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MD Research News

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Drug treatment

Retina. 2015 Sep 9. [Epub ahead of print]

INTRAVITREAL RANIBIZUMAB FOR CHOROIDAL NEOVASCULARIZATION IN ANGIOID STREAKS: Four-Year Follow-up.

Tilleul J, Mimoun G, Querques G, Puche N, Zerbib J, Lalloum F, Srour M, Souied EH.

PURPOSE: To analyze retrospectively the efficacy of intravitreal ranibizumab injections for the management of choroidal neovascularization in patients with angioid streaks over a long term.

METHODS: In this "nonrandomized," double-center, retrospective, interventional case series, a consecutive series of patients affected with choroidal neovascularization associated with angioid streaks were treated with intravitreal ranibizumab injections (0.5 mg/0.05 mL). Best-corrected visual acuity, fundus photography, optical coherence tomography, and fluorescein angiography were examined before and after treatment. The primary endpoint was the percentage of eyes with stable or improved visual acuity at the end of follow-up (loss of less than 3 Early Treatment Diabetic Retinopathy Study lines). Secondary endpoints were the percentage of eyes with stable or decreased macular thickness on optical coherence tomography (less than a 10% increase in macular thickness) and the percentage of eyes with persistent leakage on fluorescein angiography at the last observation carried forward.

RESULTS: Thirty-five eyes of 27 patients were treated with repeated intravitreal ranibizumab injections (mean of 9.9 ± 7.2 injections, range 2-26) for a mean of 48.6 ± 17.1 months (range 8-66). At the end of follow-up, best-corrected visual acuity was stabilized or improved in 22 of 35 eyes (62.9%). Macular thickness had stabilized or decreased in 16 of 35 eyes (45.7%). At the last follow-up examination, on fluorescein angiography, no further leakage was observed in 27 of 35 eyes (77.1%).

CONCLUSION: In this large series of patients with choroidal neovascularization associated with angioid streaks followed for 4 years, ranibizumab injections allowed stabilization of best-corrected visual acuity in most eyes. Ranibizumab appear as an effective therapeutic option in CNV associated with angioid streaks over long time.

PMID: 26355947 [PubMed - as supplied by publisher]

Angiogenesis. 2015 Sep 7. [Epub ahead of print]

Aflibercept administration in neovascular age-related macular degeneration refractory to previous anti-vascular endothelial growth factor drugs: a critical review and new possible approaches to move forward.

Lazzeri S, Ripandelli G, Sartini MS, Parravano M, Varano M, Nardi M, Di Desidero T, Orlandi P, Bocci G.

PURPOSE: The recent introduction of anti-VEGF drugs has widely changed the prognosis of exudative age

-related macular degeneration (AMD), even if a variable percentage of patients showed an insufficient response. Aflibercept is a new anti-VEGF drug approved by FDA for the treatment of exudative AMD with a wider binding capacity than either bevacizumab or ranibizumab. Therefore, the purposes were as follows: (i) to report anatomical and functional outcomes of switching from bevacizumab/ranibizumab to aflibercept previously described in the scientific literature, (ii) to hypothesize the possible pathophysiological mechanisms of the resistance and tachyphylaxis to anti-VEGF drugs, and (iii) to suggest possible clinical actions to increase the chances of success for such difficult cases.

METHODS: We reviewed the available scientific literature in Medline, Cochrane database, Current Contents, PubMed, and cross-referencing from identified articles, regarding the treatment of exudative AMD patients refractory to bevacizumab and/or ranibizumab and switched to aflibercept monotherapy. We included in this review all the cases in which the diagnosis of refractory or resistant exudative AMD was properly made, and the results of at least one aflibercept injection were described.

FINDINGS: We reported the outcomes of 21 papers for a total of 1066 eyes affected by exudative AMD resistant to previous anti-VEGF drug injections and switched to aflibercept. Enrolled reports were divided into two groups: 5 prospective reports and 16 retrospective reports. All the reported papers conclude their analysis, stating that switching from bevacizumab/ranibizumab to aflibercept injections can improve outcomes successfully in refractory neovascular AMD patients.

IMPLICATIONS: Analysis of the papers reported in this review demonstrates that switching from bevacizumab/ranibizumab to aflibercept injections can improve outcomes successfully in refractory neovascular AMD patients. The mechanism for these effects is not yet completely understood.

PMID: 26346237 [PubMed - as supplied by publisher]

Expert Opin Biol Ther. 2015 Sep 11:1-13. [Epub ahead of print]

Intravitreal steroid and anti-vascular endothelial growth agents for the management of retinal vein occlusion: evidence from randomized trials.

Chatziralli I, Nicholson L, Sivaprasad S, Hykin P.

INTRODUCTION: Retinal vein occlusion (RVO) is a common retinal vascular disorder, affecting visual acuity and quality of life. Macular edema (ME) and retinal ischemia are the main causes for visual impairment in RVO. Although several modalities have been evaluated for the treatment of ME secondary to RVO in clinical trials, various questions need to be clarified when translating clinical trials into real-world practice.

Areas covered: Intravitreal steroids and anti-VEGF agents are now widely used for the treatment of ME due to RVO. Herein, evidence from randomized controlled trials regarding the use of steroids and anti-VEGF agents in ME related to RVO are presented. In addition, an approach regarding the optimal treatment regimen, the most suitable time for initiating treatment and monitoring patients, as well as the potential role of ischemia in the response to treatment and the impact of treatment on the natural course of the disease was made.

Expert opinion: A comprehensive presentation of randomized clinical trials evaluating intravitreal steroids and anti-VEGF treatment for RVO indicates that both are effective and safe. However, the comparative effectiveness of the various anti-VEGF agents, the most suitable dosing regimen and the effect of these agents on retinal ischemia remains unclear.

PMID: 26358547 [PubMed - as supplied by publisher]

J Clin Pharmacol. 2015 Sep 11. [Epub ahead of print]

Ocular pharmacology.

Novack GD, Robin AL.

Abstract: Ophthalmic diseases include those both analogous to systemic diseases (e.g., inflammation, infection, neuronal degeneration) and not analogous (e.g., cataract, myopia). Many anterior segment diseases are treated pharmacologically through eye drops, which have an implied therapeutic index of local therapy. Unlike administering pills for systemic diseases, eyedrops require patients not only to adhere to treatment, but to be able to accurately perform - i.e., instill drops correctly. Anatomical and physiological barriers make topical delivery to the anterior chamber challenging - in some cases more challenging than absorption through the skin, nasal passages, or gut. Treatment of the posterior segment (e.g., vitreous, retina, choroid, and optic nerve) is more challenging due to additional barriers. Recently, intravitreal injections have become a standard of care with biologics for the treatment of macular degeneration and other diseases. While the eye has esterases, hydroxylases and transporters, it has relatively little CYP450 enzymes. As it is challenging to obtain drug concentrations at the target site, ocular clinical pharmacokinetics, and thus pharmacokinetic-pharmacodynamic interactions are rarely available. Ophthalmic pharmaceuticals require consideration of solubility, physiological pH and osmolarity, as well as sterility and stability, which in turn requires optimal pharmaceutics. While applied locally, ocular medications may be absorbed systemically which result in morbidity and mortality (e.g., systemic hypotension, bronchospasm and bradycardia).

PMID: 26360129 [PubMed - as supplied by publisher]

Clin Ophthalmol. 2015 Aug 24;9:1537-41. eCollection 2015.

Submacular predominantly hemorrhagic choroidal neovascularization: resolution of bleedings under anti-VEGF therapy.

Dimopoulos S, Leitritz MA, Ziemssen F, Voykov B, Bartz-Schmidt KU, Gelisken F.

PURPOSE: To report the visual and morphological outcomes following intravitreal bevacizumab in neovascular age-related macular degeneration (nAMD) with submacular, predominantly hemorrhagic, lesions.

METHODS: Retrospective study of patients with a follow-up after 1 year. All eyes with submacular hemorrhages larger than 50% of the total lesion size and received only anti-VEGF (vascular endothelial growth factor) monotherapy (intravitreous administration of 1.25 mg bevacizumab, PRN). The primary endpoint was the change in hemorrhage size and time to resolution, in association with the mean best-corrected visual acuity (BCVA). The eyes were grouped based on the size of the hemorrhage: group A (≥1 to <4 disc area [DA]), group B (≥4 to <9 DA), and group C (≥9 DA).

RESULTS: Forty-six consecutive eyes were included. The mean area of the hemorrhage was 6 DA at baseline. Eyes with smaller bleeding (group A) had better chances of stabilized or improved vision. Complete resolution of the hemorrhage was seen in 96% of the eyes within 1 year. The mean BCVA increased from 0.81 logarithm of the minimum angle of resolution (logMAR) (95% confidence interval [CI]: 0.70-0.92) (Snellen 20/125) at baseline to 0.75 logMAR (95% CI: 0.62-0.88) (20/125) after 1 year (P=0.11). BCVA improved (one or more ETDRS [Early Treatment of Diabetic Retinopathy Study] lines) in 57% of the eyes (13/23) in group A; 53% (8/15) in group B; and 38% (3/8) in group C.

CONCLUSION: Many of the eyes with hemorrhagic lesions showed stabilization or improvement of the mean BCVA after treatment within 1 year. Anti-VEGF treatment can be considered as a useful treatment option in eyes with hemorrhages secondary to nAMD.

PMID: 26346691 [PubMed] PMCID: PMC4554429

Klin Oczna. 2015;117(1):35-9.

[Endophthalmitis as a complication of intravitreal anti-VEGF therapy in patients with exudative age-related macular degeneration and degenerative myopia]. [Article in Polish]

Kuhicka-Trząska A, Jędrychowska-Jamhorska JJ, Kulig-Stochmal A, Morawski K, Romanowska-Dixon B.

Abstract: Anti-vascular endothelial growth factor agents, injected intravitreally, became a standard therapy for choroidal neovascularization in a course of wet age-related macular degeneration and degenerative myopia. Endophthalmitis is a very rare but the most serious complication associated with this procedure. The purpose of this paper is to present three patients with endophthalmitis following intravitreal injections of anti-VEGF agents. In the analysed material, the authors confirmed endophthalmitis in 2 of 4176 patients with exudative age-related macular degeneration and choroidal neovascularization associated with degenerative myopia (0.048%). The third reported case is a patient with endophthalmitis following the injection of bevacizumab performed in another center. The time interval between the injection and the onset of endophthalmitis was 2-5 days. In two patients who underwent pars plana vitrectomy--one patient regained best corrected visual acuity, while another showed no improvement and developed eye atrophy. In one case the microbiological examination showed a growth of Staphylococcus epidermidis, while in another a negative culture result was present. Endopthalmitis is a rare complication following the intravitreal injections of anti-VEGF agents. The proper selection of therapy depends on presenting best corrected visual acuity and severity of intraocular inflammation. The time of commencing treatment is a crucial prognostic factor, however, our observations showed that prompt and repeated surgical procedures cannot prevent irreversible vision loss in all cases.

PMID: 26349157 [PubMed - in process]

Klin Oczna. 2015;117(1):31-4.

[Complete and permanent regression of persistent uveitic cystoid macular edema after single intravitreal injection of aflibercept in patient previously treated with multiple intravitreal injections of ranibizumab and bevacizumab]. [Article in Polish]

Swituła M.

Abstract: A case report of a twenty-year-old man with quiescent, idiopathic intermediate uveitis in his right eye treated with systemic corticosteroids and persistent cystoid macular edema, admitted for further treatment due to chronic reduction in visual acuity, is presented. A therapy involving intravitreal injections of ranibizumab (Lucentis), followed by bevacizumab (Avastin) was started, leading to transient improvement of visual acuity and edema reduction confirmed in optical coherent tomography. A de cision of switching to intravitreal aflibercept (Eylea) was made. After a single intravitreal injection of aflibercept, a complete and sustained resolution of macular edema was achieved. aflibercept, uveitis, cystoid macular edema.

PMID: 26349156 [PubMed - in process]

Klin Oczna. 2015;117(1):9-13.

[Visual and anatomical outcomes of three intravitreal aflibercept injections in eyes with neovascular form of age-related macular degeneration]. [Article in Polish]

Kałuiny JJ, Majer A, Jaworowska-Cieślińska I.

PURPOSE: To evaluate results of treatment of choroidal neovascularization due to age-related macular degeneration with aflibercept in a group of patients representative for Polish population.

MATERIAL AND METHODS: Three intravitreal injections of 2.0 mg of aflibercept were administrated to 48 eyes with active choroidal neovascularization at the four week intervals. In the evaluated population there were 19 eyes previously treated with other anti-VEGF drugs and 29 treatment naive eyes.

RESULTS: The mean best corrected visual acuity at baseline in the entire group was 0.47. During the follow-up exam after the first injection, the best corrected visual acuity increased to 0.58. After the second and third injection, it reached the level of 0.62 and 0.63, respectively. Such improvement in visual acuity was accompanied by the reduction of central retinal thickness. Eyes with intraretinal fluid presence confirmed in baseline spectral domain optical coherence tomography had significantly lower best corrected visual acuity throughout the entire follow up.

CONCLUSION: Three intravitreal aflibercept injections in eyes with neovascular age-related macular degeneration resulted in significant improvement of best corrected visual acuity and reduction of central retinal thickness both in eyes previously treated using other anti-VEGF drugs and newly diagnosed ones.

PMID: 26349151 [PubMed - in process]

Curr Pharm Des. 2015 Sep 8. [Epub ahead of print]

Anti-VEGF molecules for the management of diabetic macular edema.

Bandello F, Cicinelli MV, Parodi MB.

Abstract: Diabetic macular edema (DME) represents the most common cause of vision loss in patients affected by diabetes mellitus. Although the pathophysiology of DME is not wholly understood, vascular endothelial growth factor (VEGF) has been identified as a key contributor to the development of DME. In addition, latest information suggests that acute and chronic inflammatory changes occur, contributing to the DME pathogenesis. The current therapeutic approach for DME is mainly based on the administration of anti -VEGF molecules. In particular, VEGF-inhibitors that have been studied for diabetic retinopathy include pegaptanib, ranibizumab, bevacizumab, and aflibercept. The present review analyzes the main characteristics of each molecule, describing the most important results of clinical trails.

PMID: 26350530 [PubMed - as supplied by publisher]

Arch Soc Esp Oftalmol. 2015 Sep 4. [Epub ahead of print]

Laser and ranibuzumab combination for retinal vasoproliferative tumor's management.[Article in English, Spanish]

Fernández-Martínez C, Martínez-Toldos JJ, Hernández-Artola F.

CASE REPORT: A 34 year-old man presented with progressive visual loss in his right eye. Ocular fundus showed a vasoproliferative tumor in the peripheral retina with an associated epiretinal macular membrane. Angiography showed a rapid filling of tumor vessels. The treatment consisted of laser photocoagulation and a single injection of intravitreal ranibizumab. After 8 weeks, there was a residual area of fibrosis, the posterior hyaloid was detached, and the epiretinal membrane disappeared. Visual acuity returned to 20/25.

DISCUSSION: Laser photocoagulation and intravitreal ranibizumab combination could be useful for vasoproliferative tumors.

PMID: 26347320 [PubMed - as supplied by publisher]

Other treatment & diagnosis

J Ophthalmol. 2015;2015:359747. Epub 2015 Aug 17.

Preservation of the Photoreceptor Inner/Outer Segment Junction in Dry Age-Related Macular Degeneration Treated by Rheohemapheresis.

Rencová E, Bláha M, Studnička J, Bláha V, Lánská M, Renc O, Stepanov A, Kratochvílová V, Langrová H.

Aim: To evaluate the long-term effect of rheohemapheresis (RHF) treatment of age-related macular degeneration (AMD) on photoreceptor IS/OS junction status.

Methods: In our study, we followed 24 patients with dry AMD and drusenoid retinal pigment epithelium detachment (DPED) for a period of more than 2.5 years. Twelve patients (22 eyes) were treated by RHF and 12 controls (18 eyes) were randomized. The treated group underwent 8 RHF standardized procedures. We evaluated best-corrected visual acuity, IS/OS junction status (SD OCT), and macular function

(multifocal electroretinography) at baseline and at 2.5-year follow-up.

Results: RHF caused a decrease of whole-blood viscosity/plasma viscosity at about 15/12%. BCVA of treated patients increased insignificantly (P = 0.187) from median 74.0 letters (56.2 to 81.3 letters) to median 79.0 letters (57.3 to 83.4 letters), but it decreased significantly from 74.0 letters (25.2 to 82.6 letters) to 72.5 letters (23.4 to 83.1 letters) in the control group (P = 0.041). The mfERG responses in the region of eccentricity between 1.8° and 7° were significantly higher in treated patients (P = 0.04).

Conclusions: RHF contributed to sparing of photoreceptor IS/OS junction integrity in the fovea, which is assumed to be a predictive factor for preservation of visual acuity.

PMID: 26351571 [PubMed]

Eur J Ophthalmol. 2015 Aug 26:0. [Epub ahead of print]

Prevalence of reticular pseudodrusen in eyes with newly presenting neovascular age-related macular degeneration.

Wilde C, Patel M, Lakshmanan A, Morales MA, Dhar-Munshi S, Amoaku WM.

PURPOSE: To use multimodal imaging to evaluate the prevalence of reticular pseudodrusen (RPD) in eyes with newly presenting neovascular age-related macular degeneration (nAMD) in a UK population and explore associations with RPD and angiographic subtypes of nAMD.

METHODS: A retrospective review of all spectral-domain optical coherence tomography, color fundus photographs, red-free and blue channel images, and fundus fluorescein angiograms of 202 consecutive patients who presented to a rapid access macular clinic over a 4-year period was performed. All images were graded by at least 2 ophthalmologists for the presence of RPD and choroidal neovascular membrane (CNV) subtypes.

RESULTS: A total of 231 consecutive eyes were studied, of which 131 (56.7%) were in women. Of these, 51 eyes with CNV (22.1%) had identifiable RPD, with one or more imaging methods in that eye. A total of 30.3% of patients with newly presenting CNV in either or both eyes had identifiable RPD. The RPD were bilateral in 85.4% of patients and were identified more commonly in women than men (72.5% vs 27.5%), a difference that reached statistical significance (p = 0.011). No association between RPD and any particular CNV subtype was demonstrated, including for retinal angiomatous proliferations (RAP).

CONCLUSIONS: Reticular pseudodrusen have a high prevalence in eyes presenting with nAMD (22.1%), although at rates much lower than that of conventional drusen. They are largely a bilateral finding, occurring more frequently in women. Unlike other previous reports, we found no difference in their occurrence between the different subtypes of CNV including RAPs.

PMID: 26350997 [PubMed - as supplied by publisher]

Retina. 2015 Sep 9. [Epub ahead of print]

BRIDGE ARCH-SHAPED SEROUS RETINAL DETACHMENT IN AGE-RELATED MACULAR DEGENERATION.

Fajnkuchen F, Cohen SY, Thay N, Ayrault S, Delahaye-Mazza C, Grenet T, Nghiem-Buffet S, Quentel G, Giocanti-Auregan A.

PURPOSE: To describe bridge arch-shaped serous retinal detachment (SRD) in exudative age-related macular degeneration and evaluate its functional outcomes.

METHODS: In this monocentric, retrospective, noncomparative case series, patients were included. Patients with exudative age-related macular degeneration and bridge arch-shaped SRD treated with ranibizumab were included. Anatomical patterns of SRD and functional outcomes were assessed.

RESULTS: Twenty-two eyes with bridge arch-shaped SRD of 22 patients with age-related macular degeneration were included. Serous retinal detachments were characterized by a steep angle at the junction between the retinal pigment epithelium and the sensory retina (mean, 53.45 ± 12.5°), and characterized by the presence of adhesion areas between the sensory retina and a fibrous complex developed from the choroidal neovascularization. In 15 eyes, the choroidal neovascularization was classic choroidal neovascularization and a fibrotic evolution was observed. Serous retinal detachments were compartmentalized in 14 eyes, leading to a multipocket structure. Visual acuity decreased from 49.9 ± 19.2 letters (20/100) to 40.3 ± 18.6 letters (20/160), corresponding to a mean change of -9.6 ± 19.4 letters.

CONCLUSION: This was the first study to describe the specific morphologic features of bridge arch-shaped SRD, a previously undescribed type of SRD complicating exudative age-related macular degeneration. Patients with bridge arch-shaped SRD responded to intravitreal injections of ranibizumab, but their visual prognosis was unfavorable, compared with the literature. The presence of bridge arch-shaped SRD seemed to be a marker for the fibrotic evolution of the choroidal neovascularization.

PMID: 26355948 [PubMed - as supplied by publisher]

Invest Ophthalmol Vis Sci. 2015 Sep 1;56(10):5862-70.

In Vivo Imaging of Retinal Oxidative Stress Using a Reactive Oxygen Species-Activated Fluorescent Probe.

Prunty MC, Aung MH, Hanif AM, Allen RS, Chrenek MA, Boatright JH, Thule PM, Kundu K, Murthy N, Pardue MT.

PURPOSE: In vivo methods for detecting oxidative stress in the eye would improve screening and monitoring of the leading causes of blindness: diabetic retinopathy, glaucoma, and age-related macular degeneration.

METHODS: To develop an in vivo biomarker for oxidative stress in the eye, we tested the efficacy of a reactive oxygen species (ROS)-activated, near-infrared hydrocyanine-800CW (H-800CW) fluorescent probe in light-induced retinal degeneration (LIRD) mouse models. After intravitreal delivery in LIRD rats, fluorescent microscopy was used to confirm that the oxidized H-800CW appeared in the same retinal layers as an established ROS marker (dichlorofluorescein).

RESULTS: Dose-response curves of increasing concentrations of intravenously injected H-800CW demonstrated linear increases in both intensity and total area of fundus hyperfluorescence in LIRD mice, as detected by scanning laser ophthalmoscopy. Fundus hyperfluorescence also correlated with the duration of light damage and functional deficits in vision after LIRD. In LIRD rats with intravitreal injections of H-800CW, fluorescent labeling was localized to photoreceptor inner segments, similar to dichlorofluorescein.

CONCLUSIONS: Hydrocyanine-800CW detects retinal ROS in vivo and shows potential as a novel biomarker for ROS levels in ophthalmic diseases.

PMID: 26348635 [PubMed - in process]

Br J Ophthalmol. 2015 Sep 7. [Epub ahead of print]

Choroidal maps in non-exudative age-related macular degeneration.

Capuano V, Souied EH, Miere A, Jung C, Costanzo E, Querques G.

PURPOSE: To compare choroidal thickness maps (CMs) in patients with non-exudative age-related macular degeneration (AMD) and control subjects using swept source optical coherence tomography (Swept-OCT).

METHODS: CMs were automatically measured in the different Early Treatment of Diabetic Retinopathy Study (ETDRS) sectors in eyes with early non-exudative AMD (early AMD) (large soft drusen: group 1;

reticular pseudodrusen: group 2 and variable combination of large soft drusen and reticular pseudodrusen: group 3), late non-exudative AMD/geographic atrophy (GA) (late AMD) (group 4) and control subjects (group 5). Fundus autofluorescence (FAF) images were overlaid to sectorial CMs in late-AMD group (group 4).

RESULTS: A total of 90 eyes (90 patients, 79.7±8.34 years old) were included. CMs were significantly reduced in early-AMD group 2 and 3 and late-AMD group 4 compared with control subjects in group 5 and early-AMD group 1 (large soft drusen alone) for each ETDRS sectors ($p<0.05$). No difference in CMs was found by comparing group 2 with 3 and group 2 and 3 with group 4. No statistical differences in CMs were found among ETDRS sectors with >50% absence of FAF ('Hypo FAF' sectors) resulting from retinal atrophy versus ≤50% absence of FAF ('hyper/iso FAF' sectors owing to >50% preserved retina) in late-AMD group (group 4) ($p=0.328$).

CONCLUSIONS: CMs appeared thinner in early non-exudative AMD with intermediate distribution of reticular pseudodrusen versus control subjects and early non-exudative AMD with drusen alone. Same results were found in the group with variable combination of large soft drusen and reticular pseudodrusen. In GA eyes, a choroidal thinning could be detected independently of the retinal pigmented epithelium status.

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Transl Vis Sci Technol. 2015 Sep 1;4(5):2. eCollection 2015.

Restricted Summed-Area Projection for Geographic Atrophy Visualization in SD-OCT Images.

Chen Q, Niu S, Shen H, Leng T, de Sisternes L, Rubin DL.

PURPOSE: To enhance the rapid assessment of geographic atrophy (GA) across the macula in a single projection image generated from three-dimensional (3D) spectral-domain optical coherence tomography (SD-OCT) scans by introducing a novel restricted summed-area projection (RSAP) technique.

METHODS: We describe a novel en face GA visualization technique, the RSAP, by restricting the axial projection of SD-OCT images to the regions beneath the Bruch's membrane (BM) boundary and also considering the choroidal vasculature's influence on GA visualization. The technique analyzes the intensity distribution beneath the retinal pigment epithelium (RPE) layer to fit a cross-sectional surface in the sub-RPE region. The area is taken as the primary GA projection. A median filter is then adopted to smooth the generated GA projection image. The RSAP technique was evaluated in 99 3D SD-OCT data sets from 27 eyes of 21 patients presenting with advanced nonexudative age-related macular degeneration and GA. We used the mean difference between GA and background regions and GA separability metric to measure GA contrast and distinction in the generated images, respectively. We compared our results with two existing GA projection techniques, the summed-voxel projection (SVP) and Sub-RPE Slab techniques.

RESULTS: Comparative results demonstrate that the RSAP technique is more effective in displaying GA than the SVP and Sub-RPE Slab. The average of the mean difference between GA and background regions and the GA separability based on SVP, Sub-RPE Slab, and RSAP were 0.129/0.880, 0.238/0.919, and 0.276/0.938, respectively.

CONCLUSIONS: The RSAP technique was more effective for GA visualization than the conventional SVP and Sub-RPE Slab techniques. Our technique decreases choroidal vasculature influence on GA projection images by analyzing the intensity distribution characteristics in sub-RPE regions. The generated GA projection image with the RSAP technique has improved contrast and distinction.

TRANSLATIONAL RELEVANCE: Our method for automated generation of GA projection images from SD-OCT images may improve the visualization of the macular abnormalities and the management of GA.

PMID: 26347016 [PubMed] PMCID: PMC4559218

Acta Ophthalmol. 2015 Sep 11. [Epub ahead of print]

Structural brain MRI studies in eye diseases: are they clinically relevant? A review of current findings.

Prins D, Hanekamp S, Cornelissen FW.

Abstract: Many eye diseases reduce visual acuity or are associated with visual field defects. Because of the well-defined retinotopic organization of the connections of the visual pathways, this may affect specific parts of the visual pathways and cortex, as a result of either deprivation or transsynaptic degeneration. For this reason, over the past several years, numerous structural magnetic resonance imaging (MRI) studies have examined the association of eye diseases with pathway and brain changes. Here, we review structural MRI studies performed in human patients with the eye diseases albinism, amblyopia, hereditary retinal dystrophies, age-related macular degeneration (AMD) and glaucoma. We focus on two main questions. First, what have these studies revealed? Second, what is the potential clinical relevance of their findings? We find that all the aforementioned eye diseases are indeed associated with structural changes in the visual pathways and brain. As such changes have been described in very different eye diseases, in our view the most parsimonious explanation is that these are caused by the loss of visual input and the subsequent deprivation of the visual pathways and brain regions, rather than by transsynaptic degeneration. Moreover, and of clinical relevance, for some of the diseases - in particular glaucoma and AMD - present results are compatible with the view that the eye disease is part of a more general neurological or neurodegenerative disorder that also affects the brain. Finally, establishing structural changes of the visual pathways has been relevant in the context of new therapeutic strategies to restore retinal function: it implies that restoring retinal function may not suffice to also effectively restore vision. Future structural MRI studies can contribute to (i) further establish relationships between ocular and neurological neurodegenerative disorders, (ii) investigate whether brain degeneration in eye diseases is reversible, (iii) evaluate the use of neuroprotective medication in ocular disease, (iv) determine optimal timing for retinal implant insertion and (v) establish structural MRI examination as a diagnostic tool in ophthalmology.

PMID: 26361248 [PubMed - as supplied by publisher]

Graefes Arch Clin Exp Ophthalmol. 2015 Sep 8. [Epub ahead of print]

Assessment of retinal vessel caliber changes in eyes with non-neovascular age-related macular degeneration after progression to neovascular age-related macular degeneration.

Sarwar S, Sadiq MA, Hanout M, Nguyen QD.

PMID: 26345526 [PubMed - as supplied by publisher]

Pathogenesis

J Ocul Pharmacol Ther. 2015 Sep;31(7):366-70. Epub 2015 Jun 3.

Thrombospondin-1-Based Antiangiogenic Therapy.

Sims JN, Lawler J.

Abstract: Ocular angiogenesis is one of the underlying causes of blindness and vision impairment and may occur in a spectrum of disorders, including diabetic retinopathy, neovascular age-related macular degeneration, retinal artery or vein occlusion, and retinopathy of prematurity. As such, strategies to inhibit angiogenesis by suppressing vascular endothelial growth factor activity have proven to be effective in the clinic for the treatment of eye diseases. A complementary approach would be to increase the level of naturally occurring inhibitors of angiogenesis, such as thrombospondin (TSP)-1. This article summarizes the development of TSP-1-based inhibitors of angiogenesis.

PMID: 26352160 [PubMed - in process]

Prog Retin Eye Res. 2015 Sep 3. [Epub ahead of print]

Defects in Retinal Pigment Epithelial Cell Proteolysis and the Pathology Associated with Age-related Macular Degeneration.

Ferrington DA, Sinha D, Kaarniranta K.

Abstract: Maintenance of protein homeostasis, also referred to as "Proteostasis", integrates multiple pathways that regulate protein synthesis, folding, translocation, and degradation. Failure in proteostasis may be one of the underlying mechanisms responsible for the cascade of events leading to age-related macular degeneration (AMD). This review covers the major degradative pathways (ubiquitin-proteasome and lysosomal involvement in phagocytosis and autophagy) in the retinal pigment epithelium (RPE) and summarizes evidence of their involvement in AMD. Degradation of damaged and misfolded proteins via the proteasome occurs in coordination with heat shock proteins. Evidence of increased content of proteasome and heat shock proteins in retinas from human donors with AMD is consistent with increased oxidative stress and extensive protein damage with AMD. Phagocytosis and autophagy share key molecules in phagosome maturation as well as degradation of their cargo following fusion with lysosomes. Phagocytosis and degradation of photoreceptor outer segments ensures functional integrity of the neural retina. Autophagy rids the cell of toxic protein aggregates and defective mitochondria. Evidence suggesting a decline in autophagic flux includes the accumulation of autophagic substrates and damaged mitochondria in RPE from AMD donors. An age-related decrease in lysosomal enzymatic activity inhibits autophagic clearance of outer segments, mitochondria, and protein aggregates, thereby accelerating the accumulation of lipofuscin. This cumulative damage over a person's lifetime tips the balance in RPE from a state of para-inflammation, which strives to restore cell homeostasis, to the chronic inflammation associated with AMD.

PMID: 26344735 [PubMed - as supplied by publisher]

Epidemiology

PLoS One. 2015 Sep 10;10(9):e0137322. eCollection 2015.

Age Related Macular Degeneration and Total Hip Replacement Due to Osteoarthritis or Fracture: Melbourne Collaborative Cohort Study.

Chong EW, Wang Y, Robman LD, Aung KZ, Makeyeva GA, Giles GG, Graves S, Cicuttini FM, Guymer RH.

Abstract: Osteoarthritis is the leading cause of total hip replacement, accounting for more than 80% of all total hip replacements. Emerging evidence suggests that osteoarthritis has a chronic inflammatory component to its pathogenesis similar to age-related macular degeneration. We evaluated the association between age-related macular degeneration and total hip replacement as proxy for severe osteoarthritis or fractured neck of femur in the Melbourne Collaborative Cohort Study. 20,744 participants had complete data on both age-related macular degeneration assessed from colour fundus photographs taken during 2003-2007 and total hip replacement. Total hip replacements due to hip osteoarthritis and fractured neck of femur during 2001-2011 were identified by linking the cohort records to the Australian Orthopedic Association National Joint Replacement Registry. Logistic regression was used to examine the association between age-related macular degeneration and risk of total hip replacement due to osteoarthritis and fracture separately, adjusted for confounders. There were 791 cases of total hip replacement for osteoarthritis and 102 cases of total hip replacement due to fractured neck of femur. After adjustment for age, sex, body mass index, smoking, and grouped country of birth, intermediate age-related macular degeneration was directly associated with total hip replacement for osteoarthritis (odds ratio 1.22, 95% CI 1.00-1.49). Late age-related macular degeneration was directly associated with total hip replacement due to fractured neck of femur (odds ratio 5.21, 95% CI2.25-12.02). The association between intermediate age-related macular degeneration and an increased 10-year incidence of total hip replacement due to osteoarthritis suggests the possibility of similar inflammatory processes underlying both chronic diseases. The association of late age-related macular degeneration with an increased 10-year incidence of total hip replacement due to fractured neck of femur may be due to an increased prevalence of fractures in those with poor central vision associated with the late complications of age-related macular degeneration.

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Genetics

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Searching High-Order SNP Combinations for Complex Diseases Based on Energy Distribution Difference.

Xiaojun Ding, Jianxin Wang, Zelikovsky A, Xuan Guo, Minzhu Xie, Yi Pan.

Abstract: Single nucleotide polymorphisms, a dominant type of genetic variants, have been used successfully to identify defective genes causing human single gene diseases. However, most common human diseases are complex diseases and caused by gene-gene and gene-environment interactions. Many SNP-SNP interaction analysis methods have been introduced but they are not powerful enough to discover interactions more than three SNPs. The paper proposes a novel method that analyzes all SNPs simultaneously. Different from existing methods, the method regards an individual's genotype data on a list of SNPs as a point with a unit of energy in a multi-dimensional space, and tries to find a new coordinate system where the energy distribution difference between cases and controls reaches the maximum. The method will find different multiple SNPs combinatorial patterns between cases and controls based on the new coordinate system. The experiment on simulated data shows that the method is efficient. The tests on the real data of age-related macular degeneration (AMD) disease show that it can find out more significant multi-SNP combinatorial patterns than existing methods.

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Diet, lifestyle and low vision

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Joint Associations of Diet, Lifestyle, and Genes with Age-Related Macular Degeneration.

Meyers KJ, Liu Z, Millen AE, Iyengar SK, Blodi BA, Johnson E, Snodderly DM, Klein ML, Gehrs KM, Tinker L, Sarto GE, Robinson J, Wallace RB, Mares JA.

PURPOSE: Unhealthy lifestyles have been associated with increased odds for age-related macular degeneration (AMD). Whether this association is modified by genetic risk for AMD is unknown and was investigated.

DESIGN: Interactions between healthy lifestyles AMD risk genotypes were studied in relation to the prevalence of AMD, assessed 6 years later.

PARTICIPANTS: Women 50 to 79 years of age in the Carotenoids in Age-Related Eye Disease Study with exposure and AMD data (n = 1663).

METHODS: Healthy lifestyle scores (0-6 points) were assigned based on Healthy Eating Index scores, physical activity (metabolic equivalent of task hours/week), and smoking pack years assessed in 1994 and 1998. Genetic risk was based on Y402H in complement factor H (CFH) and A69S in age-related maculopathy susceptibility locus 2 (ARMS2). Additive and multiplicative interactions in odds ratios were assessed using the synergy index and a multiplicative interaction term, respectively.

MAIN OUTCOME MEASURES: AMD presence and severity were assessed from grading of stereoscopic fundus photographs taken in 2001-2004. AMD was present in 337 women, 91% of whom had early AMD.

RESULTS: The odds of AMD were 3.3 times greater (95% confidence interval [CI], 1.8-6.1) in women with both low healthy lifestyle score (0-2) and high-risk CFH genotype (CC), relative to those who had low genetic risk (TT) and high healthy lifestyle scores (4-6). There were no significant additive (synergy index [SI], 1.08; 95% CI, 0.70-1.67) or multiplicative (Pinteraction = 0.94) interactions in the full sample. However, when limiting the sample to women with stable diets before AMD assessment (n = 728) the odds for AMD associated with low healthy lifestyle scores and high-risk CFH genotype were strengthened (odds ratio, 4.6;

95% CI, 1.8-11.6) and the synergy index was significant (SI, 1.34; 95% CI, 1.05-1.70). Adjusting for dietary lutein and zeaxanthin attenuated, and therefore partially explained, the joint association. There were no significant additive or multiplicative interactions for ARMS2 and lifestyle score.

CONCLUSIONS: Having unhealthy lifestyles and 2 CFH risk alleles increased AMD risk (primarily in the early stages), in an or additive or greater (synergistic) manner. However, unhealthy lifestyles increased AMD risk regardless of AMD risk genotype.

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Controversies in the use of nutritional supplements in ophthalmology.

Lawrenson JG, Grzybowski A.

Abstract: Nutritional supplements are widely taken by the general population and several of these products are marketed specifically to improve eye health. The aim of this review is to summarise the evidence for the benefit of supplementation with antioxidant vitamins and other micronutrients for three of the most common eye diseases of the elderly: age-related macular degeneration (AMD), cataract and dry eye syndrome (DES). Although the potential importance of diet and nutrition in these conditions is strongly supported by data from observational studies, evidence from randomised controlled trials (RCTs) on the benefit of nutritional supplementation is generally lacking. However, there is high quality evidence to support the use of an Age-related Eye-disease Study (AREDS) supplement containing antioxidants (β-carotene, vitamin C and vitamin E) and zinc to slow progression in those at moderate to high risk of developing advanced AMD. Recent data from the AREDS2 trial provided data to suggest that β-carotene could be replaced with lutein and zeaxanthin on the based on improved safety without compromising efficacy. Although there is currently insufficient evidence to recommend the routine use of any of the commercially available supplements in cataract and DES, given the public health importance of these conditions further research into the benefit of dietary modification or nutritional supplementation should be a priority.

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