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MD Research News

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Drug treatment

Br J Ophthalmol. 2014 Apr 10. doi: 10.1136/bjophthalmol-2013-304556. [Epub ahead of print]

Reducing the clinical burden of ranibizumab treatment for neovascular age-related macular degeneration using an individually planned regimen.

Mantel I, Niderprim SA, Gianniou C, Deli A, Ambresin A.

AIMS: The purpose of this study was to clinically validate an individually planned treatment regimen for neovascular age-related macular degeneration (nAMD), termed, observe and plan. This regimen was based on the predictability of an individual's need for retreatment and aimed to reduce the clinical burden, while obtaining good functional results.

METHODS: This was a prospective case series that included 104 patients (115 eyes) with treatment-naive nAMD. Following three loading doses of ranibizumab, monthly observation visits allowed the disease recurrence interval to be determined. The recurrence interval was reduced by 2 weeks to give the retreatment interval for the next three injections. Periodical control visits (at least every 6 months) allowed the effectiveness of the treatment to be assessed and individual intervals adjusted.

RESULTS: Mean visual acuity (VA) improved by 8.7 and 9.8 letters in months 3 and 12, respectively. The mean number of injections during the 12-month study was 7.8, while the mean number of ophthalmic examinations between months 3 and 12 was 3.97. The mean treatment interval after the loading doses was 2.08 months.

CONCLUSIONS: The observe-and-plan regimen significantly improved VA. This was obtained with fewer clinic visits compared with other regimens, which could ease the burden of nAMD treatment.

PMID: 24729031 [PubMed - as supplied by publisher]

Am J Ophthalmol. 2014 Apr 10. pii: S0002-9394(14)00191-3. doi: 10.1016/j.ajo.2014.04.004. [Epub ahead of print]

Sporadic Visual Acuity Loss in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Kim BJ, Ying GS, Huang J, Levy NE, Maguire MG; CATT Research Group.

PURPOSE: To evaluate transient, large visual acuity (VA) decreases, termed sporadic vision loss, during

anti-vascular endothelial growth factor treatment for neovascular age-related macular degeneration (AMD).

DESIGN: Cohort within a randomized clinical trial.

METHODS: Setting: Comparison of AMD Treatments Trials (CATT). Study Population: 1185 CATT patients. Main Outcome Measures: incidence of sporadic vision loss and odds ratio (OR) for association with patient and ocular factors. Sporadic vision loss was a decline of ≥ 15 letters from the previous visit, followed by a return at the next visit to no more than 5 letters worse than the visit before the VA loss.

RESULTS: There were 143 sporadic vision loss events in 122/1185 (10.3%) patients. Mean VA at two years for those with and without sporadic vision loss was 58.5 (~20/63) and 68.4 (~20/40) letters, respectively (P < 0.001). Among patients treated pro re nata, no injection was given for 27.6% (27/98) of sporadic vision loss events. Multivariate analysis demonstrated that baseline predictors for sporadic vision loss included worse baseline VA (OR 2.92, 95%CI:1.65-5.17 for ≤ 20/200 compared with ≥ 20/40), scar (OR 2.21, 95%CI:1.22-4.01), intraretinal foveal fluid on optical coherence tomography (OR 1.80, 95% CI:1.11-2.91), and medical history of anxiety (OR 1.90, 95%CI:1.12-3.24) and syncope (OR 2.75, 95% CI:1.45-5.22). Refraction decreased the likelihood of sporadic vision loss (OR 0.62, 95%CI:0.42-0.91).

CONCLUSIONS: Approximately 10% of CATT patients had sporadic vision loss. Baseline predictors included AMD-related factors and factors independent of AMD. These data are relevant for clinicians in practice and those involved in clinical trials.

PMID: 24727261 [PubMed - as supplied by publisher]

Drugs Aging. 2014 Apr 17. [Epub ahead of print]

Intravitreal Aflibercept (Eylea®): A Review of Its Use in Patients with Macular Oedema Secondary to Central Retinal Vein Occlusion.

Yang LP, McKeage K.

Abstract: Aflibercept is a fully human, recombinant fusion protein that acts as a soluble decoy receptor for vascular endothelial growth factor (VEGF) family members, including VEGF-A, VEGF-B and placental growth factor (P1GF), thereby inhibiting downstream signalling mediated by these ligands. Aflibercept binds all isoforms of VEGF-A with high affinity, and a markedly higher affinity than that of ranibizumab or bevacizumab. A formulation of aflibercept developed specifically for intravitreal injection (Eylea®) is approved for use in several countries for the treatment of patients with macular oedema secondary to central retinal vein occlusion (CRVO). In clinical trials (GALILEO and COPERNICUS) in patients with this condition, intravitreal aflibercept 2 mg every month improved best corrected visual acuity (BCVA), as measured by the proportion of study eyes with a gain of ≥15 Early Treatment Diabetic Retinopathy Study letters from baseline, significantly more than sham injections at week 24 (primary analysis). The significant improvements achieved with intravitreal aflibercept compared with sham in the first 6 months were maintained in the second 6 months with as-needed (prn) dosing and monthly monitoring. Continued prn dosing with a reduced monitoring frequency was associated with decreased improvements. More data are needed to confirm the optimal monitoring frequency for use with prn dosing, subsequent to initial monthly injections, in order to maintain long-term efficacy. Intravitreal aflibercept was generally well tolerated in clinical trials and there is little potential for systemic drug accumulation. Thus, intravitreal aflibercept is an effective and generally well tolerated agent that extends the options available for the treatment of macular oedema secondary to CRVO.

PMID: 24740170 [PubMed - as supplied by publisher]

Ophthalmic Physiol Opt. 2014 Apr 14. doi: 10.1111/opo.12134. [Epub ahead of print]

Monitoring intraocular pressure changes after intravitreal Ranibizumab injection using rebound tonometry.

Fuest M, Kotliar K, Walter P, Plange N.

PURPOSE: Direct drug delivery by intravitreal injection is an essential tool in the treatment of retinal diseases and can trigger transient and intermediate intraocular pressure (IOP) peaks. So far no reliable risk factors for pronounced IOP increments have been outlined, which might be particularly important for patients with increased IOP susceptibility such as glaucoma. In this prospective, interventional study IOP changes were analysed directly before and after injection in sitting and supine positions using the Icare rebound tonometer (RT).

METHODS: The IOP of 29 patients with macular oedema, who underwent intravitreal injection of 0.05 mL Ranibizumab, was measured in a sitting position 5 min before and two, five and 10 min after surgery. In addition, IOP was also acquired 30 s before and 10 s after injection in a supine position. The effect of age, gender, pseudophakia, axial length, anterior chamber depth, central corneal thickness, scleral thickness and iridocorneal angle width was analysed.

RESULTS: Mean pre-injection IOP sitting was 14.3 ± 2.6 mmHg for the treated and 15.5 ± 2.2 mmHg for the control eye. After injection mean IOP rose to 47.2 ± 11.2 mmHg on the treated eye. The IOP of 17 patients returned to values ≤21 mmHg within 10 min. In 12 patients, IOP remained above 21 mmHg after 10 min. No specific risk factor for this group was found. The absolute IOP increase 10 s after injection was significantly correlated to scleral thickness ($r = 0.49$, $p = 0.036$) and to the absolute ($r = 0.40$, $p = 0.03$) and relative increase ($r = 0.39$, $p = 0.035$) of IOP from sitting 5 min before injection to supine position 10 s before injection.

CONCLUSIONS: Posture change related IOP increments might have a predictive value for post injection IOP increase. In 40% of the eyes higher IOP-levels (>21 mmHg) remained persistent for a longer period of time. This should be considered especially for glaucomatous eyes.

PMID: 24731161 [PubMed - as supplied by publisher]

J Immunol Res. 2014;2014:632307. Epub 2014 Feb 5.

Anti-VEGF for the Management of Diabetic Macular Edema.

Stefanini FR, Badaró E, Falabella P, Koss M, Farah ME, Maia M.

Abstract: Diabetic retinopathy (DR) is an important cause of vision loss around the world, being the leading cause in the population between 20 and 60 years old. Among patients with DR, diabetic macular edema (DME) is the most frequent cause of vision impairment and represents a significant public health issue. Macular photocoagulation has been the standard treatment for this condition reducing the risk of moderate visual loss by approximately 50%. The role of vascular endothelial growth factor (VEGF) in DR and DME pathogenesis has been demonstrated in recent studies. This review addresses and summarizes data from the clinical trials that investigated anti-VEGF for the management of DME and evaluates their impact on clinical practice. The literature searches were conducted between August and October 2013 in PubMed and Cochrane Library with no date restrictions and went through the most relevant studies on pegaptanib, ranibizumab, bevacizumab, and aflibercept for the management of DME. The efficacy and safety of intravitreal anti-VEGF as therapy for DME have recently been proved by various clinical trials providing significantly positive visual and anatomical results. Regarding clinical practice, those outcomes have placed intravitreal injection of anti-VEGF as an option that must be considered for the treatment of DME.

PMID: 24741610 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Dev Ophthalmol. 2014;53:1-32. doi: 10.1159/000358536. Epub 2014 Apr 10.

Age-related macular degeneration: clinical findings, histopathology and imaging techniques.

Zarbin MA, Casaroli-Marano RP, Rosenfeld PJ.

Abstract: Age-related macular degeneration (AMD) is the most common cause of blindness among people over age 55 years in industrialized countries. Known major risk factors for AMD include: age >55 years, history of smoking, white race, and mutations in various components of the complement system. Early AMD is characterized by the presence of drusen and pigmentary abnormalities. Late AMD is associated with central visual loss and is characterized by the presence of choroidal neovascularization and/or geographic atrophy. Early AMD is associated with a number of biochemical abnormalities including oxidative damage to retinal pigment epithelium (RPE) cells, complement deposition in the RPE-Bruch's membrane-choriocapillaris complex, lipidization of Bruch's membrane, and extracellular matrix abnormalities (e.g. collagen crosslinking, advanced glycation end product formation). Antiangiogenic drugs block the vascular leakage associated with choroidal new vessels, thus reducing retinal edema and stabilizing or restoring vision. At this time, there are no proven effective treatments for the nonexudative complications of AMD. Modern ocular imaging technologies (including spectral domain and phase variance optical coherence tomography, short- and long-wavelength fundus autofluorescence, adaptive optics-scanning laser ophthalmoscopy, and near-infrared reflectance) enable one to follow changes in the RPE, photoreceptors, and choriocapillaris quantitatively as the disease progresses. In addition, one can quantitatively assess the volume of drusen and areas of atrophy. These data, when correlated with the known histopathology of AMD, may provide useful measures of treatment efficacy that are likely to be more sensitive and reproducible than conventional end points such as visual acuity and rate of enlargement of geographic atrophy. As a result, these imaging technologies may be valuable in assessing the effects of cell-based therapy for patients with AMD.

PMID: 24732758 [PubMed - in process]

Retina. 2014 Apr 11. [Epub ahead of print]

THE RELATIONSHIP BETWEEN PSEUDODRUSEN AND CHOROIDAL THICKNESS.

Mrejen S, Spaide RF.

PURPOSE: To determine the relationship between pseudodrusen as evidenced by the presence of subretinal drusenoid deposits and choroidal thickness using a multimodal imaging approach.

METHODS: Two sets of data were analyzed. The first set was composed of consecutive patients older than 60 years with either high myopia or pseudodrusen. Correlations were calculated between the subfoveal choroidal thickness and the presence of pseudodrusen. The second set of data was obtained from a previously published data examining 90 consecutive eyes with nonexudative age-related macular degeneration so that the relationship between pseudodrusen and subfoveal choroidal thickness could be analyzed.

RESULTS: There were 96 eyes of 53 patients in the first data set, 36 (67.9%) were female and 17 (32.1%) were male. There were 34 patients (61 eyes) in the High Myopia group and 19 patients (35 eyes) in the Primary Pseudodrusen group. The mean age of the Primary Pseudodrusen group was 83.7 years and that of the High Myopia group was 74.9 years, a difference that was significant ($P < 0.001$). Of the 61 eyes in the High Myopia group, only 3 (4.9%) had pseudodrusen and 0 had conventional drusen. In the Primary Pseudodrusen group, all had pseudodrusen by definition, but 28 (80%) also had conventional drusen. The mean subfoveal choroidal thickness was 181.7 μm (median, 147; interquartile range, 65-225 μm) in the Primary Pseudodrusen group and 59 μm (median, 36; interquartile range, 21-90 μm) in the myopic group.

Generalized estimating equation analysis showed that eyes with pseudodrusen had thicker subfoveal choroidal thickness than eyes without, a result driven by the High Myopia group. In the second set of data, while the absolute number of eyes with pseudodrusen had a choroidal thickness between 201 μm and 250 μm, the proportion with pseudodrusen was higher in eyes with thinner choroids, with a broad peak between 50 μm and 100 μm.

CONCLUSION: Our results are not consistent with a simple cause or consequence relationship between pseudodrusen and choroidal thinning, but rather with a third yet unknown factor impacting both the pseudodrusen appearance and the choroidal thinning in susceptible populations. The reasons for the relative lack of drusen and pseudodrusen formation in high myopes need to be ascertained.

PMID: 24732697 [PubMed - as supplied by publisher]

Retina. 2014 Apr 14. [Epub ahead of print]

HYPERREFLECTIVE PYRAMIDAL STRUCTURES ON OPTICAL COHERENCE TOMOGRAPHY IN GEOGRAPHIC ATROPHY AREAS.

Bonnet C, Querques G, Zerbib J, Oubraham H, Garavito RB, Puche N, Souied EH.

PURPOSE: We observed hyperreflective dome-shaped or pyramidal structures (HPS) on spectral domain optical coherence tomography (SD-OCT) in patients affected with geographic atrophy (GA). Our purpose was to describe the multimodal imaging features of HPS identified in areas of GA in patients with age-related macular degeneration.

METHODS: This is a retrospective case series of patients with GA harboring HPS in atrophic areas. Multimodal imaging examination including infrared reflectance, fundus autofluorescence, and SD-OCT, was performed for each patient. Infrared and fundus autofluorescence appearance and mean SD-OCT height of HPS in GA were analyzed.

RESULTS: A total of 36 eyes of 25 patients (20 women; mean age, 82.3 ± 5.9 years, range, 73-92 years) with GA were included. A total of 96 HPS in GA were analyzed by SD-OCT. In all HPS (96/96, 100%), the peripheral part was hyperreflective. In 66 of 96 HPS (69%), the center was heterogeneously hyperreflective, whereas in 30 of 96 HPS (31%), the center was hyporeflective. On infrared reflectance images, HPS in GA appeared as hyporeflective lesions surrounded by hyperreflective halos, within an area of background hyperreflectivity because of GA in all eyes. On fundus autofluorescence, 39 of 96 HPS (41%) were heterogeneously hyperautofluorescent, whereas 57 of 96 HPS (59%) were hypoautofluorescent. Mean height of HPS was 91 ± 50.9 μm in the foveal scan (range, 42-291 μm).

CONCLUSION: We describe a multimodal imaging of distinctive lesions that presented as hyperreflective pyramidal structures on SD-OCT. We suggest the name "ghost drusen" because these HPS appear in GA areas, and because of their pyramidal or dome-shaped aspect on SD-OCT.

PMID: 24736463 [PubMed - as supplied by publisher]

Biomed Res Int. 2013;2013:858219. doi: 10.1155/2014/858219. Epub 2014 Mar 6.

Dynamics of blood count after rheohemapheresis in age-related macular degeneration: possible association with clinical changes.

Košťál M, Bláha M, Rencová E, Lánská M, Rozsíval P, Kratochvilová V, Langrová H.

Background: Rheohemapheresis (RHF) is a method that can stop the activity of the dry form of age-related macular degeneration (AMD). The pathophysiologic mechanisms are not well understood, and the effects of the RHF procedures extend beyond the time of the individual procedures.

Patients and Methods: We present the data for 46 patients with AMD treated with a series of 8 rheohemapheretic procedures. Blood count parameters were measured before the first and the last procedures. The clinical effect was judged by changes in the drusenoid pigment epithelium detachment (DPED) area before and after the rheopheretic sessions.

Results: Rheopheresis caused a decrease in hemoglobin ($P < 0.001$), a decrease in leukocytes ($P < 0.034$), and an increase in platelets ($P < 0.005$). We found a negative correlation between the amount of platelets and their volume ($P < 0.001$, Pearson correlation coefficient: -0.509). We identified the platelet/MPV ratio as a good predictor of the clinical outcome. Patients with a platelet/MPV ratio greater than 21.5 (before the last rheopheresis) had a significantly better outcome ($P = 0.003$, sensitivity of 76.9% and specificity of 80%).

Conclusion: Several basic blood count parameters after RHF can be concluded to significantly change, with some of those changes correlating with the clinical results (reduction of the DPED area).

PMID: 24734249 [PubMed - in process] PMCID: PMC3966403

Dev Ophthalmol. 2014;53:155-66. doi: 10.1159/000357375. Epub 2014 Apr 10.

Microdevice-based cell therapy for age-related macular degeneration.

Lu B, Tai YC, Humayun MS.

Abstract: This chapter reports the application of a micromachined parylene-C device as an artificial Bruch's membrane for the stem cell-based therapy of age-related macular degeneration. The feasibility of parylene-C as a substitute substrate material is demonstrated by evaluating the permeability of membranes of submicron thicknesses. It has been found that parylene-C membranes thinner than 0.3 μm possess similar molecular weight exclusion limit and nutrient diffusion flux to that of the healthy human Bruch's membrane. This conclusion is further validated by the in vitro perfusion cell viability test. Since the submicron parylene-C itself is difficult to handle, we design a mesh-supported submicron parylene membrane (MSPM) to provide sufficient mechanical support. This MSPM can support the growth of retinal pigment epithelial (RPE) cells in a monolayer with well-polarized morphology. Human embryonic stem cell-derived H9-RPE cells are cultured in vitro on the MSPM for one month before the implantation of the MSPM into the rat's retina. To facilitate the surgical implantation, a parylene-C/SU-8 hybrid microfluidic device is designed as an inserter. Histological studies with hematoxylin-eosin staining and immunofluorescence staining show that the implanted RPE cells adhere well to the artificial Bruch's membrane and are able to maintain high viability and normal morphology in vivo.

PMID: 24732769 [PubMed - in process]

Dev Ophthalmol. 2014;53:143-54. doi: 10.1159/000357369. Epub 2014 Apr 10.

Approaches to cell delivery: substrates and scaffolds for cell therapy.

Kundu J, Michaelson A, Baranov P, Young MJ, Carrier RL.

Abstract: Retinal degeneration, associated with loss of photoreceptors, is the primary cause of permanent vision impairment, impacting millions of people worldwide. Age-related macular degeneration and retinitis pigmentosa are two common retinal diseases resulting in photoreceptor loss and vision impairment or blindness. Presently, available treatments can only delay the progress of retinal degeneration, and there are no treatments that can restore permanent vision loss. Research is underway to develop methods of regenerating the impaired retina by delivering photoreceptor precursor cells and retinal pigment epithelium to the subretinal space. Challenges to cell transplantation include limited survival upon implantation and the formation of abnormal cell architectures in vivo. Retinal tissue engineering shows immense promise and

potential in treatment of retinal degeneration by employing scaffold-based delivery systems of retinal progenitor cells to the subretinal space. Scaffold delivery strategy has been shown to enhance the cell survival and direct cell differentiation in a variety of retinal degenerative models. In this chapter, we summarize the research findings on different scaffold- or substrate-based transplantation techniques used to deliver retinal progenitor/photoreceptor precursors and retinal pigment epithelial cells to the subretinal space.

PMID: 24732768 [PubMed - in process]

Dev Ophthalmol. 2014;53:133-42. doi: 10.1159/000358531. Epub 2014 Apr 10.

Biochemical Restoration of Aged Human Bruch's Membrane: Experimental Studies to Improve Retinal Pigment Epithelium Transplant Survival and Differentiation.

Sugino IK, Sun Q, Cheewatrakoolpong N, Malcuit C, Zarbin MA.

Abstract: Suspensions of human embryonic stem cell-derived retinal pigment epithelium (hES-RPE) and human fetal RPE resurface aged and age-related macular degeneration (AMD) Bruch's membrane to a limited degree at day 21 in organ culture. Survival and differentiation of hES-RPE and human fetal RPE on aged or AMD Bruch's membrane are enhanced greatly (200%) if a biologically synthesized extracellular matrix (bovine corneal endothelial cell extracellular matrix) is laid down on Bruch's membrane prior to transplantation. Transplanted RPE survival is enhanced even more (400-1,000%) if Bruch's membrane is treated with bovine corneal endothelial cell-conditioned medium during organ culture of hES-RPE or fetal RPE on aged or AMD Bruch's membrane. Future efforts are focused on identifying the bioactive components of bovine corneal endothelial cell-conditioned medium, so that this material can be reconstituted for clinical use as an adjunct to improve RPE transplant survival and differentiation in AMD eyes.

PMID: 24732767 [PubMed - in process]

Dev Ophthalmol. 2014;53:81-96. doi: 10.1159/000357361. Epub 2014 Apr 10.

Differentiation of pluripotent stem cells into retinal pigmented epithelium.

Croze RH, Clegg DO.

Abstract: Ocular diseases affect millions worldwide and dramatically influence the quality of life. Although much is known about ocular biology and disease pathologies, effective treatments are still lacking. The eye is well suited for application of emerging cell-based therapies. This chapter explores the development of stem cell-based treatments for age-related macular degeneration (AMD), a prevalent ocular disease in the elderly. Retinal pigmented epithelium (RPE), a cell type implicated in AMD, has been derived from both induced pluripotent stem cells and embryonic stem cells (ESC). Rapidly advancing research has generated various methods of RPE differentiation and several transplantation strategies. Clinical trials are already underway using suspensions of ESC-derived RPE and others are soon to follow. This chapter will provide an overview of current derivation and transplantation strategies for stem cell-derived RPE for the treatment of AMD and other related ocular diseases.

PMID: 24732763 [PubMed - in process]

Dev Ophthalmol. 2014;53:44-52. doi: 10.1159/000357293. Epub 2014 Apr 10.

Juvenile-onset macular degeneration and allied disorders.

North V, Gelman R, Tsang SH.

Abstract: While age-related macular degeneration (AMD) is a leading cause of central vision loss among the elderly, many inherited diseases that present earlier in life share features of AMD. These diseases of juvenile-onset macular degeneration include Stargardt disease, Best disease, retinitis pigmentosa, X-linked retinoschisis, and other allied disorders. In particular, they can be accompanied by the appearance of drusen, geographic atrophy, macular hyperpigmentation, choroidal neovascularization, and disciform scarring just as in AMD, and often may be confused for the adult form of the disease. Diagnosis based on funduscopic findings alone can be challenging. However, the use of diagnostic studies such as electroretinography, electrooculography, optical coherence tomography, and fundus autofluorescence in conjunction with genetic testing can lead to an accurate diagnosis.

PMID: 24732760 [PubMed - in process]

Curr Treat Options Psychiatry. 2014 Mar;1(1):15-26.

Problem-Solving Therapy in the Elderly.

Kiosses DN, Alexopoulos GS.

Abstract: We systematically reviewed randomized clinical trials of problem-solving therapy (PST) in older adults. Our results indicate that PST led to greater reduction in depressive symptoms of late-life major depression than supportive therapy (ST) and reminiscence therapy. PST resulted in reductions in depression comparable with those of paroxetine and placebo in patients with minor depression and dysthymia, although paroxetine led to greater reductions than placebo. In home health care, PST was more effective than usual care in reducing symptoms of depression in undiagnosed patients. PST reduced disability more than ST in patients with major depression and executive dysfunction. Preliminary data suggest that a home-delivered adaptation of PST that includes environmental adaptations and caregiver involvement is efficacious in reducing disability in depressed patients with advanced cognitive impairment or early dementia. In patients with macular degeneration, PST led to improvement in vision-related disability comparable to that of ST, but PST led to greater improvement in measures of vision-related quality of life. Among stroke patients, PST participants were less likely to develop a major or minor depressive episode than those receiving placebo treatment, although the results were not sustained in a more conservative statistical analysis. Among patients with macular degeneration, PST participants had significantly lower 2-month incidence rates of major depression than usual care participants and were less likely to suffer persistent depression at 6 months. Finally, among stroke patients, PST participants were less likely to develop apathy than those receiving placebo treatment. PST also has been delivered via phone, Internet, and videophone, and there is evidence of feasibility and acceptability. Further, preliminary data indicate that PST delivered through the Internet resulted in a reduction in depression comparable with that of in-person PST in home-care patients. PST delivered via videophone results in an improvement in hospice caregivers' quality of life and a reduction in anxiety comparable to those of in-person PST. PST-treated patients with cognitive impairment may require additional compensatory strategies, such as written notes, memory devices, environmental adaptations, and caregiver involvement.

PMID: 24729951 [PubMed] PMCID: PMC3981073

Ophthalmic Physiol Opt. 2014 Apr 15. doi: 10.1111/opo.12132. [Epub ahead of print]

How effective is eccentric viewing training? A systematic literature review.

Gaffney AJ, Margrain TH, Bunce CV, Binns AM.

PURPOSE: The global prevalence of age-related macular degeneration and associated central vision loss is rising. Central vision loss hinders the performance of many activities of daily living. Adaptive strategies

such as eccentric viewing and steady eye strategy may be used to compensate for central vision loss. In order to establish the potential of these rehabilitation strategies, this systematic review evaluates current literature regarding the effectiveness of eccentric viewing and steady eye strategy training in people with central vision loss.

RESULTS: The search strategies identified 2605 publications, 36 of which met the inclusion criteria for the review, but only three of which were randomised controlled trials. This literature shows that eccentric viewing and steady eye strategy training can improve near visual acuity, reading speed, and performance of activities of daily living in people with central vision loss. However, there was insufficient literature to establish a relationship between training and distance visual acuity or quality of life. There is no conclusive evidence to show that a particular model of eccentric viewing training is superior to another, little clear evidence of a relationship between participant characteristics and training outcomes and no data regarding the cost effectiveness of training.

CONCLUSION: This report highlights the need for further robust research to establish the true potential and cost effectiveness of eccentric viewing and steady eye strategy training as a rehabilitation strategy for individuals with central vision loss.

PMID: 24735182 [PubMed - as supplied by publisher]

Pathogenesis

Retina. 2014 Apr 14. [Epub ahead of print]

ENDOTHELIAL PROGENITOR CELLS AND RESPONSE TO RANIBIZUMAB IN AGE-RELATED MACULAR DEGENERATION.

Scotti F, Maestroni A, Palini A, Introini U, Setaccioli M, Lorenzi M, Zerbini G.

BACKGROUND: Choroidal neovascularization (CNV) is the main cause of vision loss in age-related macular degeneration (AMD). In experimental CNV, endothelial progenitor cells (EPCs) contribute to the formation of new vessels. The aim of this study was to investigate whether the behavior of EPCs in patients with AMD supports a role for EPCs in human CNV.

METHODS: The number of circulating EPCs that are considered pure endothelial precursors and EPCs with monocytic characteristics, and the plasma levels of regulatory cytokines were evaluated in 23 patients with AMD with active CNV and 20 matched controls. In the patients, this profile was re-evaluated after ranibizumab.

RESULTS: When compared with controls, the patients with AMD showed a lower number of both EPC types ($P = 0.03$) and higher plasma levels ($P = 0.03$) of stromal cell-derived factor 1. Three monthly injections of ranibizumab returned to control levels the number of circulating EPCs considered pure endothelial precursors and of stromal cell-derived factor 1, but not of monocytic EPCs.

CONCLUSION: The observations indicate responsiveness of circulating EPCs to the CNV process in AMD. They suggest the hypothesis that increased stromal cell-derived factor 1 production at the CNV site (reflected in higher plasma levels) recruits EPCs from the circulation, and that antivascular endothelial growth factor therapy selectively decreases the recruitment of cells to be incorporated into new vessels.

PMID: 24736462 [PubMed - as supplied by publisher]

Dev Ophthalmol. 2014;53:33-43. doi: 10.1159/000357294. Epub 2014 Apr 10.

General pathophysiology in retinal degeneration.

Wert KJ, Lin JH, Tsang SH.

Abstract: Retinal degeneration, including that seen in age-related macular degeneration and retinitis pigmentosa (RP), is the most common form of neural degenerative disease in the world. There is great genetic and allelic heterogeneity of the various retinal dystrophies. Classifications of these diseases can be ambiguous, as there are similar clinical presentations in retinal degenerations arising from different genetic mechanisms. As would be expected, alterations in the activity of the phototransduction cascade, such as changes affecting the renewal and shedding of the photoreceptor OS, visual transduction, and/or retinol metabolism have a great impact on the health of the retina. Mutations within any of the molecules responsible for these visual processes cause several types of retinal and retinal pigment epithelium degenerative diseases. Apoptosis has been implicated in the rod cell loss seen in a mouse model of RP, but the precise mechanisms that connect the activation of these pathways to the loss of phosphodiesterase (PDE6β) function has yet to be defined. Additionally, the activation of apoptosis by CCAAT/-enhancer-binding protein homologous protein (CHOP), after activation of the unfolded protein response pathway, may be responsible for cell death, although the mechanism remains unknown. However, the mechanisms of cell death after loss of function of PDE6, which is a commonly studied mammalian model in research, may be generalizable to loss of function of different key proteins involved in the phototransduction cascade.

PMID: 24732759 [PubMed - in process]

Am J Ophthalmol. 2014 Apr 10. pii: S0002-9394(14)00192-5. doi: 10.1016/j.ajo.2014.04.005. [Epub ahead of print]

Choroidal Changes Associated with Bruch Membrane Pathology in Pseudoxanthoma Elasticum.

Gliem M, Fimmers R, Müller PL, Brinkmann CK, Finger RP, Hendig D, Holz FG, Issa PC.

PURPOSE: To investigate the impact of Bruch Membrane pathology on the choroid in Pseudoxanthoma elacticum (PXE)

DESIGN: Monocenter cross sectional prospective case series.

METHODS: The study included 61 eyes of 51 patients with PXE and 54 eyes of 54 normal subjects. The diagnosis of PXE was based on skin biopsy and/or genetic analysis. Eyes with PXE were subdivided into 3 groups: Eyes without choroidal neovascularization (CNV) or chorioretinal atrophy (group 1), eyes with active or fibrotic CNV (group 2) and eyes with chorioretinal atrophy only (group 3). Choroidal thickness was measured using enhanced depth imaging optical coherence tomography (EDI-OCT).

RESULTS: Compared to controls (331µm±24; mean±95%CI), mean subfoveal choroidal thickness in eyes of PXE patients was significantly reduced within all three groups (group 1: 243µm±29; group 2: 184µm±28; group 3: 104µm±28; $p<0.001$). Associated structural changes included apparent loss of small choroidal vessels. The difference of PXE compared to control eyes was most obvious close to the optic disc and approximated the level of controls towards the periphery. Within the PXE subgroups eyes without CNV or chorioretinal atrophy (group 1) showed the least reduction of choroidal thickness, while it was most pronounced within group 3.

CONCLUSIONS: The results indicate that changes of Bruch Membrane can be associated with choroidal alterations, which are most pronounced in presence of advanced disease. A role of Bruch Membrane for choroidal homeostasis may reflect a possible contribution of Bruch Membrane alterations to CNV and geographic atrophy development in age-related macular degeneration.

PMID: 24727260 [PubMed - as supplied by publisher]

Metallomics. 2014 Apr 17. [Epub ahead of print]

Correlations in distribution and concentration of calcium, copper and iron with zinc in isolated extracellular deposits associated with age-related macular degeneration.

Flinn JM, Kakalec P, Tappero R, Jones B, Lengyel I.

Abstract: Zinc (Zn) is abundantly enriched in sub-retinal pigment epithelial (RPE) deposits, the hallmarks of age-related macular degeneration (AMD), and is thought to play a role in the formation of these deposits. However, it is not known whether Zn is the only metal relevant for sub-RPE deposit formation. Because of their involvement in the pathogenesis of AMD, we determined the concentration and distribution of calcium (Ca), iron (Fe) and copper (Cu) and compared these with Zn in isolated and sectioned macular (MSD), equatorial (PHD) and far peripheral (FPD) sub-RPE deposits from an 86 year old donor eye with post mortem diagnosis of early AMD. The sections were mounted on Zn free microscopy slides and analyzed by microprobe synchrotron X-ray fluorescence (μSXRF). Metal concentrations were determined using spiked sectioned sheep brain matrix standards, prepared the same way as the samples. The heterogeneity of metal distributions was examined using pixel by pixel comparison. The orders of metal concentrations were Ca ⋙ Zn > Fe in all three types of deposits but Cu levels were not distinguishable from background values. Zinc and Ca were consistently present in all deposits but reached highest concentration in MSD. Iron was present in some but not all deposits and was especially enriched in FPD. Correlation analysis indicated considerable variation in metal distribution within and between sub-RPE deposits. The results suggest that Zn and Ca are the most likely contributors to deposit formation especially in MSD, the characteristic risk factor for the development of AMD in the human eye.

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Epidemiology

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Common ophthalmic problems of urban and rural postmenopausal women in a population sample of Raciborz district, a RAC-OST-POL Study.

Rokicki W, Drozdzowska B, Czekajło A, Grzeszczak W, Karpe J, Wiktor K, Pluskiewicz W.

Abstract: Introduction and objective. We wished to establish the prevalence of eye diseases and eye disease risk factors at postmenopausal age and to compare ophthalmic problems in urban and rural areas of Raciborz.

Patients and methods. The study was performed in 2010. Out of the whole population of Raciborz, Poland, 10 percent (1750) of women were randomly selected for the reported study. Finally, ocular diseases, ophthalmic agents, health status (physical activity level, body mass index - BMI, reproductive history, the use of psychotropic drugs and hormone replacement therapy - HRT) were recorded in 623 women. The women underwent visual acuity test and anterior segment examination, applanation tonometry and indirect ophthalmoscopy.

Results. The mean age of the selected patients was 66.01±7.76 years, 275 (44%) of them originating from rural and 348 (56%) from urban regions. The average woman was obese (BMI=30.54±5.38 kg/m2), with near normal agility and reproductive history of 2.59±1.55 births, 147 (24%) subjects remained under regular HRT support. According to the WHO, the visual acuity was classified as normal or near normal in 87.5%, while no blindness was recorded at all. Visual acuity depended, first of all, on lens status and was better among subjects with good agility (R=-0.31, p=0.001). Dry eye prevalence increased significantly over age of 67 years (p=0.000) and HRT seemed to be a dry eye protective factor (p=0.010). Except age, No other risk factors of cataract, other than age, were identified. Normal agility (p=0.003) and HRT (p=0.032) were associated with lower AMD (age-related macular degeneration) prevalence rates. The differences between

urban and rural participants were presented only in education, reproductive history, hypertension and frequency of ophthalmic examinations.

Conclusions. Older adult women living in neighboring urban and rural areas present no differential in ophthalmic health problems.

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Complement Factor I Polymorphism Is Not Associated with Neovascular Age-Related Macular Degeneration and Polypoidal Choroidal Vasculopathy in a Chinese Population.

Yang F, Sun Y, Jin Z, Cheng Y, Li S, Bai Y, Huang L, Li X.

Purpose: To identify the associations of the two complement factor I (CFI) polymorphisms rs10033900 and rs2285714 with risk of neovascular age-related macular degeneration (nAMD) and polypoidal choroidal vasculopathy (PCV) in a Chinese case-control study.

Methods: A total of 900 subjects - 300 controls, 300 cases with nAMD and 300 cases with PCV - were included in the present study. Genomic DNA was extracted from venous blood leukocytes. The allelic variants of rs10033900 and rs2285714 were determined by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. The differences in allele distribution between the cases and controls were tested by a $\chi 2$ test with age and gender adjusted for by logistic regression analysis. We also performed a meta-analysis of the case-control studies of rs10033900 and rs2285714 based on the currently available evidence from the literature. The meta-analysis was conducted via an inverse-variance, fixed-effects model, as previously described.

Results: No statistically significant association was observed between the two polymorphisms of CFI and AMD risk, including nAMD, PCV and combined AMD ($p > 0.05$ for all comparisons). By meta-analysis, we detected significant associations between both of the SNPs and late AMD, which is consistent with previous results (odds ratio, OR, rs10033900 = 0.814, p rs10033900 < 0.001; OR rs2285714 = 1.221, p rs2285714 < 0.001). For rs2285714, the results of the meta-analysis were less reliable due to its heterogeneity.

Conclusions: In our case-control study, neither of the two SNPs most studied (rs10033900 or rs2285714) in the CFI gene was a risk factor for developing nAMD or PCV in a Chinese population. Additional large, comprehensive and well-designed association studies are needed to better understand the role of ethnicity and other gene interactions in the association between the CFI gene and AMD.

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Genetics

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Analysis of rare variants in the c3 gene in patients with age-related macular degeneration.

Duvvari MR, Paun CC, Buitendijk GH, Saksens NT, Volokhina EB, Ristau T, Schoenmaker-Koller FE, van de Ven JP, Groenewoud JM, van den Heuvel LP, Hofman A, Fauser S, Uitterlinden AG, Klaver CC, Hoyng CB, de Jong EK, den Hollander AI.

Abstract: Age-related macular degeneration (AMD) is a progressive retinal disorder affecting over 33 million people worldwide. Genome-wide association studies (GWASs) for AMD identified common variants at 19 loci accounting for 15-65% of the heritability and it has been hypothesized that the missing heritability may be attributed to rare variants with large effect sizes. Common variants in the complement component 3 (C3)

gene have been associated with AMD and recently a rare C3 variant (Lys155Gln) was identified which exerts a large effect on AMD susceptibility independent of the common variants. To explore whether additional rare variants in the C3 gene are associated with AMD, we sequenced all coding exons in 84 unrelated AMD cases. Subsequently, we genotyped all identified variants in 1474 AMD cases and 2258 controls. Additionally, because of the known genetic overlap between AMD and atypical hemolytic uremic syndrome (aHUS), we genotyped two recurrent aHUS-associated C3 mutations in the entire cohort. Overall, we identified three rare variants (Lys65Gln (P=0.04), Arg735Trp (OR=17.4, 95% CI=2.2-136; P=0.0003), and Ser1619Arg (OR=5.2, 95% CI=1.0-25; P=0.05) at the C3 locus that are associated with AMD in our EUGENDA cohort. However, the Arg735Trp and Ser1619Arg variants were not found to be associated with AMD in the Rotterdam Study. The Lys65Gln variant was only identified in patients from Nijmegen, the Netherlands, and thus may represent a region-specific AMD risk variant.

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Diet & lifestyle

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Xanthophyll content of selected vegetables commonly consumed in the Philippines and the effect of boiling.

Pasaporte MS, Rabaya FJ, Toleco MM, Flores DM.

Abstract: The purpose of this study was to quantify xanthophylls in selected vegetables commonly consumed in the Philippines and to investigate the effect of boiling on their availability. Thirteen vegetables were grouped into green-leafy and non-leafy. Results showed that fresh malunggay contains the highest amount of lutein (167.1±6.1μg/g), neoxanthin (48.66±2.31μg/g), and violaxanthin (37.86±1.76μg/g) while mais has the highest zeaxanthin (269.1±11.8μg/g). Statistically, there is no significant difference ($p>0.1$) in xanthophyll content between fresh leafy and non-leafy samples. However, 15-min boiling (100°C) changed this, resulting in a significant difference ($p<0.1$) in xanthophyll content between the two groups. Boiling increased the availability of lutein and neoxanthin, while an opposite effect was observed for zeaxanthin and violaxanthin. Results also showed that consuming 20g of cooked malunggay (Moringa oleifera) can provide 100% the recommended level of lutein (10mg) for eye health, while 8g of cooked mais (Zea mays) a day can provide a high enough level (2mg) of zeaxanthin.

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Resveratrol Suppresses Expression of VEGF by Human Retinal Pigment Epithelial Cells: Potential Nutraceutical for Age-related Macular Degeneration.

Nagineni CN, Raju R, Nagineni KK, Kommineni VK, Cherukuri A, Kutty RK, Hooks JJ, Detrick B.

Abstract: Age-related macular degeneration (AMD) is a sight threating retinal eye disease that affects millions of aging individuals world-wide. Choroid-retinal pigment epithelium (RPE)-neuroretina axis in the posterior compartment of the eye is the primary site of AMD pathology. There are compelling evidence to indicate association of vascular endothelial growth factors (VEGF) to AMD. Here, we report the inhibitory actions of resveratrol (RSV) on inflammatory cytokine, TGF-β and hypoxia induced VEGF secretion by human retinal pigment epithelial cells (HRPE). HRPE cultures prepared from aged human donor eyes were used for the studies in this report. HRPE secreted both VEGF-A and VEGF-C in small quantities constitutively. Stimulation with a mixture of inflammatory cytokines (IFN-γ, TNF-α, IL-1β), significantly increased the secretion of both VEGF-A and VEGF-C. RSV, in a dose dependent (10-50 uM) manner,

suppressed VEGF-A and VEGF-C secretion induced by inflammatory cytokines significantly. RT-PCR analysis indicated that effects of RSV on VEGF secretion were possibly due to decreased mRNA levels. TGF-β and cobalt chloride (hypoxia mimic) also upregulated HRPE cell production of VEGF-A, and this was inhibited by RSV. In contrast, RSV had no effect on anti-angiogenic molecules, endostatin and pigment epithelial derived factor secretion. Studies using an in vitro scratch assay revealed that wound closure was also inhibited by RSV. These results demonstrate that RSV can suppress VEGF secretion induced by inflammatory cytokines, TGF-β and hypoxia. Under pathological conditions, over expression of VEGF is known to worsen AMD. Therefore, RSV may be useful as nutraceutical in controlling pathological choroidal neovascularization processes in AMD.

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