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MD Research News

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Drug treatment

Ophthalmology. 2013 May 29. pii: S0161-6420(13)00153-X. doi: 10.1016/j.ophtha.2013.02.019. [Epub ahead of print]

Two-Year Safety and Efficacy of Ranibizumab 0.5 mg in Diabetic Macular Edema: Interim Analysis of the RESTORE Extension Study.

Lang GE, Berta A, Eldem BM, Simader C, Sharp D, Holz FG, Sutter F, Gerstner O, Mitchell P; RESTORE Extension Study Group.

Division of Medical Retina and Laser Surgery, Department of Ophthalmology, University of Ulm, Ulm, Germany. Electronic address: gabriele.lang@uniklinik-ulm.de.

OBJECTIVE:To evaluate the 2-year safety and efficacy of ranibizumab 0.5 mg in diabetic macular edema (DME).

DESIGN:Twenty-four-month, open-label, multicenter, Phase IIIb extension study.

PARTICIPANTS:Two hundred forty of 303 patients with visual impairment due to DME who completed the RESTORE core study and entered the extension.

METHODS:All patients were eligible to receive ranibizumab 0.5 mg pro re nata (PRN) from month 12 (end of core study) to month 36 based on best-corrected visual acuity (BCVA) stability and disease progression retreatment criteria. Patients were also eligible to receive laser PRN according to Early Treatment Diabetic Retinopathy Study guidelines. A preplanned interim analysis was performed at month 24, stratifying by treatment groups as in the RESTORE core study and referred to as prior ranibizumab, ranibizumab plus laser, or laser groups in the extension.

MAIN OUTCOME MEASURES:Incidence of ocular and nonocular adverse events (AEs) and mean change in BCVA.

RESULTS:Two hundred twenty patients (92%) completed the month 24 visit. Over 2 years, the most frequent ocular serious AE (SAE) and AE were cataract (2.1%) and eye pain (14.6%), respectively. The main nonocular AEs were nasopharyngitis (18.8%) and hypertension (10.4%). There were no cases of endophthalmitis, and the incidences of nonocular SAEs were low. Of the patients entering the extension, 4 deaths were reported in the second year, none of which were related to study drug or procedure. Mean BCVA gain, central retinal thickness (CRT) decrease, and National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) composite score observed at month 12 were maintained at month 24 (prior ranibizumab: +7.9 letters, -140.6 μm, and 5.6, respectively; prior ranibizumab plus laser: +6.7 letters, -133.0 μm, and 5.8, respectively), with an average of 3.9 (prior ranibizumab) and 3.5 ranibizumab injections (prior

ranibizumab plus laser). In patients treated with laser alone in the core study, the mean BCVA, CRT, and NEI VFQ-25 composite score improved from month 12 to month 24 (+5.4 letters, -126.6 µm, and 4.3, respectively), with an average of 4.1 ranibizumab injections.

CONCLUSIONS:Ranibizumab 0.5 mg administered according to prespecified visual stability and disease progression criteria was well tolerated, with no new safety concerns identified over 2 years. Overall, an average of 3.8 ranibizumab injections was sufficient to maintain (prior ranibizumab) or improve (prior laser) BCVA, CRT, and NEI VFQ-25 outcomes through the second year.

PMID: 23725735 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2013 Jun;88(6):216-222. doi: 10.1016/j.oftal.2012.07.003. Epub 2012 Oct 24.

Clinical course of patients with exudative-haemorrhagic age-related macular degeneration treated with ranibizumab. Eye2Eye study.

[Article in English, Spanish]

Araiz J, Fernández-Baca I, Roura M; en representación del Grupo de Estudio EYE2EYE.

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OBJECTIVE: To assess the mean best-corrected visual acuity (BCVA) change in patients with exudative-haemorrhagic age-related macular degeneration (EH-ARMD) after 12-month period of treatment with ranibizumab.

METHODS: A retrospective, multicentre and national study of intravitreal administered ranibizumab was conducted on 2 groups of EH-ARMD patients: only one eye affected (group 1) versus second eye affected (group 2), having the first one affected. Eligible subjects were ≥ 50 years old with primary or secondary active subfoveal EH-ARMD-related choroidal neovascularisation (CNV).

RESULTS: A total of 184 patients (91 group 1 and 93 group 2) were included. Mean age (SD) was 75.3 (7.5) years, and 53.6% were women. The BCVA showed a VA improvement at 12 months of 9.3 (18.0) number of letters in group 1 and 5.1 (16.8) number of letters in group 2 (P<.0001 and P=.0042, respectively). No statistical differences between groups were observed. Lesion characteristics in the total population (baseline vs 12-month) were: drusen (69.1% vs 61.1%), macular haemorrhages (59.0% vs 7.3%), lipid exudates (28.1% vs 8.2%), and retinal pigment epithelium detachment (46.8% vs 19.0%). The optical coherence tomography (OCT) in the total population (baseline vs 12-month) showed a reduction in macular oedema (73.6% vs 20.9%), subretinal fluids (71.3% vs 14.7%), and intraretinal cysts (38.5 vs 19.7%), as well as a reduction of the mean foveal thickness 377.4 ± 109.8µm vs 249.1 ± 67.8µm in group 1 and 354.1 ± 123.2µm vs 254.6 ± 67.4µm in group 2, P<.0001, both groups, with no significant differences between groups.

CONCLUSIONS: Intravitreal administration of ranibizumab for a minimum of 12-months significantly improved the BCVA, decreased lesion characteristics, and reduced the initial mean foveal thickness in patients with CNV primary or secondary to EH-ARMD, both in patients with only one eye affected and in patients with a second eye affected, having the first one affected.

PMID: 23726306 [PubMed - as supplied by publisher]

Eye (Lond). 2013 Jun 7. doi: 10.1038/eye.2013.93. [Epub ahead of print]

Is it necessary to use three mandatory loading doses when commencing therapy for neovascular age-related macular degeneration using bevacizumab? (BeMOc Trial).

Menon G, Chandran M, Sivaprasad S, Chavan R, Narendran N, Yang Y.

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Purpose: To determine whether a Pro Re Nata (PRN) regimen with three initial mandatory loading doses results in better functional and anatomical outcome compared with a PRN regimen without initial loading when using intravitreal bevacizumab in patients with minimal classic or occult choroidal neovascularisation secondary to age-related macular degeneration.

Methods: Patients were randomised (1 : 1) to Loading (LD group) or No Loading (NLD group) and treated with open label intravitreal bevacizumab. In the LD group, patients received two mandatory doses after the baseline dose before entering the PRN phase and in the NLD group, patients did not receive mandatory doses after the baseline dose. Six-weekly evaluations were performed up to week 54 and retreatment was done based on OCT criteria. Visual stability and reduction in central retinal thickness were compared between groups.

Results: 49 patients were in the NLD group and 50 patients were in the LD group. At the 12-month end point, 84% of the patients in the LD group achieved visual stability (<15 letter loss) compared with 67% of the patients in the NLD group (P<0.05). The mean reduction in central macular thickness was 105.35 μm in the LD group and 81.45 μm in the NLD group (P>0.05). There was no significant difference in scores of VFQ-25 questionnaire testing between the two groups and no serious ocular or systemic side effects were observed.

Conclusion: The results supported our hypothesis that a loading dose leads to slightly better visual stability in terms of proportions of patients experiencing moderate visual loss, but did not support the hypothesised difference in anatomical outcome. Eye advance online publication, 7 June 2013; doi:10.1038/eye.2013.93.

PMID: 23743535 [PubMed - as supplied by publisher]

Eye (Lond). 2013 Jun 7. doi: 10.1038/eye.2013.114. [Epub ahead of print]

Two-year results of intravitreal ranibizumab for polypoidal choroidal vasculopathy with recurrent or residual exudation.

Saito M, Iida T, Kano M, Itagaki K.

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Aim: To clarify the 2-year efficacy of ranibizumab for patients with polypoidal choroidal vasculopathy (PCV) with recurrent or residual exudation from branching vascular networks after previous photodynamic therapy (PDT).

Methods: We retrospectively reviewed 26 eyes of 26 Japanese patients (22 men, 4 women) in this pilot study. All eyes had PCV with complete regression of polypoidal lesions resulting from PDT detected by indocyanine green angiography (ICGA), but recurrent or residual leakage from branching vascular networks on fluorescein angiography and evidence of persistent fluid on optical coherence tomography (OCT). Three consecutive intravitreal injections of ranibizumab (0.5 mg/0.05 ml) were administered to all eyes.

Results: The mean logarithm of the minimum angle of resolution best-corrected visual acuity (BCVA) improved significantly from 0.55 at baseline to 0.35 at 12 months (P<0.0001) and 0.43 at 24 months (P=0.0012). The mean increases in the BCVA 12 and 24 months after baseline were 1.95 and 1.23 lines, respectively. The mean central retinal thickness significantly decreased from 295 μm at baseline to 189 μm at 12 months (P<0.0038) and 163 μm at 24 months (P<0.001). The mean numbers of intravitreal ranibizumab (IVR) injections at months 12 and 24, including the initial treatments, were 5.8 and 8.8, respectively. Five (19.2%) eyes had recurrent polypoidal lesions on ICGA at a mean of 15.7 months after baseline. At month 24, OCT showed no exudation in 17 (65.4%) of the 26 eyes. No adverse events

developed.

Conclusions: IVR injections maintained or improved the VA and retinal thickness at 24 months in eyes with PCV with recurrent or residual exudation from branching vascular networks after previous PDT.Eye advance online publication, 7 June 2013; doi:10.1038/eye.2013.114.

PMID: 23743532 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2013 Jun;88(6):240-243. doi: 10.1016/j.oftal.2011.12.005. Epub 2012 Jul 19.

Antiangiogenic therapy in Sorsby's fundus dystrophy without a mutation in the TIMP-3 gene.

[Article in English, Spanish]

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CASE REPORT: The case is presented of a 32-year-old man referring to metamorphopsia and blurred vision in both eyes for 3 days. Best corrected visual acuity of 20/32 in the right eye and 20/25 in the left eye. Fundus examination revealed the presence of drusen-like deposits, suggestive of Sorsby's fundus dystrophy (SFD) and choroidal neovascularization (CNV) bilaterally. The patient received intravitreal ranibizumab. Visual acuity improved to 20/20 in both eyes at 6-months follow-up, and results of fundus examination showed complete regression of neovascularization. No mutations were found in the TIMP-3 gene. DISCUSSION: The known mutations in TIMP-3 may not be extended to all patients with SFD. The use of intravitreal ranibizumab may be considered as a therapeutic option in CNV secondary to SFD.

PMID: 23726310 [PubMed - as supplied by publisher]

Am J Manag Care. 2013 May;19(5 Suppl):s76-84.

Current treatment strategies for age-related ocular conditions.

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Abstract: Treatment for several major age-related ocular diseases has undergone a paradigm shift in recent years. Advances in basic science and clinical research have led to a more thorough understanding of the complex pathophysiology underlying common ocular diseases of aging, and to the development of highly effective new therapies for these conditions. The use of intraocular anti-angiogenic drugs, for example, has transformed the management of neovascular age-related macular degeneration and diabetic retinopathy. Many patients achieve impressive and durable gains in vision with these agents that were unattainable with older treatments. For glaucoma and dry eye disease, clinicians have a variety of pharmacologic and surgical options to choose from. However, significant challenges remain: not all patients respond to treatment, many older patients have difficulty complying with complex drug regimens, frequent office visits put a substantial strain on patients and caregivers, and therapies may cause unpleasant side effects. This article reviews the current treatment landscape for 4 major age-related ocular diseases: age-related macular degeneration, glaucoma, diabetic retinopathy, and dry eye.

PMID: 23725499 [PubMed - in process]

Other treatment & diagnosis

Retina. 2013 Jun 5. [Epub ahead of print]

QUANTIFICATION OF RETINAL PIGMENT EPITHELIUM TEAR AREA IN AGE-RELATED MACULAR DEGENERATION.

Clemens CR, Alten F, Baumgart C, Heiduschka P, Eter N.

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PURPOSE: To compare different quantification tools based on confocal scanning laser ophthalmoscopy for assessment of retinal pigment epithelium (RPE) tear area size.

METHODS: Confocal scanning laser ophthalmoscopy fundus autofluorescence (FAF) and near-infrared reflectance (IR) images were retrospectively evaluated in 23 patients with RPE tear after intravitreal injection for pigment epithelium detachment due to exudative age-related macular degeneration at baseline and additionally in 11 patients after 5.1 ± 1.8 months of follow-up. Retinal pigment epithelium tear area was measured by three independent readers using three methods: manually on confocal scanning laser ophthalmoscopy FAF images, manually on confocal scanning laser ophthalmoscopy IR images, and using an FAF-based semiautomated software.

RESULTS: Confidence intervals were 0.08 and 0.12 for FAF, 0.11 and 0.09 for FAF-based semiautomated software, and 0.25 and 0.27 for IR for intraobserver (Reader 1) and interobserver agreements (Readers 1 and 2), respectively. The average values of the square errors of the quantification methods were 0.040 ± 0.033 mm (FAF), 0.035 ± 0.060 mm (software), and 0.187 ± 0.219 mm (IR). Mean area of RPE tears at baseline given as the average measurement of all 3 readers using FAF-based semiautomated software was 5.77 ± 4.62 mm (range, 0.13-14.74 mm). Follow-up measurements of unilobular RPE tears (8 patients) showed no change in lesion area size (0.14 ± 0.33 mm); in contrast, multilobular RPE tears (3 patients) showed a progression in lesion area size of 1.80 ± 0.74 mm.

CONCLUSION: Manual FAF-based and semiautomated FAF-based quantifications of RPE tear area are accurate and reproducible and superior to manual IR-based measurement. Retinal pigment epithelium tear area quantification is clinically relevant regarding further intravitreal treatment, particularly in multilobular RPE tears.

PMID: 23743641 [PubMed - as supplied by publisher]

Retina. 2013 Jun 5. [Epub ahead of print]

SUBRETINAL DRUSENOID DEPOSITS WITH INCREASED AUTOFLUORESCENCE IN EYES WITH RETICULAR PSEUDODRUSEN.

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PURPOSE: To characterize a variant type of drusenoid deposit with different imaging features in comparison to reticular pseudodrusen.

METHODS: Retrospective observational consecutive case series. Eyes showing atypical drusenoid lesions were sorted out from 257 eyes of 133 patients previously diagnosed as reticular pseudodrusen. Eyes were evaluated using color fundus photography, confocal scanning laser ophthalmoscopy, and spectral domain optical coherence tomography.

RESULTS: A variant type of drusenoid deposits showing different imaging features from reticular pseudodrusen was found in 17 eyes of 12 patients (6.6%). The mean age of patients was 62.7 ± 11.6 years, and all patients were women. These deposits were observed as yellowish white, round to oval lesions on color photographs, located under the sensory retina and above the retinal pigment epithelium on spectral domain optical coherence tomography similar to reticular pseudodrusen. However, they were present in a smaller number as discrete lesions and showed increased autofluorescence. None of them were accompanied by late age-related macular degeneration.

CONCLUSION: Subretinal drusenoid deposits are not homogeneous and can be classified into two types according to the fundus autofluorescence. Multimodal imaging tests are needed for the differential diagnosis of subretinal drusenoid deposits.

PMID: 23743636 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2013 Jun 4. pii: iovs.12-11396v1. doi: 10.1167/iovs.12-11396. [Epub ahead of print]

Automated segmentation of pathological cavities in optical coherence tomography scans.

Pilch M, Stieger K, Wenner Y, Preising MN, Friedburg C, Meyer Zu Bexten E, Lorenz B.

Department of Ophthalmology, Justus-Liebig-University Giessen, Germany.

PURPOSE: To develop and evaluate a method for automated segmentation and quantitative analysis of pathological cavities in the retina visualized by Spectral-Domain (SD)-OCT scans.

METHODS: The algorithm is based on the segmentation of the grey-level intensities within a B-Scan by a k -means cluster analysis and subsequent classification by a k-nearest neighbor algorithm. Accuracy was evaluated against three clinical experts using 130 bullous cavities identified on 8 SD-OCT B-scans of 3 patients with wet age-related macular degeneration (AMD) and 5 patients with X-linked retinoschisis, as well as on one volume scan of a patient with X-linked retinoschisis. The algorithm calculated (i) the surface area of the cavities for the B-scans and (ii) the volume of all cavities for the volume scan. In order to validate the applicability of the algorithm in clinical use, 31 volume scans of one AMD patient with a serous retinal detachment taken over the course of 4 years were analyzed.

RESULTS: Discrepancies in area measurements between the segmentation results of the algorithm and the experts were within the range of the area deviations among the experts. Volumes interpolated from the b-scan series of the volume scan were comparable among experts and algorithm (0.249 mm3; for the algorithm, 0.271 mm3; for expert #1, 0.239 mm3; for expert #2 and 0.262 mm3; for expert #3). Volume changes of the serous retinal detachment were quantifiable.

CONCLUSIONS: The segmentation algorithm represents a method for the automated analysis of large numbers of volume scans during routine diagnostics and in clinical trials.

PMID: 23737469 [PubMed - as supplied by publisher]

Am J Manag Care. 2013 May;19(5 Suppl):s85-91.

Managed care implications of age-related ocular conditions.

Cardarelli WJ, Smith RA.

Abstract: The economic costs of age-related ocular diseases and vision loss are increasing rapidly as our society ages. In addition to the direct costs of treating age-related eye diseases, elderly persons with vision loss are at significantly increased risk for falls and fractures, experiencing social isolation, and suffering

from an array of comorbid medical conditions compared with individuals with normal vision. Recent studies estimate the total economic burden (direct and indirect costs) of adult vision impairment in the United States at $51.4 billion. This figure is expected to increase as the baby boomer generation continues to age. While a number of highly effective new therapies have caused a paradigm shift in the management of several major age-related ocular diseases in recent years, these treatments come at a substantial cost. This article reviews the economic burdens and treatment-related costs of 4 major ocular diseases of aging-glaucoma, age-related macular degeneration, diabetic retinopathy, and dry eye disease-and the implications for managed care.

PMID: 23725500 [PubMed - in process]

Ophthalmology. 2013 Jun;120(6):1307-1308.e1. doi: 10.1016/j.ophtha.2012.12.047.

Second Reflective Band Intensity in Age-related Macular Degeneration.

Wu Z, Ayton LN, Guymer RH, Luu CD.

Centre for Eye Research Australia, University of Melbourne, Royal Victorian Eye and Ear Hospital, Victoria, Australia.

PMID: 23732057 [PubMed - in process]

JAMA Ophthalmol. 2013 Jun 6:1-3. doi: 10.1001/jamaophthalmol.2013.432. [Epub ahead of print]

Age-Related Macular Degeneration, Anti-VEGF Therapy, and Ophthalmic Imaging: Is There a Best Practice?

Han DP.

PMID: 23744293 [PubMed - as supplied by publisher]

Ocul Immunol Inflamm. 2013 Jun 3. [Epub ahead of print]

Age-Related Macular Degeneration, third edition. (Book review)

Lim J, Editor

PMID: 23730952 [PubMed - as supplied by publisher]

Pathogenesis

J Cell Commun Signal. 2013 Jun 7. [Epub ahead of print]

Cysteine-rich protein 61 (CCN1) and connective tissue growth factor (CCN2) at the crosshairs of ocular neovascular and fibrovascular disease therapy.

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Abstract: The vasculature forms a highly branched network investing every organ of vertebrate organisms. The retinal circulation, in particular, is supported by a central retinal artery branching into superficial

arteries, which dive into the retina to form a dense network of capillaries in the deeper retinal layers. The function of the retina is highly dependent on the integrity and proper functioning of its vascular network and numerous ocular diseases including diabetic retinopathy, age-related macular degeneration and retinopathy of prematurity are caused by vascular abnormalities culminating in total and sometimes irreversible loss of vision. CCN1 and CCN2 are inducible extracellular matrix (ECM) proteins which play a major role in normal and aberrant formation of blood vessels as their expression is associated with developmental and pathological angiogenesis. Both CCN1 and CCN2 achieve disparate cell-type and context-dependent activities through modulation of the angiogenic and synthetic phenotype of vascular and mesenchymal cells respectively. At the molecular level, CCN1 and CCN2 may control capillary growth and vascular cell differentiation by altering the composition or function of the constitutive ECM proteins, potentiating or interfering with the activity of various ligands and/or their receptors, physically interfering with the ECM-cell surface interconnections, and/or reprogramming gene expression driving cells toward new phenotypes. As such, these proteins emerged as important prognostic markers and potential therapeutic targets in neovascular and fibrovascular diseases of the eye. The purpose of this review is to highlight our current knowledge and understanding of the most recent data linking CCN1 and CCN2 signaling to ocular neovascularization bolstering the potential value of targeting these proteins in a therapeutic context.

PMID: 23740088 [PubMed - as supplied by publisher]

Acta Ophthalmol. 2013 Jun 7. doi: 10.1111/aos.12146. [Epub ahead of print]

Early changes in gene expression induced by blue light irradiation of A2E-laden retinal pigment epithelial cells.

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Purpose: Accumulation of bisretinoids as lipofuscin in retinal pigment epithelial (RPE) cells is implicated in the pathogenesis of some blinding diseases including age-related macular degeneration (AMD). To identify genes whose expression may change under conditions of bisretinoid accumulation, we investigated the differential gene expression in RPE cells that had accumulated the lipofuscin fluorophore A2E and were exposed to blue light (430 nm).

Methods: A2E-laden RPE cells were exposed to blue light (A2E/430 nm) at various time intervals. Cell death was quantified using Dead Red staining, and RNA levels for the entire genome was determined using DNA microarrays (Affymetrix GeneChip Human Genome 2.0 Plus). Array results for selected genes were confirmed by real-time reverse-transcriptase polymerase chain reaction.

Results: Principal component analysis revealed that the A2E-laden RPE cells irradiated with blue light were clearly distinguishable from the control samples. We found differential regulation of genes belonging to the following functional groups: transcription factors, stress response, apoptosis and immune response. Among the last mentioned were downregulation of four genes that coded for proteins that have an inhibitory effect on the complement cascade: (complement factor H, complement factor H-related 1, complement factor I and vitronectin) and of two belonging to the classical pathway (complement component 1, s subcomponent and complement component 1, r subcomponent).

Conclusion: This study demonstrates that blue light irradiation of A2E-laden RPE cells can alter the transcription of genes belonging to different functional pathways including stress response, apoptosis and the immune response. We suggest that these molecules may be associated to the pathogenesis of AMD and can potentially serve as future therapeutic targets.

PMID: 23742627 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2013 Jun 5. [Epub ahead of print]

Age-related macular degeneration: choroidal ischaemia?

Coleman DJ, Silverman RH, Rondeau MJ, Lloyd HO, Khanifar AA, Chan RV.

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AIM: Our aim is to use ultrasound to non-invasively detect differences in choroidal microarchitecture possibly related to ischaemia among normal eyes and those with wet and dry age-related macular degeneration (AMD).

DESIGN: Prospective case series of subjects with dry AMD, wet AMD and age-matched controls.

METHODS: Digitised 20 MHz B-scan radiofrequency ultrasound data of the region of the macula were segmented to extract the signal from the retina and choroid. This signal was processed by a wavelet transform, and statistical modelling was applied to the wavelet coefficients to examine differences among dry, wet and non-AMD eyes. Receiver operating characteristic (ROC) analysis was used to evaluate a multivariate classifier.

RESULTS: In the 69 eyes of 52 patients, 18 did not have AMD, 23 had dry AMD and 28 had wet AMD. Multivariate models showed statistically significant differences between groups. Multiclass ROC analysis of the best model showed an excellent volume-under-curve of 0.892±0.17. The classifier is consistent with ischaemia in dry AMD.

CONCLUSIONS: Wavelet augmented ultrasound is sensitive to the organisational elements of choroidal microarchitecture relating to scatter and fluid tissue boundaries such as seen in ischaemia and inflammation, allowing statistically significant differentiation of dry, wet and non-AMD eyes. This study further supports the association of ischaemia with dry AMD and provides a rationale for treating dry AMD with pharmacological agents to increase choroidal perfusion. CLINICALTRIALS.GOV REGISTRATION: NCT00277784.

PMID: 23740965 [PubMed - as supplied by publisher]

Mol Med Rep. 2013 Jun 4. doi: 10.3892/mmr.2013.1508. [Epub ahead of print]

Potassium ion channels in retinal ganglion cells (Review).

Zhong YS, Wang J, Liu WM, Zhu YH.

Department of Ophthalmology, Ruijin Hospital Affiliated Medical School, Shanghai Jiaotong University, Shanghai 200025, P.R. China.

Abstract: Retinal ganglion cells (RGCs) consolidate visual processing and constitute the last step prior to the transmission of signals to higher brain centers. RGC death is a major cause of visual impairment in optic neuropathies, including glaucoma, age‑related macular degeneration, diabetic retinopathy, uveoretinitis and vitreoretinopathy. Discharge patterns of RGCs are primarily determined by the presence of ion channels. As the most diverse group of ion channels, potassium (K+) channels play key roles in modulating the electrical properties of RGCs. Biochemical, molecular and pharmacological studies have identified a number of K+ channels in RGCs, including inwardly rectifying K+ (Kir), ATP‑sensitive K+ (KATP), tandem‑pore domain K+ (TASK), voltage‑gated K+ (Kv), ether‑à‑go‑go (Eag) and Ca2+‑activated K+ (KCa) channels. Kir channels are important in the maintenance of the resting membrane potential and controlling RGC excitability. KATP channels are involved in RGC survival and neuroprotection. TASK channels are hypothesized to contribute to the regulation of resting membrane potentials and firing patterns of RGCs. Kv channels are important regulators of cellular excitability, functioning to modulate the amplitude, duration and frequency of action potentials and subthreshold

depolarizations, and are also important in RGC development and protection. Eag channels may contribute to dendritic repolarization during excitatory postsynaptic potentials and to the attenuation of the back propagation of action potentials. KCa channels have been observed to contribute to repetitive firing in RGCs. Considering these important roles of K+ channels in RGCs, the study of K+ channels may be beneficial in elucidating the pathophysiology of RGCs and exploring novel RGC protection strategies.

PMID: 23732984 [PubMed - as supplied by publisher]

Epidemiology

Ophthalmology. 2013 May 30. pii: S0161-6420(13)00317-5. doi: 10.1016/j.ophtha.2013.03.032. [Epub ahead of print]

Long-term Changes in Visual Acuity in an Older Population over a 15-Year Period: The Blue Mountains Eye Study.

Hong T, Mitchell P, Rochtchina E, Sze-Un Fong C, Chia EM, Wang JJ.

Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia.

PURPOSE:To describe the change in visual acuity (VA) and incidence of visual impairment (VI) in an older population over a 15-year period.

DESIGN:Population-based cohort.

PARTICIPANTS:Of the 3654 participants of the Blue Mountains Eye Study (BMES) baseline examination from 1992 through 1994, 1149 were re-examined during the 15-year follow-up between 2007 and 2010.

METHODS:Best-corrected VA by means of subjective refraction was measured with a logarithm of the minimum angle of resolution chart using Early Treatment Diabetic Retinopathy Study methods at each examination.

MAIN OUTCOME MEASURES:Unilateral VI was defined as VA worse than 20/40 and blindness was defined as VA worse than 20/200 in the worse eye. Incident bilateral VI and blindness were determined according to VA in the better eye at the 15-year visit. Doubling of the visual angle was defined as a loss of 15 letters or more from baseline to the 15-year visit. Halving of the visual angle was defined as a VA improvement of 15 letters or more over the same period. Causes of VI were determined at examination, by photographic grading, and from medical records.

RESULTS:Cumulative 15-year incidence of unilateral and bilateral VI was 12.3% (95% confidence interval [CI], 11.0-13.6) and 5.2% (95% CI, 4.3-6.1), respectively, and for unilateral and bilateral blindness, the cumulative incidence was 3.7% (95% CI, 3.0-4.4) and 0.9% (95% CI, 0.5-1.3), respectively. These incidence rates increased significantly with increasing age (P<0.01 for trend). Doubling and halving of the visual angle occurred in 6.9% (95% CI, 5.9-7.9) and 1.6% (95% CI, 1.0-2.2) of participants, respectively. Cataract accounted for 48.5% of unilateral and bilateral incident VI, followed by age-related macular degeneration (26.9%). Age-related macular degeneration accounted for 56.9% of unilateral and bilateral incident blindness cases, followed by cataract (20.7%).

CONCLUSIONS:These data provide population-based estimates of long-term incidence of visual impairment among older persons. Our estimate for cumulative incidence of blindness, accounting for competing risk of death, was similar to that of the Beaver Dam Eye Study (BDES) after age standardization. However, our estimate for cumulative incidence of VI was lower compared with that observed in the BDES population. This difference may be explained in part by a higher mortality rate among our population.

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Am J Manag Care. 2013 May;19(5 Suppl):s67-75.

Overview of age-related ocular conditions.

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Abstract: The United States is an aging society. The number of Americans 65 years or older is expected to more than double over the next 40 years, from 40.2 million in 2010 to 88.5 million in 2050, with aging baby boomers accounting for most of the increase. As the society ages, the prevalence of age-related diseases, including diseases of the eye, will continue to increase. By 2020, age-related macular degeneration, one of the leading causes of vision loss, is expected to affect 2.95 million individuals in the United States. Likewise, the prevalence of open-angle glaucoma, estimated at 2.2 million in 2000, is projected to increase by 50%, to 3.36 million by 2020. As the eye ages, it undergoes a number of physiologic changes that may increase susceptibility to disease. Environmental and genetic factors are also major contributors to the development of age-related ocular diseases. This article reviews the physiology of the aging eye and the epidemiology and pathophysiology of 4 major age-related ocular diseases: age-related macular degeneration, glaucoma, diabetic retinopathy, and dry eye.

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Genetics

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Genetic association study of mitochondrial polymorphisms in neovascular age-related macular degeneration.

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PURPOSE:Age-related macular degeneration (AMD) is a multifactorial disease involving genetic and environmental factors. Most of the genetic factors identified so far involve the nuclear genome. Recently, two studies in North America and Australia reported an association between advanced AMD and the mitochondrial T2 haplogroup. Our purpose was to assess this association in a large French population.

METHODS:This case control study included 1,224 patients with neovascular AMD and 559 controls with normal fundus. Mitochondrial DNA polymorphisms at and around nucleotides 4917, 11,812, and 14,233 were determined using PCR amplification and direct sequencing of mitochondrial DNA.

RESULTS:No association was found between the mitochondrial T2 haplogroup and neovascular AMD in the French population: 94/1,152 patients with neovascular AMD had the T2 haplogroup (8.2%) versus 34/482 controls (7.1%; odds ratio=0.9 [0.5-1.5], p=0.66).

CONCLUSIONS:An association between AMD and the T2 haplogroup, previously described in North American and Australian populations, was not confirmed in a large French population.

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Diet

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Oxidative stress, polyunsaturated fatty acids-derived oxidation products and bisretinoids as potential inducers of CNS diseases: focus on age-related macular degeneration.

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Abstract: Many pathologies of the central nervous system (CNS) originate from excess of reactive free radicals, notably reactive oxygen species (ROS), and oxidative stress. A phenomenon which usually runs in parallel with oxidative stress is unsaturated lipid peroxidation, which, via a chain reaction, contributes to the progression of disbalanced redox homeostasis. Among long-chain (LC) polyunsaturated fatty acids (PUFAs) abundantly occurring in the CNS, docosahexaenoic acid (DHA), a member of ω-3 LC-PUFAs, deserves special attention, as it is avidly retained and uniquely concentrated in the nervous system, particularly in retinal photoreceptors and synaptic membranes; owing to the presence of the six double bonds between carbon atoms in its polyene chain (C=C), DHA is exquisitely sensitive to oxidative damage. In addition to oxidative stress and LC-PUFAs peroxidation, other stress-related mechanisms may also contribute to the development of various CNS malfunctions, and a good example of such mechanisms is the process of lipofuscin formation occurring particularly in the retina, an integral part of the CNS. The retinal lipofuscin is formed and accumulated by the retinal pigment epithelial (RPE) cells as a consequence of both visual process taking place in photoreceptor-RPE functional complex and metabolic insufficiency of RPE lysosomal compartment. Among various retinal lipofuscin constituents, bisretinoids, originating from all -trans retinal substrate - a photometabolite of visual pigment cofactor 11-cis-retinal (responsible for photon capturing), are endowed with cytotoxic and complement-activating potential which increases upon illumination and oxidation. This survey deals with oxidative stress, PUFAs (especially DHA) peroxidation products of carboxyalkylpyrrole type and bisretinoids as potential inducers of the CNS pathology. A focus is put on vision-threatening disease, i.e., age-related macular degeneration (AMD), as an example of the CNS disorder whose pathogenesis has strong background in both oxidative stress and lipid peroxidation products.

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Observation of human retinal remodeling in octogenarians with a resveratrol based nutritional supplement.

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Purpose: Rare spontaneous remissions from age-related macular degeneration (AMD) suggest the human retina has large regenerative capacity, even in advanced age. We present examples of robust improvement of retinal structure and function using an OTC oral resveratrol (RV) based nutritional supplement called Longevinex® or L/RV (circa 2004, Resveratrol Partners, LLC, Las Vegas, NV, USA). RV, a polyphenolic phytoalexin caloric-restriction mimic, induces hormesis at low doses with widespread beneficial effects on systemic health. RV alone inhibits neovascularization in the murine retina. Thus far, published evidence includes L/RV mitigation of experimentally induced murine cardiovascular reperfusion injury, amelioration of human atherosclerosis serum biomarkers in a human Japanese randomized placebo controlled trial, modulation of micro RNA 20b and 539 that control hypoxia-inducing-factor (HIF-1) and vascular endothelial

growth factor (VEGF) genes in the murine heart (RV inhibited micro RNA20b 189-fold, L/RV 1366-fold). Little is known about the effects of L/RV on human ocular pathology.

Methods: Absent FDA IRB approval, but with permission from our Chief of Staff and medical center IRB, L/RV is reserved for AMD patients, on a case-by-case compassionate care basis. Patients include those who progress on AREDS II type supplements, refuse intra-vitreal anti-VEGF injections or fail to respond to Lucentis®, Avastin® or Eylea®. Patients are clinically followed traditionally as well as with multi-spectral retinal imaging, visual acuity, contrast sensitivity, cone glare recovery and macular visual fields. Three cases are presented.

Results: Observed dramatic short-term anti-VEGF type effect including anatomic restoration of retinal structure with a suggestion of improvement in choroidal blood flow by near IR multispectral imaging. The visual function improvement mirrors the effect seen anatomically. The effect is bilateral with the added benefit of better RPE function. Effects have lasted for one year or longer when taken daily, at which point one patient required initiation of anti-VEGF agents. Unanticipated systemic benefits were observed.

Conclusions: Preliminary observations support previous publications in animals and humans. Restoration of structure and visual function in octogenarians with daily oral consumption of L/RV is documented. Applications include failure on AREDS II supplements, refusing or failing conventional anti-VEGF therapy, adjunct therapy to improve RPE function, and compassionate use in medically underserved or economically depressed third-world countries.

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Should we be taking B vitamins to prevent age-related macular degeneration? Not yet, but worth doing more research.

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Effect of Lutein and Antioxidant Supplementation on VEGF Expression, MMP-2 Activity, and Ultrastructural Alterations in Apolipoprotein E-Deficient Mouse.

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Abstract: Oxidative stress is involved in the pathogenesis of several diseases such as atherosclerosis and age-related macular degeneration (AMD). ApoE-deficient mice (apoE(-/-)) are a well-established model of genetic hypercholesterolemia and develop retinal alterations similar to those found in humans with AMD. Thus supplementation with lutein or multivitamin plus lutein and glutathione complex (MV) could prevent the onset of these alterations. ApoE(-/-) mice (n = 40, 3 months old) were treated daily for 3 months with lutein (AE-LUT) or MV (two doses): AE-MV15 (15 mg/kg/day) and AE-MV50 (50 mg/kg/day) and were compared to controls with vehicle (AE-C). Wild-type mice (n = 10) were also used as control (WT-C). ApoE(-/-) mice showed higher retinal lipid peroxidation and increased VEGF expression and MMP-2 activity, associated with ultrastructural alterations such as basal laminar deposits, vacuoles, and an increase in Bruch's

membrane thickness. While lutein alone partially prevented the alterations observed in apoE(-/-) mice, MV treatment substantially reduced VEGF levels and MMP-2 activity and ameliorated the retinal morphological alterations. These results suggest that oxidative stress in addition to an increased expression and activity of proangiogenic factors could participate in the onset or development of retinal alterations of apoE(-/-) mice. Moreover, these changes could be prevented by efficient antioxidant treatments.

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