pachychoroid pigment epitheliopathy falls within a spectrum of diseases associated with choroidal thickening that includes central serous chorioretinopathy and polypoidal choroidal vasculopathy, and it should be suspected in eyes with a characteristic fundus appearance related to choroidal thickening and associated retinal pigment epithelial abnormalities but no history of subretinal fluid. Enhanced depth imaging optical coherence tomography confirming an abnormally thick choroid and characteristic retinal pigment epithelial changes on fundus autofluorescence support the diagnosis. Because these patients are frequently misdiagnosed, the recognition of pachychoroid pigment epitheliopathy may avoid unnecessary diagnostic testing and interventions.

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Pathogenesis

Mol Vis. 2013 Jun 2;19:1211-21. Print 2013.

Vascular endothelial growth factor A polymorphisms and age-related macular degeneration: a systematic review and meta-analysis.

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PURPOSE: In the present work, the aim was to systematically review all studies about the association of vascular endothelial growth factor A (VEGF-A) polymorphisms with age-related macular degeneration (AMD) and to perform a meta-analysis.

METHODS: Relevant studies were searched using PubMed, Embase, Wanfang (Chinese), VIP (Chinese), and the Chinese National Knowledge Infrastructure databases up to October, 2011. A meta-analysis was conducted using Stata software, version 11.0.

RESULTS: A total of nine studies with 2,281 AMD cases and 2,820 controls met our eligibility criteria, and meta-analyses of four polymorphisms of the VEGF-A gene (rs1413711, rs833061, rs2010963, and rs3025039) were performed. This meta-analysis revealed moderate evidence supporting an association between the VEGF-A polymorphisms and AMD. For rs1413711, the TT genotype was associated with an increased risk of overall AMD (TT versus CT model, odds ratio (OR) 1.74, 95% confidence interval (CI) 1.22-2.48) and of wet AMD (TT versus CT model, OR 1.82, 95% CI 1.22-2.71; TT versus (CC+CT) model, OR 1.63, 95% CI 1.13-2.35). For rs833061, the C allele (C allele versus T allele, OR 1.72, 95% CI 1.00-2.96) and CC genotype (CC versus TT model, OR 1.77, 95% CI 1.00-3.11) were the risk factors for overall AMD, while the C allele was also associated with an increased risk of wet AMD (C allele versus T allele,

OR 1.54, 95% CI 1.03-2.31). No association was observed between AMD risk and the variant genotypes of VEGF-A rs2010963 and rs3025039 polymorphisms in different genetic models.

CONCLUSIONS: The results suggest the VEGF-A rs1413711 and rs833061 polymorphisms may contribute to AMD susceptibility.

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Ann Clin Biochem. 2013 Jun 10. [Epub ahead of print]

Increased homocysteine, homocysteine-thiolactone, protein homocysteinylation and oxidative stress in the circulation of patients with Eales' disease.

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BACKGROUND: Eales' disease (ED) is an idiopathic retinal vascular disorder. It presents with inflammation and neovascularization in the retina. Adult men, aged between 15 and 40 years are more susceptible than women. Homocysteine has been implicated in other ocular diseases including age-related macular degeneration (ARMD), central retinal vein occlusion (CRVO) and optic neuropathy. The present study investigates the role of homocysteine in ED.

METHODS: Forty male subjects, 20 with ED and 20 healthy controls, were recruited to the study. Their blood samples were used to measure thiobarbituric acid reactive substances (TBARS), glutathione (GSH), homocysteine, homocysteine-thiolactone, extent of homocysteine conjugation with proteins and plasma copper concentration.

RESULTS: In the ED group, plasma homocysteine (18.6 ± 1.77 μmol/L, $P < 0.001$) and homocysteine-thiolactone (45.3 ± 6.8 nmol/L, $P < 0.0001$) concentrations were significantly higher compared to homocysteine (11.2 ± 0.64 μmol/L) and homocysteine-thiolactone (7.1 ± 0.94 nmol/L) concentrations in control subjects. TBARS ($P < 0.011$) and protein homocysteinylation ($P < 0.030$) were higher in the ED group while GSH (5.9 ± 0.44 μmol/L, $P < 0.01$) and copper (6.6 ± 0.42 μmol/L, $P < 0.001$) were lower compared to GSH (8.1 ± 0.41 μmol/L) and copper (15.4 ± 0.73 μmol/L) concentrations in control subjects.

CONCLUSIONS: Increased homocysteine, and its metabolite thiolactone, is associated with the functional impairment of protein due to homocysteinylation in ED.

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Fundus Autofluorescence in the Abca4-/- Mouse Model of Stargardt Disease - Correlation with Accumulation of A2E, Retinal Function and Histology.

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PURPOSE: To investigate fundus autofluorescence (AF) characteristics in the Abca4-/-mouse, an animal model for age-related macular degeneration and Stargardt disease, and to correlate findings with functional, structural and biochemical assessments.

METHODS: Blue (488nm) and near-infrared (790nm) fundus AF images were quantitatively and

qualitatively analyzed in pigmentedAbca4-/-mice and wild type controls in vivo. Functional, structural and biochemical assessments included electroretinography (ERG), light and electron microscopic analysis, and A2E quantification. All assessments were performed across age groups.

RESULTS: In Abca4-/- mice, lipofuscin-related 488nm-AF increased early in life with a ceiling effect after 6 months. This increase was first paralleled by an accumulation of typical lipofuscin granules in the retinal pigment epithelium (RPE). Later, lipofuscin and melanin granules decreased in number whereas melanolipofuscin granules increased. This increase in melanolipofuscin granules paralleled an increase in melanin-related 790nm AF. Old Abca4-/- mice revealed a flecked fundus AF pattern at both excitation wavelengths. The amount of A2E, a major lipofuscin component, increased 10- to 12-fold in 6- to 9-month-old Abca4-/- mice compared to controls, while 488 nm AF intensity only increased 2-fold. Despite pronounced lipofuscin accumulation in the RPE of Abca4-/- mice, ERG and histology showed a slow age-related thinning of the photoreceptor layer similar to wild type controls up to 12 months.

CONCLUSIONS: Fundus AF can be used to monitor lipofuscin accumulation and melanin-related changes in vivo in mouse models of retinal disease. High RPE lipofuscin may not adversely affect retinal structure or function over prolonged time intervals, and melanin-related changes (melanolipofuscin formation) may occur before the decline in retinal function.

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Invest Ophthalmol Vis Sci. 2013 Jun 11. pii: iovs.12-11572v1. doi: 10.1167/iovs.12-11572. [Epub ahead of print]

Disruption of cell-cell junctions and induction of pathological cytokines in the retinal pigment epithelium of light-exposed mice.

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Purpose: To elucidate the influences of light exposure on the retinal pigment epithelium (RPE) in vivo, that may be involved in the pathogenesis of age-related macular degeneration (AMD).

Methods: Six to seven-week-old BALB/c mice were exposed to light at 2000 lux for 3 hours. Flat-mount RPE samples were immunostained with anti-ZO-1 antibody for evaluating tight junction, anti-N-cadherin and anti-β-catenin antibodies for adherens junction, and stained with phalloidin for actin cytoskeleton. The reactive oxygen species (ROS) level was measured using DCFH-DA, Rho-associated coiled-coil forming kinase (ROCK) activity was by ELISA. Cytokine expression was analyzed by realtime RT-PCR and/or ELISA in the RPE-choroid, and macrophage recruitment was by realtime RT-PCR and immunohistochemistry. Either an antioxidant, N-Acetyl-L-cysteine (NAC), or a ROCK inhibitor, Y-27632, were administered to analyze the roles of ROS and ROCK activation, respectively.

Results: Light exposure disrupted staining patterns of tight junctions, adherens junctions and actin cytoskeleton in the RPE, where ROS was elevated. However, NAC treatment avoided the RPE changes, reducing ROS. ROCK activity increased after light exposure was suppressed by NAC, and the structural disruptions were suppressed by Y-27632. The levels of MCP-1, CCL11, and IL-6 increased after light exposure were suppressed by NAC. Light-induced MCP-1 and IL-6 were suppressed by Y-27632. Macrophage recruitment after light exposure was also suppressed either by NAC or Y-27632.

Conclusions: Light exposure induced ROS and Rho/ROCK activation, which caused disruption of cell-cell junctions (tight junctions and adherens junctions) and actin cytoskeleton, the RPE's barrier structure, and induced AMD-associated pathological changes in the RPE-choroid.

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Int J Inflam. 2013;2013:348092. doi: 10.1155/2013/348092. Epub 2013 May 23.

The role of the immune response in age-related macular degeneration.

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Abstract: Age-related macular degeneration (AMD) is the leading cause of blindness in developed countries; with the aging population, the negative health impacts and costs of the disease will increase dramatically over the next decade. Although the exact cause of AMD is unknown, genetic studies have implicated the complement system as well as other immune responses in disease pathogenesis and severity. Furthermore, histologic studies have shown the presence of macrophages, lymphocytes, and mast cells, as well as fibroblasts, in both atrophic lesions and with retinal neovascularization. This review summarizes discussions from the fifth annual conference of the Arnold and Mabel Beckman Initiative for Macular Research by the Inflammation and Immune Response Task Force. These deliberations focused on the role of inflammatory immune responses, including complement, inflammasomes, adaptive immune responses, and para-inflammation, unanswered questions and studies to address these questions, and potential immune-related therapeutic targets for AMD.

PMID: 23762772 [PubMed]

J Genet Syndr Gene Ther. 2013 Mar 11;4(2). pii: 128.

The Molecular Chaperone GRP78/BiP as a Therapeutic Target for Neurodegenerative Disorders: A Mini Review.

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Abstract: The glucose regulated protein 78 (GRP78), also known as BiP, is the endoplasmatic reticulum (ER) homologue of HSP70, which plays a dual role in the ER by controlling protein folding, in order to prevent aggregation, and by regulating the signaling of the unfolded protein response (UPR). Most neurodegenerative disorders including Parkinson's, Alzheimer's diseases and progressive retinal degeneration are characterized by activation of the UPR and modified expression of GRP78. The expression levels and activity of GRP78 are altered with age raising the question of whether the lack of GRP78 could be a predisposing factor for many neurodegenerative disorders associated with age including PD, Alzheimer and Age-related macular degeneration. Attempts to induce or upregulate GRP78 in animal models of neurodegeneration have recently been made with the help of pharmacological BiP protein Inducer X (BIX) and GRP78 cDNA delivery via adeno-associated virus (AAV) vectors. The results of these studies validate GRP78 as a new therapeutic target for treatments of forebrain ischemia, Parkinson disease and retinal degeneration. These data, together with the results from age-related studies, highlight the importance for developing drugs to induce elevation of endogenous GRP78 in order to increase cellular survival and extend functional longevity.

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Vascular endothelial growth factor regulates primate choroid-retinal endothelial cell proliferation and tube formation through PI3K/Akt and MEK/ERK dependent signaling.

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Abstract: Vascular endothelial growth factor (VEGF) is a hypoxia-induced angiogenic protein that exhibits a broad range of biological and pathological effects in wet age-related macular degeneration and proliferative diabetic retinopathy. However, its specific mechanism is still not fully understood. Here, we examined the effects of VEGF on choroid-retinal endothelial cells (RF/6A) proliferation and tube formation, and the underlying signal pathways responsible in this process. RF/6A cells were pretreated with MEK inhibitor or PI3K inhibitor, and then incubated in a hypoxia chamber. Real-time PCR and Western blot analysis were carried out to explore VEGF expression on mRNA and protein levels. Hypoxia inducible factor-1α (HIF-1α) and VEGFR2 expression levels were also investigated in the presence and absence of hypoxic conditions. CCK-8 analysis and tube formation assay were tested under hypoxia, exogenous recombinant VEGF, and different signal pathway inhibitors, respectively. Mean while, the PI3K/Akt and MEK/ERK pathways in this process were also investigated. Our results showed that VEGF, HIF-1α, VEGFR2, p-ERK, and p-Akt were up-regulated in RF/6A cells under hypoxic conditions. MEK inhibitor (PD98059) and PI3K inhibitor (LY294002) decreased ERK and Akt activity, respectively, and reduced VEGF expression. VEGF-induced RF/6A proliferation and tube formation requires MEK/ERK and PI3K/Akt signaling, and both of the two pathways were needed in regulating VEGF expression. These suggest that VEGF plays an important role in RF/6A proliferation and tube formation, and MEK/ERK and PI3K/Akt pathway may be responsible for this process.

PMID: 23749166 [PubMed - as supplied by publisher]

Ageing Res Rev. 2013 Jun 4. pii: S1568-1637(13)00042-1. doi: 10.1016/j.arr.2013.05.006. [Epub ahead of print]

Phagocyte dysfunction, tissue aging and degeneration.

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Abstract: Immunologically-silent phagocytosis of apoptotic cells is critical to maintaining tissue homeostasis and innate immune balance. Aged phagocytes reduce their functional activity, leading to accumulation of unphagocytosed debris, chronic sterile inflammation and exacerbation of tissue aging and damage. Macrophage dysfunction plays an important role in immunosenescence. Microglial dysfunction has been linked to age-dependent neurodegenerations. Retinal pigment epithelial (RPE) cell dysfunction has been implicated in the pathogenesis of age-related macular degeneration (AMD). Despite several reports on the characterization of aged phagocytes, the role of phagocyte dysfunction in tissue aging and degeneration is yet to be fully appreciated. Lack of knowledge of molecular mechanisms by which aging reduces phagocyte function has hindered our capability to exploit the therapeutic potentials of phagocytosis for prevention or delay of tissue degeneration. This review summarizes our current knowledge of phagocyte dysfunction in aged tissues and discusses possible links to age-related diseases. We highlight the challenges to decipher the molecular mechanisms, present new research approaches and envisage future strategies to prevent phagocyte dysfunction, tissue aging and degeneration.

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Br J Ophthalmol. 2013 Jun 13. [Epub ahead of print]

Pro-inflammatory and anti-angiogenic effects of bisphosphonates on human cultured retinal pigment epithelial cells.

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AIM: Bisphosphonates have been shown to induce ocular inflammatory diseases such as uveitis and scleritis, while being protective against angiogenic diseases like neovascular age-related macular degeneration (AMD). Therefore, we studied the effects of bisphosphonates on primary culture of human fetal retinal pigment epithelium (hRPE), a cell type known to secrete both inflammatory and angiogenic factors. Alendronate and etidronate were selected for this experiment as they are members of the two structurally different classes of bisphosphonates.

METHODS: Primary cultures of hRPE were serum-starved for 24 h and then treated for 24 h with alendronate (0.0001, 0.1, 100 µM) or etidronate (0.01, 1 µM). Cell viability was measured using the MTT assay. Investigation of secreted cytokines induced by bisphosphonates was performed using a human cytokine 29-Plex Panel (Bio-Plex) array and the results were analysed with an analysis of variance (ANOVA).

RESULTS: Etidronate, at the lower concentration, significantly increased the expression of interleukin (IL)-6 ($p=0.03$) and IL-8 ($p=0.04$). At the higher concentration, etidronate significantly decreased the expression of granulocyte macrophage colony-stimulating factor ($p=0.02$) and basic fibroblast growth factor (bFGF) ($p=0.02$). Alendronate, at the highest concentration, significantly increased the expression of IL-8 ($p=0.02$) and decreased the expression of eotaxin ($p=0.02$). Alendronate also significantly decreased the expression of bFGF at all concentrations ($p<0.05$) and demonstrated a trend towards decreasing vascular endothelial growth factor expression at low concentration.

CONCLUSIONS: Alendronate and etidronate display dose dependent effects in hRPE cells. Alendronate and etidronate administration resulted in concentration dependent elevations in inflammatory cytokines. Furthermore, alendronate and etidronate administration resulted in reduced expression of a number of angiogenic factors. These findings may explain the increased incidence of ocular inflammation as well as the therapeutic effect on neovascular AMD which have been described with bisphosphonates.

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Epidemiology

Br J Ophthalmol. 2013 Jun 12. [Epub ahead of print]

Lactation, female hormones and age-related macular degeneration: the Tromso Study.

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OBJECTIVE: Some risk factors for age-related macular degeneration (AMD) have been shown to act differently in women and men. The present study aims to investigate this disparity by examining associations between female hormones, reproductive history and AMD.

METHODS: Women aged 65-87 years were invited to this cross-sectional, population-based study in Norway. Participants underwent physical examination, retinal photography, answered questionnaires and had blood samples taken.

RESULTS: The sample included 1512 women, of whom 48 (3.2%) had late AMD and 378 (25%) had large drusen >125 µm phenotype. Length of breast feeding per child was significantly associated with late AMD (OR per month 0.80, 95% CI 0.68 to 0.94) in multivariable regression analysis. We observed no associations between late AMD or drusen >125 µm and contraceptives, oral hormonal replacement

therapy, parity, age at first childbirth, age of menarche, age of menopause, number of menstruating years or the reason for menopause.

CONCLUSIONS: Longer duration of lactation was associated with lower frequency of maternal late AMD when controlled for confounders. Other reproductive factors and hormone replacement therapy were not significantly associated with AMD.

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Genetics

Am J Pathol. 2013 Jun 5. pii: S0002-9440(13)00326-X. doi: 10.1016/j.ajpath.2013.04.008. [Epub ahead of print]

Complement Component C3 Plays a Critical Role in Protecting the Aging Retina in a Murine Model of Age-Related Macular Degeneration.

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Abstract: Complement component C3 is the central complement component and a key inflammatory protein activated in age-related macular degeneration (AMD). AMD is associated with genetic variation in complement proteins that results in enhanced activation of C3 through the complement alternative pathway. These include complement factor H (CFH), a negative regulator of C3 activation. Both C3 inhibition and/or CFH augmentation are potential therapeutic strategies in AMD. Herein, we examined retinal integrity in aged (12 months) mice deficient in both factors H and C3 (CFH-/-.C3-/-), CFH alone (CFH-/-), or C3 alone (C3-/-), and wild-type mice (C57BL/6). Retinal function was assessed by electroretinography, and retinal morphological features were analyzed at light and electron microscope levels. Retinas were also stained for amyloid β (Aβ) deposition, inflammation, and macrophage accumulation. Contrary to expectation, electroretinograms of CFH-/-.C3-/- mice displayed more severely reduced responses than those of other mice. All mutant strains showed significant photoreceptor loss and thickening of Bruch's membrane compared with wild-type C57BL/6, but these changes were greater in CFH-/-.C3-/- mice. CFH-/-.C3-/- mice had significantly more Aβ on Bruch's membrane, fewer macrophages, and high levels of retinal inflammation than the other groups. Our data show that both uncontrolled C3 activation (CFH-/-) and complete absence of C3 (CFH-/-.C3-/- and C3-/-) negatively affect aged retinas. These findings suggest that strategies that inhibit C3 in AMD may be deleterious.

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Age-Related Macular Degeneration Is Associated with Increased Proportion of CD56+ T Cells in Peripheral Blood.

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PURPOSE: To examine the association between age-related changes in the T-cell compartment and prevalence of age-related macular degeneration (AMD).

DESIGN: Case-control study.

PARTICIPANTS: A total of 117 AMD cases and 106 controls were included prospectively.

METHODS: Fresh-drawn peripheral blood samples were processed for flow cytometric analysis of T-cell populations. Plasma samples were analyzed for anti-cytomegalovirus (CMV) immunoglobulin (Ig)G and complement factor H (CFH) Y402H genotype. The diagnosis of AMD was made according to the Clinical Age-Related Maculopathy Staging System.

MAIN OUTCOME MEASURES: Association between frequency of aged T cells and prevalence of AMD.

RESULTS: The prevalence of AMD was associated with distinct age-related changes in the T-cell compartment. Specifically, the patients with AMD had an increased frequency of CD28- T cells that expressed the CD56 surface marker (patients, 34.9% vs. aged controls, 25.8%; P = 0.002). Participants in the highest tertile of CD56+ CD28- T cells had an odds ratio (OR) for the presence of AMD of 3.2 (95% confidence interval [CI], 1.2-8.8) after adjustment for CFH genotype, anti-CMV IgG positivity, age, sex, and smoking history. The adjusted OR of the presence of AMD for persons having at least 1 CFH H402 risk allele increased from 3.5 (95% CI, 1.5-8.1) to 13.3 (95% CI, 3.3-53.6) for persons with at least 1 CFH H402 risk allele and above the median level of CD56+ CD28- T cells.

CONCLUSIONS: We found increased levels of circulating aged CD56+ CD28- T cells in patients with AMD. Although this supports the notion of AMD as a systemic disease, it also suggests that the adaptive immune system is implicated in its pathogenesis.

PMID: 23747161 [PubMed - as supplied by publisher]

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Common Variant in VEGFA and Response to Anti-VEGF Therapy for Neovascular Age-Related Macular Degeneration.

Zhao L, Grob S, Avery R, Kimura A, Pieramici D, Lee J, Rabena M, Ortiz S, Quach J, Cao G, Luo H, Zhang M, Tornambe P, Goldbaum M, Ferreyra H, Kozak I, Zhang K.

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Abstract: Age-related macular degeneration (AMD) is a leading cause of visual impairment in aging populations in industrialized countries. Here we investigated whether the genotype of vascular endothelial growth factor A (VEGFA) gene is associated with response to anti-VEGF therapy. 223 eyes with neovascular AMD were treated with intravitreal anti-VEGF therapy. Responders were defined as patients who had an improvement in best corrected visual acuity (BCVA) of at least 5 letters or one line on the EDTRS visual acuity chart along with resolution of intraretinal or subretinal fluid over 12 months. Patients who did not meet the definition of responders were classified as poor-responders. The vision of responders (n = 148) improved while the vision of poor-responders (n = 75) worsened (P <0.001). Responders on average had a decrease in central foveal thickness (CFT), while poor-responders had an increase in CFT (P <0.001). Compared with the responder group, the poor-responder group had a higher frequency of the risk (T) allele (Allelic P = 0.019) and TT genotype (P = 0.002 under a recessive model) for the VEGFA-rs943080 polymorphism. VEGFA expression was 1.8-fold higher in cells with the VEGFA rs943080 TT genotype than in cells with the VEGFA rs943080CC genotype (P = 0.012). Age, gender, smoking, diabetes mellitus, and hypertension did not play a significant role in treatment response, but BMI was found to be significantly different between responders and poor-responders (P = 0.033). In conclusion, we demonstrated a potential pharmacogenetic relationship between the VEGFA gene and treatment response to anti-VEGF therapy. The studies are registered at ClinicalTrials.gov under the identifiers NCT00474695.

PMID: 23745581 [PubMed - as supplied by publisher]

Epigenomics. 2013 Jun;5(3):239-41. doi: 10.2217/epi.13.19.

Age-related macular degeneration and DNA methylation.

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PMID: 23750638 [PubMed - in process]

Oftalmologia. 2012;56(4):15-8.

[Genotyping in the age-related macular degeneration progression].

[Article in Romanian]

Calugaru D.

Clinica de Oftalmologie Iaşi.

Abstract: After presenting both the prevalence and the staging of the age-related macular degeneration (AMD), the disease progression is discussed; it is determined primarily by genetic factors but is also influenced by environmental, demographic and behavioral factors. The genes working by means of the high -density lipoprotein cholesterol (HDL) pathway have critical roles in the drusen initiation in the early AMD stages. After the drusen have accumulated between retinal pigment epithlium (RPE) and Bruch's membrane, the genes acting in the alternative complement pathway are activated so influencing in this way the progression from the intermediate and large drusen to the advanced AMD stages (e.g. the geographic atrophy of the RPE and neovascular stages).

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Diet

BMC Public Health. 2013 Jun 10;13(1):564. [Epub ahead of print]

Advice about diet and smoking for people with or at risk of age-related macular degeneration: a cross-sectional survey of eye care professionals in the UK.

Lawrenson JG, Evans JR.

BACKGROUND: In the absence of a cure, there has been considerable interest in attempts to prevent or reduce the progression of age-related macular degeneration (AMD) by targeting particular modifiable risk factors. The aim of this study was to conduct a cross-sectional survey of the current practice of UK eye care professionals in relation to advice given on diet and other lifestyle modifications for patients with or at risk of AMD.

METHODS: Optometrists and ophthalmologists on the membership databases of professional organisations for the two professions were invited to participate in an online survey. The survey was open for 12 weeks between July and September 2012

RESULTS: A total of 1,468 responses were received (96.3% from optometrists and 3.7% from ophthalmologists). The response rate of those receiving the invitation was 16.2% (1,414/8735) for optometrists and 6% (54/1460) for ophthalmologists. A majority of respondents reported that they frequently provide dietary advice to patients with established AMD (67.9%) and those at risk of AMD (53.6%). Typical advice consisted of a recommendation to eat plenty of leafy green vegetables and eat more oily fish. The

decision to recommend nutritional supplements was based on the risk of progression to advanced AMD, with approximately 93% of respondents recommending supplementation in a patient with advanced AMD in one eye. However for the majority, the type of supplement recommended did not comply with current best research evidence, based on the findings of the Age-related Eye Disease Study (AREDS). Only one in three optometrists regularly assessed smoking status and advised on smoking cessation.

CONCLUSIONS: Within a large sample of eye care professionals, consisting predominantly of optometrists, who responded to a cross-sectional survey, there was active engagement in providing nutritional advice to patients with or at risk of AMD. However, the results demonstrate a need to raise awareness of the evidence underpinning the use of nutritional supplements together with an increased involvement in targeted smoking cessation.

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Nutrients. 2013 May 29;5(6):1962-9. doi: 10.3390/nu5061962.

Macular pigment and its contribution to vision.

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Abstract: Three dietary carotenoids, lutein (L), zeaxanthin (Z) and meso-zeaxanthin (MZ) accumulate at the central retina (macula), where they are collectively referred to as macular pigment (MP). MP's pre-receptoral absorption of blue light and consequential attenuation of the effects of chromatic aberration and light scatter are important for optimal visual function. Furthermore, antioxidant activity of MP's constituent carotenoids and the same blue light-filtering properties underlie the rationale for its putative protective role for age-related macular degeneration (AMD). Supplementation with L, Z and MZ augments MP and enhances visual performance in diseased and non-diseased eyes, and may reduce risk of AMD development and/or progression.

PMID: 23760061 [PubMed - in process]