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MD Research News

Issue 273

Tuesday 5 April, 2016

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Drug treatment

Br J Ophthalmol. 2016 Mar 30. [Epub ahead of print]

UK Neovascular Age-Related Macular Degeneration Database. Report 6: time to retreatment after a pause in therapy. Outcomes from 92 976 intravitreal ranibizumab injections.

Madhusudhana KC, Lee AY, Keane PA, Chakravarthy U, Johnston RL, Egan CA, Sim D, Zarranz-Ventura J, Tufail A, McKibbin M; UK AMD EMR Study Group.

BACKGROUND/AIMS: To study the time to retreatment in eyes with neovascular age-related macular degeneration (nAMD) that had been treatment-free for intervals of 3 months, 6 months, 9 months and 12 months during the maintenance phase of ranibizumab therapy within the UK National Health Service.

METHODS: In this multicentre national nAMD database study, structured data were collected from 14 centres (involving 12 951 eyes receiving 92 976 ranibizumab injections). Patients were treated with three fixed, monthly injections in a loading phase of treatment, followed by a pro re nata retreatment regimen in a maintenance phase. Eyes with a treatment-free interval (TFI) of 3 months, 6 months, 9 months or 12 months in the maintenance phase were identified and the time to retreatment after these TFIs was determined.

RESULTS: The time to retreatment for the 20th and 50th centiles was 0.58/2.54 months after a 3-month TFI, 2.07/9.62 months after a 6-month TFI, 3.69/15.84 months after a 9-month TFI and 5.90/22.49 months after a 12-month TFI. Following a TFI of 3 months, 6 months, 9 months and 12 months, 68%, 44%, 31% and 21% of eyes required retreatments after an additional 6 months of follow-up, respectively. Similarly, after 12 months of follow-up, 77%, 56%, 43% and 34% of these eyes required retreatment.

CONCLUSIONS: This study provides times to retreatment in eyes with nAMD that have been treatment-free for intervals of 3-12 months and demonstrates the likelihood of repeat therapy within the next year, even after a TFI of 12 months. These outcomes can help plan appropriate follow-up intervals for patients who have been treatment-free for intervals of up to 12 months.

PMID: 27030276 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 Mar 30. [Epub ahead of print]

Key drivers of visual acuity gains in neovascular age-related macular degeneration in real life: findings from the AURA study.

Holz FG, Tadayoni R, Beatty S, Berger A, Cereda MG, Hykin P, Staurenghi G, Wittrup-Jensen K, Altemark A, Nilsson J, Kim K, Sivaprasad S.

BACKGROUND/AIMS: To identify predictive markers for the outcomes of anti-vascular endothelial growth factor therapy for neovascular age-related macular degeneration (nAMD).

METHODS: AURA was a retrospective, observational, multicentre study that monitored the 2-year outcomes following intravitreal ranibizumab treatment in patients with nAMD. Using stepwise regression analysis, we evaluated the association between visual acuity outcomes, baseline characteristics and resource utilisation in order to determine which variables are significantly linked to outcomes in AURA. We also examined the relationship between visual acuity outcomes and number of injections received.

RESULTS: Analyses were performed using data from year 1 (n=1695) and year 2 completers (n=1184). Logistic analysis showed that baseline visual acuity score, age at start of therapy, number of ophthalmoscopies and optical coherence tomography (OCT) (combined) and number of injections (ranibizumab) were significant ($p<0.05$) prognostic factors for vision maintenance (loss <15 letters) or vision gain (≥15 letters). Patients who received >7 injections (in 1 year) or >14 injections (over 2 years) gained more letters and demonstrated greater vision maintenance (loss of <15 letters) than patients who received fewer injections. There was a significant ($p<0.05$) association between number of injections and national reimbursement schemes and OCT.

CONCLUSIONS: A number of factors that are predictive of treatment outcomes in a real-life setting were identified. Notably, the decline of treatment benefits may be linked to number of injections and a failure to visit clinicians and receive OCT as required. These findings may be helpful in guiding ophthalmologist treatment decisions under limited time and financial constraints.

PMID: 27030279 [PubMed - as supplied by publisher]

Br J Ophthalmol. 2016 Mar 30. [Epub ahead of print]

Three-month outcome of ziv-aflibercept for exudative age-related macular degeneration.

Mansour AM, Chhablani J, Antonios RS, Yogi R, Younis MH, Dakroub R, Chahine H.

PURPOSE: In vitro and in vivo studies did not detect toxicity to the retinal pigment epithelium cells using intravitreal ziv-aflibercept. Our purpose is to ascertain the 3-month safety and efficacy in wet age-related macular degeneration (AMD) treated with intravitreal ziv-aflibercept.

METHODS: Prospectively, consecutive patients with wet AMD underwent ziv-aflibercept intravitreal injection (1.25 mg/0.05 mL) from March 2015 to November 2015. Monitoring of best-corrected visual acuity, intraocular inflammation, cataract progression and by spectral domain optical coherence tomography were carried out at baseline day 1, 1 week, 1 month, 2 months and 3 months after injections.

RESULTS: 30 eyes were treated (22 Caucasians, 8 Indians; 16 men, 14 women; 14 right eyes and 16 left eyes) with mean age of 74.3 years with 11 treatment-naïve cases and 19 having had treatment-non-naïve. Best-corrected visual acuity improved from baseline logMAR 1.08-0.74 at 1 week, 0.72 at 1 month, 0.67 at 2 months and 0.71 at 3 months ($p<0.001$ for all time periods). Central macular thickness in microns decreased from 332.8 to 302.0 at 1 week, 244.8 at 1 month, 229.0 at 2 months and 208.2 at 3 months ($p<0.001$ for all time periods). There were no signs of intraocular inflammation, or change in lens status or increase in intraocular pressure throughout the study.

CONCLUSIONS: Off label use of ziv-aflibercept improves visual acuity, without detectable ocular toxicity and offers a cheaper alternative to the same molecule aflibercept, especially in low/middle-income countries and in countries where aflibercept (Eylea) is not available.

PMID: 27030277 [PubMed - as supplied by publisher]

Ophthalmic Res. 2016 Mar 31. [Epub ahead of print]

Is There Any Difference between Ranibizumab and Aflibercept Injections in Terms of Inflammation Measured with Anterior Chamber Flare Levels in Age-Related Macular Degeneration Patients: A Comparative Study.

Demirel S, Bilici S, Batıoğlu F, Özmert E.

PURPOSE: To evaluate the inflammatory reaction to intravitreal aflibercept (IVA) or ranibizumab (IVR) in patients with age-related macular degeneration (AMD).

METHODS: A total of 60 eyes of 60 neovascular AMD patients and 30 eyes of 30 age-matched healthy people as a control group were included in this observational, prospective, comparative study. The AMD patients received 1:1 either IVA or IVR. Anterior chamber flare was measured with the Kowa FM-600 laser flare meter (Kowa Company, Ltd., Tokyo, Japan) at days 0, 1, and 30. The mean flare value and standard deviation are expressed as photon counts per millisecond.

RESULTS: There were 51 (56.7%) men and 39 (43.3%) women, with a mean age of 72.7 ± 7.5 years. Mean aqueous flare values at baseline, day 1 and day 30 were 7.08 ± 2.44, 7.23 ± 2.56, and 6.99 ± 2.29, respectively, for the IVR group, 6.87 ± 3.18, 6.86 ± 3.19, and 6.53 ± 2.79, respectively, for the IVA group, and 6.4 ± 3.29, 6.41 ± 3.06, and 6.42 ± 3.05, respectively, for the control group. There was no statistically significant difference in terms of baseline flare values for these three groups (p = 0.666). At the 1-day follow -up, a slight but not significant increase in flare was observed in the ranibizumab group. However, there was no significant change in aqueous flare values in either the ranibizumab- or the aflibercept-injected patients (p = 0.768 and p = 0.387, respectively) or between the groups (p = 0.635). No significant clinical inflammatory reactions were noted before or after intravitreal injections of either ranibizumab or aflibercept.

CONCLUSION: No significant short-term intraocular inflammation was noted in the eyes receiving aflibercept or ranibizumab for the treatment of neovascular AMD. Although aflibercept has more immunogenic properties than ranibizumab, such as having an extra Fc portion and being a larger molecule, it is likely that its more potent anti-inflammatory effects prevent it from inducing inflammation.

PMID: 27027523 [PubMed - as supplied by publisher]

Vestn Oftalmol. 2016;132(1):76-84.

[Long-term outcomes of anti-angiogenic therapy for macular neovascular disorders]. [Article in Russian]

Korotkikh SA, Bobykin EV, Nazarova NS, Melekhina EE.

AIM: to study long-term (≥2-year) RESULTS of ranibizumab treatment in patients with macular neovascular disorders.

MATERIAL AND METHODS: The study group included 27 patients (mean age±SD of 66.7±13.8 years) treated with ranibizumab for approved indications. Follow-up period ranged from 24 to 58 months (34.5±9.1 months on average).

RESULTS: Optical coherence tomography showed statistically significant improvements of functional and anatomical parameters, namely, an increase in visual acuity (from 0.34±0.20 to 0.57±0.24, p≤0.01) and a decrease in both central retinal thickness (from 372.26±96.21 μm to 272.48±69.70 μm, p≤0.01) and macular volume (from 8.01±1.46 mm3 to 7.10±1.08 mm3, p≤0.01). There was also a decreasing tendency of the average annual number of intravitreal ranibizumab injections per patient: 4.56 injections were done during the 1st year, 1.93 - during the 2nd year, and only 1.6 - during the 3rd year of follow-up. A total of 29.6% of patients showed no need in resuming the treatment at year 2 and 40.0% - at year 3. Exudation from the neovascular membrane relapsed in 24 patients (88.9%) at some time during the follow-up; at that, in 74.1% of patients the injection-free intervals lasted from 6 to 36 months. None of the 231 injections was associated with any complications concerning ocular functions and morphology and requiring additional treatment. No correlation was found between the anti-angiogenic therapy and the progression of cardiovascular disease.

CONCLUSION: Intravitreal ranibizumab has been proved effective and safe for the treatment of neovascular macular disorders. Moreover, flexible dosing schemes for ranibizumab contribute to rapid

(during the 1st year already) and stable clinical benefits.

PMID: 27030439 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2016 Mar 8;10:411-8. eCollection 2016.

Role of aflibercept for macular edema following branch retinal vein occlusion: comparison of clinical trials.

Oellers P, Grewal DS, Fekrat S.

Abstract: For years, the standard of care for branch-retinal-vein-occlusion-associated macular edema was initial observation followed by grid-pattern laser photocoagulation for persistent edema. Newer pharmacologic options have revolutionized the management of branch-retinal-vein-occlusion-associated macular edema, and the visual outcomes of these eyes are better than ever. However, a variety of available treatment options including intravitreal corticosteroids and intravitreal anti-vascular endothelial growth factor agents have established novel challenges with regard to appropriate drug selection. This review summarizes the available clinical studies with special emphasis on the comparison of intravitreal aflibercept with ranibizumab, bevacizumab, and steroid agents.

PMID: 27022238 [PubMed] PMCID: PMC4789836

BMJ Clin Evid. 2016 Mar 16;2016.

Diabetic retinopathy: intravitreal vascular endothelial growth factor inhibitors for diabetic macular oedema.

Mohamed QA, Fletcher EC, Buckle M.

INTRODUCTION: Diabetic retinopathy is the most common microvascular complication of diabetes. It is also the most common cause of blindness in working-age adults in industrialised nations. Older people and those with worse diabetes control, hypertension, and hyperlipidaemia are most at risk. Diabetic macular oedema, which can occur at any stage of diabetic retinopathy, is related to increased vascular permeability and breakdown of the blood retinal barrier, in part related to increased vascular endothelial growth factor (VEGF) levels. About 1% to 3% of people with diabetes suffer vision loss because of diabetic macular oedema.

METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical questions: What are the effects of intravitreal VEGF inhibitors versus each other for diabetic macular oedema? What are the effects of intravitreal VEGF inhibitors plus laser therapy versus intravitreal VEGF inhibitors alone for diabetic macular oedema? We searched: Medline, Embase, The Cochrane Library, and other important databases up to September 2014 (Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview).

RESULTS: At this update, searching of electronic databases retrieved 240 studies. After deduplication and removal of conference abstracts, 149 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 90 studies and the further review of 59 full publications. Of the 59 full articles evaluated, eight systematic reviews and four RCTs were added at this update. We performed a GRADE evaluation for four PICO combinations.

CONCLUSIONS: In this systematic overview, we categorised the efficacy for six comparisons based on information about the effectiveness and safety of intravitreal VEGF inhibitors aflibercept, bevacizumab, and ranibizumab, and each of these intravitreal VEGF inhibitors plus laser therapy.

PMID: 27031563 [PubMed - as supplied by publisher]

Other treatment & diagnosis

Med Phys. 2016 Apr;43(4):1649.

Choroidal vasculature characteristics based choroid segmentation for enhanced depth imaging optical coherence tomography images.

Chen Q, Niu S, Yuan S, Fan W, Liu Q.

PURPOSE: In clinical research, it is important to measure choroidal thickness when eyes are affected by various diseases. The main purpose is to automatically segment choroid for enhanced depth imaging optical coherence tomography (EDI-OCT) images with five B-scans averaging.

METHODS: The authors present an automated choroid segmentation method based on choroidal vasculature characteristics for EDI-OCT images with five B-scans averaging. By considering the large vascular of the Haller's layer neighbor with the choroid-sclera junction (CSJ), the authors measured the intensity ascending distance and a maximum intensity image in the axial direction from a smoothed and normalized EDI-OCT image. Then, based on generated choroidal vessel image, the authors constructed the CSJ cost and constrain the CSJ search neighborhood. Finally, graph search with smooth constraints was utilized to obtain the CSJ boundary.

RESULTS: Experimental results with 49 images from 10 eyes in 8 normal persons and 270 images from 57 eyes in 44 patients with several stages of diabetic retinopathy and age-related macular degeneration demonstrate that the proposed method can accurately segment the choroid of EDI-OCT images with five B-scans averaging. The mean choroid thickness difference and overlap ratio between the authors' proposed method and manual segmentation drawn by experts were -11.43 μm and 86.29%, respectively.

CONCLUSIONS:

Good performance was achieved for normal and pathologic eyes, which proves that the authors' method is effective for the automated choroid segmentation of the EDI-OCT images with five B-scans averaging.

PMID: 27036564 [PubMed - in process]

Dev Ophthalmol. 2016;56:57-61. Epub 2016 Mar 15.

Optical Coherence Tomography Angiography Features of Type 3 Neovascularization in Age-Related Macular Degeneration.

Querques G, Miere A, Souied EH.

PURPOSE: To characterize the imaging features of type 3 neovascularization secondary to exudative age-related macular degeneration on optical coherence tomography (OCT) angiography (OCTA).

METHODS: Patients diagnosed with treatment-naïve early-stage type 3 neovascularization underwent multimodal imaging, including color retinal photography or multicolor imaging, fluorescein angiography, indocyanine green angiography, spectral-domain OCT and OCTA. The OCTA features of type 3 neovascularization were analyzed and correlated with the findings on angiography and spectral-domain OCT.

RESULTS: OCTA showed lesions characterized by a retinal-retinal anastomosis. These lesions emerged from the deep capillary plexus and formed a clear, tuft-shaped, high-flow network in the outer retinal segment in all eyes, abutting in the subretinal pigment epithelium space. In most cases, a small, clew-like lesion was present in the choriocapillaris segment. Moreover, in some cases, this clew-like lesion seemed to be connected to the choroid through a small-caliber vessel.

CONCLUSION: OCTA of treatment-naïve type 3 neovascularization shows high-flow, tuft-shaped, abnormal outer retinal proliferation that is almost consistently associated with a small, clew-like lesion in the

choriocapillaris layer.

PMID: 27023917 [PubMed - in process]

Dev Ophthalmol. 2016;56:52-6. Epub 2016 Mar 15.

Optical Coherence Tomography Angiography of Type 2 Neovascularization in Age-Related Macular Degeneration.

Souied EH, El Ameen A, Semoun O, Miere A, Querques G, Cohen SY.

Abstract: Well-defined choroidal neovascularization, known as type 2 neovascularization (NV) or classic NV, is the least representative phenotype of exudative age-related macular degeneration. Clinical aspects of type 2 NV have been widely described in the literature, and to date fluorescein angiography remains the gold standard for imaging age-related macular degeneration at initial presentation. Optical coherence tomography angiography (OCT-A) can be used to image vessels based on flow characteristics without any dye injection. Type 2 NV can be visualized using OCT-A with very typical patterns. A neovascular membrane appears as either a medusa-shaped complex or a glomerulus-shaped lesion in the outer retina and the choriocapillaris layer. Furthermore, in the choriocapillaris layer, the external borders of the lesion appear as a dark ring in most cases, and one or more central feeder vessels that extend deeply into the more profound choroidal layers are visible. Identification of type 2 NV is easily feasible for any clinician using OCT-A, especially in areas where there are normally no vessels, like in subretinal space, if the interpretation rules are respected.

PMID: 27023798 [PubMed - in process]

Dev Ophthalmol. 2016;56:45-51. Epub 2016 Mar 15.

Optical Coherence Tomography Angiography of Type 1 Neovascularization in Age-Related Macular Degeneration.

Iafe NA, Phasukkijwatana N, Sarraf D.

Abstract: Age-related macular degeneration continues to be the leading cause of severe central vision loss in older adults of European descent. Optical coherence tomography angiography (OCT-A) enables more accurate identification of type 1 neovascularization in age-related macular degeneration than traditional fluorescein and indocyanine green angiographies. In addition, OCT-A facilitates the morphological classification of type 1 lesions, including features characteristic of early, mature, and fibrotic lesions. Vessel complex analysis, including lesion area and capillary density quantification, can also be readily measured and monitored over time. Performing this analysis following anti-vascular endothelial growth factor therapy may lead to a better understanding of the efficacies and responses to such treatments. Although some limitations currently exist, OCT-A is a promising imaging modality that could prove to have profound implications if incorporated into regular clinical practice.

PMID: 27023719 [PubMed - in process]

Dev Ophthalmol. 2016;56:91-100. Epub 2016 Mar 15.

Optical Coherence Tomography Angiography of Dry Age-Related Macular Degeneration.

Waheed NK, Moult EM, Fujimoto JG, Rosenfeld PJ.

Abstract: Optical coherence tomography angiography (OCTA) can be used to visualize alterations in the choriocapillaris of patients with dry age-related macular degeneration (AMD). These changes seem to be present during all stages of the disease. Earlier stages are associated with patchy thinning of the

choriocapillaris, while geographic atrophy is associated with loss of choriocapillaris lying under the area of geographic atrophy and asymmetric alteration of choriocapillaris at the margins of the geographic atrophy. The use of high-speed, long-wave-length swept-source OCT for angiography, with its better penetration into the choroid and high acquisition speeds, enable OCTA with scaled slowest detectable flow and fastest distinguishable flow. This will enable us to better investigate choriocapillaris changes in patients with dry AMD. The ability to image the choriocapillaris structure and flow impairments may be useful in the future for detecting and monitoring the progression of dry AMD and for monitoring treatment responses in clinical trials to therapies that target disease progression in dry AMD.

PMID: 27023214 [PubMed - in process]

Dev Ophthalmol. 2016;56:86-90. Epub 2016 Mar 15.

Optical Coherence Tomography Angiography of Fibrosis in Age-Related Macular Degeneration.

Souied EH, Miere A, Cohen SY, Semoun O, Querques G.

PURPOSE: To describe the optical coherence tomography angiography (OCTA) features of subretinal fibrosis in the context of exudative age-related macular degeneration.

METHODS: Patients diagnosed exudative age-related macular degeneration presenting with subretinal fibrosis were imaged by conventional multimodal imaging and OCTA. The patients were divided into the following two groups: group A, for eyes with active exudative features over the last 6 months, and group B, for eyes without any sign of exudation for >6 months.

RESULTS: In almost all of the patients, a high-flow network was detected inside of the fibrotic scar. We divided the vascular networks into the following three patterns: the pruned vascular tree, tangled network and vascular loop patterns. Furthermore, two types of low-flow structures, for which we coined the terms large flow void and dark halo, were observed. Both active and inactive lesions demonstrated the abovementioned patterns either individually or together. No difference was found between the two groups in the prevalent vascular network pattern of low-flow areas.

CONCLUSION: OCTA of subretinal fibrosis revealed a perfused, abnormal vascular network, as well as collateral architectural changes in the outer retina and the choriocapillaris layer, in the majority of the studied eyes. These features are associated with both active and inactive fibrotic choroidal neovessels.

PMID: 27023067 [PubMed - in process]

Dev Ophthalmol. 2016;56:62-70. Epub 2016 Mar 15.

Optical Coherence Tomography Angiography of Mixed Neovascularizations in Age-Related Macular Degeneration.

Liang MC, Witkin AJ.

PURPOSE: To describe the imaging of mixed neovascular age-related macular degeneration (AMD) using optical coherence tomography angiography (OCTA).

METHODS: Literature review and case series.

RESULTS: A review of mixed neovascularization in AMD is discussed, focusing on the different subtypes of neovascularization and the associated characteristics on imaging, including fluorescein angiography, optical coherence tomography, and OCTA. Three cases are presented.

CONCLUSION: OCTA is a method of identifying mixed neovascularization in AMD. Neovascular vessels can be seen on en face images of the retina, both below and above the retinal pigment epithelium, corresponding to different types of leakage observed on conventional angiography.

PMID: 27022725 [PubMed - in process]

Pathogenesis

Ophthalmic Res. 2016 Apr 2. [Epub ahead of print]

Plasmatic Ganglioside Profile and Age-Related Macular Degeneration: A Case-Control Study.

Dossarps D, Martine L, Berdeaux O, Sibille E, Bron AM, Creuzot-Garcher CP, Bretillon L, Masson EA.

PURPOSE: Gangliosides are glycosphingolipids that are particularly abundant in the nervous system, including the retina. However, their precise role in this tissue and its pathologies remain poorly understood. The objective of the present study was to characterize the ganglioside profile of human plasma and to determine whether it is affected in age-related macular degeneration (AMD).

METHODS: Eighty-three subjects were included: control subjects (n = 25), atrophic AMD patients (n = 27) and exudative AMD patients (n = 31). For each subject, gangliosides were extracted from plasma and analyzed by liquid chromatography coupled to mass spectrometry.

RESULTS: GM3 appeared to be by far the major ganglioside of human plasma, associated with GD3. No specific ganglioside class was detected in the plasma of AMD patients. Fourteen molecular species of GM3 and 9 species of GD3, accounting for the variability of the ceramide moiety of the ganglioside molecule, were identified and characterized. Analyses revealed no significant differences in the proportion of these species between control, atrophic and exudative AMD patient groups. Total GM3 levels did not differ either.

CONCLUSION: Although gangliosides are considered important for the retina's structure and function, it seems that circulating gangliosides are not associated with the retinal damage occurring during the course of AMD.

PMID: 27035458 [PubMed - as supplied by publisher]

Regen Med. 2016 Apr;11(3):331-4. Epub 2016 Mar 24.

The germline/soma dichotomy: implications for aging and degenerative disease.

West MD, Binette F, Larocca D, Chapman KB, Irving C, Sternberg H.

Abstract: Human somatic cells are mortal due in large part to telomere shortening associated with cell division. Limited proliferative capacity may, in turn, limit response to injury and may play an important role in the etiology of age-related pathology. Pluripotent stem cells cultured in vitro appear to maintain long telomere length through relatively high levels of telomerase activity. We propose that the induced reversal of cell aging by transcriptional reprogramming, or alternatively, human embryonic stem cells engineered to escape immune surveillance, are effective platforms for the industrial-scale manufacture of young cells for the treatment of age-related pathologies. Such cell-based regenerative therapies will require newer manufacturing and delivery technologies to insure highly pure, identified and potent pluripotency-based therapeutic formulations.

PMID: 27035399 [PubMed - in process]

Adv Protein Chem Struct Biol. 2016;104:157-231. Epub 2015 Dec 31.

Ion Channels in the Eye: Involvement in Ocular Pathologies.

Giblin JP, Comes N, Strauss O, Gasull X.

Abstract: The eye is the sensory organ of vision. There, the retina transforms photons into electrical signals that are sent to higher brain areas to produce visual sensations. In the light path to the retina, different types of cells and tissues are involved in maintaining the transparency of avascular structures like the cornea or lens, while others, like the retinal pigment epithelium, have a critical role in the maintenance of

photoreceptor function by regenerating the visual pigment. Here, we have reviewed the roles of different ion channels expressed in ocular tissues (cornea, conjunctiva and neurons innervating the ocular surface, lens, retina, retinal pigment epithelium, and the inflow and outflow systems of the aqueous humor) that are involved in ocular disease pathophysiologies and those whose deletion or pharmacological modulation leads to specific diseases of the eye. These include pathologies such as retinitis pigmentosa, macular degeneration, achromatopsia, glaucoma, cataracts, dry eye, or keratoconjunctivitis among others. Several disease-associated ion channels are potential targets for pharmacological intervention or other therapeutic approaches, thus highlighting the importance of these channels in ocular physiology and pathophysiology.

PMID: 27038375 [PubMed - in process]

Exp Eye Res. 2016 Mar 25;146:196-205. [Epub ahead of print]

Edaravone is a free radical scavenger that protects against laser-induced choroidal neovascularization in mice and common marmosets.

Masuda T, Shimazawa M, Takata S, Nakamura S, Tsuruma K, Hara H.

Abstract: Choroidal neovascularization (CNV) is a main characteristic in exudative type of age-related macular degeneration (AMD). Our study aimed to evaluate the effects of edaravone, a free radical scavenger on laser-induced CNV. CNV was induced by laser photocoagulation to the subretinal choroidal area of mice and common marmosets. Edaravone was administered either intraperitoneally twice a day for 2 weeks or intravenously just once after laser photocoagulation. The effects of edaravone on laser-induced CNV were evaluated by fundus fluorescein angiography, CNV area measurements, and the expression of 4 -hydroxy-2-nonenal (4-HNE) modified proteins, a marker of oxidative stress. Furthermore, the effects of edaravone on the production of H2O2-induced reactive oxygen species (ROS) and vascular endothelial growth factor (VEGF)-induced cell proliferation were evaluated using human retinal pigment epithelium cells (ARPE-19) and human retinal microvascular endothelial cells, respectively. CNV areas in the edaravone-treated group were significantly smaller in mice and common marmosets. The expression of 4-HNE modified proteins was upregulated 3 h after laser photocoagulation, and intravenously administered edaravone decreased it. In in vitro studies, edaravone inhibited H2O2-induced ROS production and VEGF-induced cell proliferation. These findings suggest that edaravone may protect against laser-induced CNV by inhibiting oxidative stress and endothelial cell proliferation.

PMID: 27018216 [PubMed - as supplied by publisher]

Sci Rep. 2016 Mar 31;6:23794. .

Connecting the innate and adaptive immune responses in mouse choroidal neovascularization via the anaphylatoxin C5a and γδT-cells.

Coughlin B, Schnabolk G, Joseph K, Raikwar H, Kunchithapautham K, Johnson K, Moore K, Wang Y, Rohrer B.

Abstract: Neovascular age-related macular degeneration (AMD) is characterized by choroidal neovascularization (CNV). An overactive complement system is associated with AMD pathogenesis, and serum pro-inflammatory cytokines, including IL-17, are elevated in AMD patients. IL-17 is produced by complement C5a-receptor-expressing T-cells. In murine CNV, infiltrating γδT- rather than Th17-cells produce the IL-17 measurable in lesioned eyes. Here we asked whether C5a generated locally in response to CNV recruits IL-17-producing T-cells to the eye. CNV lesions were generated using laser photocoagulation and quantified by imaging; T-lymphocytes were characterized by QRT-PCR. CNV resulted in an increase in splenic IL-17-producing γδT- and Th17-cells; yet in the CNV eye, only elevated levels of γδT-cells were observed. Systemic administration of anti-C5- or anti-C5a-blocking antibodies blunted the CNV-induced production of splenic Th17- and γδT-cells, reduced CNV size and eliminated ocular γδT-cell infiltration. In ARPE-19 cell monolayers, IL-17 triggered a pro-inflammatory state; and

splenocyte proliferation was elevated in response to ocular proteins. Thus, we demonstrated that CNV lesions trigger a systemic immune response, augmenting local ocular inflammation via the infiltration of IL-17-producing γδT-cells, which are presumably recruited to the eye in a C5a-dependent manner. Understanding the complexity of complement-mediated pathological mechanisms will aid in the development of an AMD treatment.

PMID: 27029558 [PubMed - in process]

Protein J. 2016 Mar 31. [Epub ahead of print]

Altered Cytoskeleton as a Mitochondrial Decay Signature in the Retinal Pigment Epithelium.

Sripathi SR, He W, Sylvester O, Neksumi M, Um JY, Dluya T, Bernstein PS, Jahng WJ.

Abstract: Mitochondria mediate energy metabolism, apoptosis, and aging, while mitochondrial disruption leads to age-related diseases that include age-related macular degeneration. Descriptions of mitochondrial morphology have been non-systematic and qualitative, due to lack of knowledge on the molecular mechanism of mitochondrial dynamics. The current study analyzed mitochondrial size, shape, and position quantitatively in retinal pigment epithelial cells (RPE) using a systematic computational model to suggest mitochondrial trafficking under oxidative environment. Our previous proteomic study suggested that prohibitin is a mitochondrial decay biomarker in the RPE. The current study examined the prohibitin interactome map using immunoprecipitation data to determine the indirect signaling on cytoskeletal changes and transcriptional regulation by prohibitin. Immunocytochemistry and immunoprecipitation demonstrated that there is a positive correlation between mitochondrial changes and altered filaments as well as prohibitin interactions with kinesin and unknown proteins in the RPE. Specific cytoskeletal and nuclear protein-binding mechanisms may exist to regulate prohibitin-mediated reactions as key elements, including vimentin and p53, to control apoptosis in mitochondria and the nucleus. Prohibitin may regulate mitochondrial trafficking through unknown proteins that include 110 kDa protein with myosin head domain and 88 kDa protein with cadherin repeat domain. Altered cytoskeleton may represent a mitochondrial decay signature in the RPE. The current study suggests that mitochondrial dynamics and cytoskeletal changes are critical for controlling mitochondrial distribution and function. Further, imbalance of retrograde versus anterograde mitochondrial trafficking may initiate the pathogenic reaction in adult-onset neurodegenerative diseases.

PMID: 27029380 [PubMed - as supplied by publisher]

Epidemiology

JAMA Ophthalmol. 2016 Mar 31. [Epub ahead of print]

Cataract Surgery and Age-Related Macular Degeneration in the 2008-2012 Korea National Health and Nutrition Examination Survey.

Park SJ, Lee JH, Ahn S, Park KH.

IMPORTANCE: In the past, concern has been raised that cataract surgery may be associated with the incidence or progression of age-related macular degeneration (AMD); inconsistent findings from previous studies have puzzled clinicians. In addition, data addressing this association in Asian populations and in the era of phacoemulsification are scarce.

OBJECTIVE: To determine the associations between cataract surgery and AMD in a representative Korean population.

DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional study used a multistage, probability-cluster survey sample to produce nationally representative estimates. Data were analyzed from the Korea National Health and Nutrition Examination Survey (KNHANES), which included results for cataract surgery status

and AMD grading from 2008 to 2012. A total of 20 419 participants 40 years or older were included. Data were analyzed from February 5 to August 20, 2015.

MAIN OUTCOMES AND MEASURES: The association between cataract surgery and AMD was assessed in each right and left eye using logistic regression models and in both eyes using generalized estimating equation models. Sample weights were applied to adjust for survey design, nonresponse, and stratification to generate nationally representative population-based results.

RESULTS: From the 20 419 eligible individuals (11 642 women [51.9%] and 5777 men [48.1%]; mean [SE] age, 55.83 [0.14] years), 17 987 had information regarding cataract surgery status and gradable fundus photographs of at least 1 eye. A total of 34 863 eyes (17 616 right eyes and 17 247 left eyes) underwent analysis. Of these, 1264 right eyes (5.5%) and 1235 left eyes (5.4%) had cataract surgery. Of 1056 right eyes and 949 left eyes with any AMD (early or late), 167 right eyes (15.2%) and 147 left eyes (13.7%) had cataract surgery. The analyses did not show any association between cataract surgery and any form of AMD (early, late, and all) except in left eyes, where cataract surgery was associated with late AMD (odds ratio, 2.34; 95% CI, 1.13-4.85).

CONCLUSIONS AND RELEVANCE: The results suggest that the association between cataract surgery and AMD is uncertain in the current era of phacoemulsification. The association for left eyes might be a chance finding.

PMID: 27031332 [PubMed - as supplied by publisher]

JAMA Ophthalmol. 2016 Mar 31. [Epub ahead of print]

Further Evidence That Cataract Surgery Is Not Associated With Macular Degeneration Progression.

Paulus YM, Johnson MW.

PMID: 27031237 [PubMed - as supplied by publisher]

Genetics

Ophthalmic Genet. 2016 Mar 30:1-6. [Epub ahead of print]

Association of polymorphisms in complement component 3 with age-related macular degeneration in an Iranian population.

Bonyadi M, Mohammadian T, Jabbarpoor Bonyadi MH, Fotouhi N, Soheilian M, Javadzadeh A, Moein H, Yaseri M.

BACKGROUND: Age related macular degeneration (AMD) is the leading cause of irreversible blindness in the elderly population. Inflammatory mediators play an important role in AMD pathogenesis and immune-related gene polymorphisms are shown to increase the risk. Complement system is an important mediator of the immunity system and several genes encoding proteins involved in this system are associated with susceptibility to AMD. The central element of the complement cascade, C3 has been a plausible candidate since its cleavage product C3a was found in drusen. This study was planned to evaluate the association of C3-rs2230199 (R102G) variants with advanced type AMD in this cohort.

MATERIALS AND METHODS: In this case-control study, 494 participants consisting of 266 AMD patients (187 wet AMD and 79 advanced dry AMD) and 228 samples from unrelated healthy controls were enrolled for evaluation. Extracted-DNA samples were amplified to obtain fragments including the polymorphic region.

RESULTS: The distribution of the R102G genotypes was significantly different in the AMD patients compared to controls (p = 0.001).The Odds Ratio compared to CC individuals was 1.69 (95% CI 1.15-2.49)

for GC individuals and 6.48 (95% CI1.87-22.43) for GG individuals. The Odds Ratio compared to the C allele was 2.31 (95% CI 0.48-11) for the G allele. GG and GC genotypes and G allele were significantly associated with both types of advanced-AMD. Individuals carrying GG genotype have over a six-fold risk of developing AMD in comparison to those carrying the CC genotype in this cohort. Our meta-analysis pooled data showed that our homozygous individuals for GG have a higher risk of AMD compared to previous publications in different nations (p = 0.017).

CONCLUSIONS: Our study shows C3 to be a relatively strong susceptibility gene for advanced-type-AMD (exudative-and-geographic-atrophy) in an Iranian population.

PMID: 27029644 [PubMed - as supplied by publisher]

Stem Cells

Int J Biol Sci. 2016 Feb 20;12(5):505-17. eCollection 2016.

Transcriptional Reactivation of OTX2, RX1 and SIX3 during Reprogramming Contributes to the Generation of RPE Cells from Human iPSCs.

Li P, Sun X, Ma Z, Liu Y, Jin Y, Ge R, Hao L, Ma Y, Han S, Sun H, Zhang M, Li R, Li T, Shen L.

Abstract: Directed differentiation of human induced pluripotent stem cells (iPSCs) into retinal pigmented epithelium (RPE) holds great promise in cell replacement therapy for patients suffering from degenerative eye diseases, including age-related macular degeneration (AMD). In this study, we generated iPSCs from human dermal fibroblasts (HDFs) by electroporation with episomal plasmid vectors encoding OCT4, SOX2, KLF4, L-MYC together with p53 suppression. Intriguingly, cell reprogramming resulted in a metastable transcriptional activation and selective demethylation of neural and retinal specification-associated genes, such as OTX2, RX1 and SIX3. In contrast, RPE progenitor genes were transcriptionally silent in HDFs and descendant iPSCs. Overexpression of OCT4 and SOX2 directly stimulated the expression of OTX2, RX1 and SIX3 in HDFs and iPSCs. Luciferase and chromatin immunoprecipitation (ChIP) assays further identified an OCT4- and two SOX2-binding sites located in the proximal promoter of OTX2. Histone acetylation and methylation on the local promoter also participated in the reactivation of OTX2. The transcriptional conversion of RX1 and SIX3 genes partially attributed to DNA demethylation. Subsequently, iPSCs were induced into the RPE cells displaying the characteristics of polygonal shapes and pigments, and expressing typical RPE cell markers. Taken together, our results establish readily efficient and safe protocols to produce iPSCs and iPSC-derived RPE cells, and underline that the reactivation of anterior neural transcription factor OTX2, eye field transcription factor RX1 and SIX3 in iPSCs is a feature of pluripotency acquisition and predetermines the potential of RPE differentiation.

PMID: 27019633 [PubMed - in process] PMCID: PMC4807412

Diet, lifestyle & low vision

Foods. 2016 Mar;5(1).

Can Xanthophyll-Membrane Interactions Explain Their Selective Presence in the Retina and Brain?

Widomska J, Zareba M, Subczynski WK.

Abstract: Epidemiological studies demonstrate that a high dietary intake of carotenoids may offer protection against age-related macular degeneration, cancer and cardiovascular and neurodegenerative diseases. Humans cannot synthesize carotenoids and depend on their dietary intake. Major carotenoids that have been found in human plasma can be divided into two groups, carotenes (nonpolar molecules, such as β-carotene, α-carotene or lycopene) and xanthophylls (polar carotenoids that include an oxygen atom in their structure, such as lutein, zeaxanthin and β-cryptoxanthin). Only two dietary carotenoids, namely lutein and

zeaxanthin (macular xanthophylls), are selectively accumulated in the human retina. A third carotenoid, meso-zeaxanthin, is formed directly in the human retina from lutein. Additionally, xanthophylls account for about 70% of total carotenoids in all brain regions. Some specific properties of these polar carotenoids must explain why they, among other available carotenoids, were selected during evolution to protect the retina and brain. It is also likely that the selective uptake and deposition of macular xanthophylls in the retina and brain are enhanced by specific xanthophyll-binding proteins. We hypothesize that the high membrane solubility and preferential transmembrane orientation of macular xanthophylls distinguish them from other dietary carotenoids, enhance their chemical and physical stability in retina and brain membranes and maximize their protective action in these organs. Most importantly, xanthophylls are selectively concentrated in the most vulnerable regions of lipid bilayer membranes enriched in polyunsaturated lipids. This localization is ideal if macular xanthophylls are to act as lipid-soluble antioxidants, which is the most accepted mechanism through which lutein and zeaxanthin protect neural tissue against degenerative diseases.

PMID: 27030822 [PubMed] PMCID: PMC4809277

Invest Ophthalmol Vis Sci. 2016 Mar 1;57(3):1476-1487.

Depth Perception and Grasp in Central Field Loss.

Verghese P, Tyson TL, Ghahghaei S, Fletcher DC.

PURPOSE: We set out to determine whether individuals with central field loss benefit from using two eyes to perform a grasping task. Specifically, we tested the hypothesis that this advantage is correlated with coarse stereopsis, in addition to binocular summation indices of visual acuity, contrast sensitivity, and binocular visual field.

METHODS: Sixteen participants with macular degeneration and nine age-matched controls placed pegs on a pegboard, while their eye and hand movements were recorded. Importantly, the pegboard was placed near eye height, to minimize the contribution of monocular cues to peg position. All participants performed this task binocularly and monocularly. Before the experiment, we performed microperimetry to determine the profile of field loss in each eye and the locations of eccentric fixation (if applicable). In addition, we measured both acuity and contrast sensitivity monocularly and binocularly, and stereopsis by using both a RanDot test and a custom stereo test.

RESULTS: Peg-placement time was significantly shorter and participants made significantly fewer errors with binocular than with monocular viewing in both the patient and control groups. Among participants with measurable stereopsis, binocular advantage in peg-placement time was significantly correlated with stereoacuity ($\rho = -0.78$; $P = 0.003$). In patients without measurable stereopsis, the binocular advantage was related significantly to the overlap in the scotoma between the two eyes ($\rho = -0.81$; $P = 0.032$).

CONCLUSIONS: The high correlation between grasp performance and stereoacuity indicates that coarse stereopsis may benefit tasks of daily living for individuals with central field loss.

PMID: 27031841 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2016 Mar 1;57(3):1448-56.

Perception of Haidinger Brushes in Macular Disease Depends on Macular Pigment Density and Visual Acuity.

Müller PL, Müller S, Gliem M, Küpper K, Holz FG, Harmening WM, Charbel Issa P.

PURPOSE: To optimize the perceptibility of Haidinger brushes (HB) and to investigate its association with visual acuity and macular pigment density.

METHODS: In this prospective cross-sectional study, each subject underwent best-corrected visual acuity (BCVA) testing, funduscopy, and assessment of macular pigment optical density (MPOD) using the two-wavelength fundus autofluorescence method. Haidinger brush visibility was tested with a rotating linear polarizer and a controllable three-color light-emitting diode (LED) panel as light source. A simple model of macular pigment absorption was used to predict HB visibility as a function of stimulus wavelength and MPOD.

RESULTS: All control eyes (n = 92) and 34% of the 198 eyes of subjects with macular disease (age-related macular degeneration, n = 40; macular telangiectasia type 2, n = 52; Stargardt disease, n = 58; other retinal dystrophies, n = 48) perceived HB when an optimized test setup (464-nm LED light) was applied. The degree of psychophysical perception and the dependency on different wavelengths were in accordance with the absorptance model. In eyes of subjects with macular disease, minimum thresholds of MPOD and BCVA required for HB perception were identified. Subjects with macular telangiectasia type 2 showed lowest values of MPOD and were mostly unable to perceive HB despite relatively preserved BCVA.

CONCLUSIONS: Macular pigment and a relatively preserved foveal function are necessary for the perception of HB. Haidinger brushes are usually not perceived by subjects with macular telangiectasia type 2, likely due to their characteristic foveal depletion of macular pigment.

PMID: 27028066 [PubMed - in process]