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MD Research News

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Drug treatment

Ophthalmologica. 2016 Nov 30. [Epub ahead of print]

Outcomes after a 1-Year Treatment with Ranibizumab for Diabetic Macular Edema in a Clinical Setting.

Hrarat L, Fajnkuchen F, Boubaya M, Lévy V, Sarda V, Grenet T, Nghiem-Buffet S, Chaine G, Giocanti-Auregan A.

PURPOSE: The aim of this study was to assess the efficacy and safety of ranibizumab in patients with diabetic macular edema (DME).

METHODS: We conducted a retrospective analysis of consecutive patients with vision loss due to DME who were treated with ranibizumab. All patients received a loading dose of 3 monthly injections followed by re-treatments on an as-needed basis. The primary endpoint was the change in best-corrected visual acuity (BCVA) at 12 months. Secondary endpoints were the change in central retinal thickness (CRT) and the number of intravitreal injections (IVI) at 12 months.

RESULTS: One hundred and six eyes of 78 patients were included. BCVA changed from 48.3 (20/100) letters at baseline to 59.0 letters (20/63) at 12 months ($p < 0.0001$; mean gain: +10.7 letters), and 38% of the patients had a final BCVA >70 letters. CRT decreased from 519 µm at baseline to 355 µm at 12 months ($p < 0.0001$). The threshold of the first quartile of the baseline VA was 40 letters. Patients with a baseline VA >40 letters had a higher final VA of 66 ± 14 letters (20/50) versus 43 ± 18 letters (20/125) for patients with a baseline VA ≤40 letters ($p < 0.0001$). A mean number of 5.4 (3-10) IVI were administered.

CONCLUSION: This study conducted in a clinical setting confirms the results of previous randomized trials. The final BCVA was mainly influenced by the baseline BCVA, which supports the utility of early DME treatment before patients experience a severe vision loss.

PMID: 27898414

Ophthalmologica. 2016 Dec 2. [Epub ahead of print]

Outcomes when Switching from a pro re nata Regimen to a Treat and Extend Regimen Using Aflibercept in Neovascular Age-Related Macular Degeneration.

Giannakaki-Zimmermann H, Ebneter A, Munk MR, Wolf S, Zinkernagel MS.

PURPOSE: To investigate outcomes in patients with neovascular age-related macular degeneration (AMD) switched from a pro re nata regimen (PRN) to a treat and extend regimen (TER) under aflibercept.

PROCEDURE: Thirty-two patients were observed over 2 years: the first year on PRN and the second year on TER. Best-corrected visual acuity (BCVA) and central retinal thickness (CRT) were evaluated. Intra- and subretinal fluid as well as the number of visits and injections were assessed.

RESULTS: Both regimens resulted in a stable BCVA. Patients in TER had a significant decrease of CRT after 1 year compared to 1 year of treatment on PRN ($p < 0.0001$). TER resulted in significantly less visits; however, significantly more injections were observed over the course of 1 year compared to PRN (10.25 vs. 7.5, $p < 0.0001$ and 5.97 vs. 7.5, $p = 0.0002$, respectively).

CONCLUSION: A switch from PRN to TER in patients treated with aflibercept for AMD appears to be safe.

PMID: 27907924

Ophthalmology. 2016 Nov 24. [Epub ahead of print]

Trends of Anti-Vascular Endothelial Growth Factor Use in Ophthalmology Among Privately Insured and Medicare Advantage Patients.

Parikh R, Ross JS, Sangaralingham LR, Adelman RA, Shah ND, Barkmeier AJ.

PURPOSE: To characterize the first 10 years of intravitreal anti-vascular endothelial growth factor (VEGF) medication use for ophthalmic disease, including bevacizumab, ranibizumab, and aflibercept.

DESIGN: A retrospective cohort study using administrative claims data from January 1, 2006 to December 31, 2015.

SUBJECTS: Total of 124 835 patients 18 years of age or over in the United States.

METHODS: OptumLabs Data Warehouse, which includes administrative claims data for over 100 million commercially insured and Medicare Advantage individuals, was used to identify patients receiving intravitreal anti-VEGF injections based on Current Procedural Terminology codes.

MAIN OUTCOME MEASURES: Total and annual numbers of intravitreal anti-VEGF injections, as well as injections per 1000 enrolled patients per general category of ophthalmic disease, overall and for each available medication.

RESULTS: There were 959 945 anti-VEGF injections among 124 835 patients from 2006 to 2015. Among all injections, 64.6% were of bevacizumab, 22.0% ranibizumab, and 13.4% aflibercept; 62.7% were performed to treat age-related macular degeneration (AMD), 16.1% to treat diabetic retinal diseases (including 0.9% of all injections that were for proliferative diabetic retinopathy), 8.3% to treat retinal vein occlusions, and 12.9% for all other uses. Use of bevacizumab and ranibizumab for AMD plateaued as of 2011/2012 and decreased thereafter (in 2006, 58.8 and 35.3 injections/1000 AMD patients, respectively; in 2015, 294.4 and 100.7 injections/1000), whereas use of aflibercept increased (1.1 injections/1000 AMD patients in 2011 to 183.0 injections/1000 in 2015). Bevacizumab use increased each year for diabetic retinal disease (2.4 injections/1000 patients with diabetic retinal disease in 2009 to 13.6 per 1000 in 2015) while that of ranibizumab initially increased significantly and then declined after 2014 (0.1 in 2009 to 4.0 in 2015). Aflibercept use increased each year in patients with diabetic retinal diseases and retinal vein occlusions (both <0.1 per 1000 retinal vein occlusion patients in 2011, 5.6 and 140.2 in 2015).

CONCLUSIONS: Intravitreal injections of anti-VEGF medications increased annually from 2006 to 2015. Bevacizumab was the most common medication used, despite its lacking U.S. Food and Drug Administration approval to treat ophthalmic disease, and AMD was the most common condition treated. Ranibizumab use declined after 2014 while both the absolute and relative use of bevacizumab and aflibercept increased.

PMID: 27890437

Aflibercept (New Therapeutic Indication) -- Benefit Assessment According to §35a Social Code Book V [Internet].

Editors: Institute for Quality and Efficiency in Health Care.

Source: Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2015 Jun. Extract of Dossier Assessment No. A15-11.

Excerpt: The aim of this report was to assess the added benefit of aflibercept in comparison with ranibizumab or grid laser therapy as appropriate comparator therapy (ACT) in adult patients with visual impairment due to macular oedema following branch retinal vein occlusion (BRVO). The ACT specified by the Federal Joint Committee (G-BA) as ranibizumab or grid laser therapy was followed for the present benefit assessment. This deviated from the company, which rejected grid laser therapy as ACT and specified ranibizumab as only ACT. The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 6 months were to be included in the assessment.

PMID: 27905791

Aflibercept (Eylea) -- Benefit Assessment According to §35a Social Code Book V [Internet].

Editors: Institute for Quality and Efficiency in Health Care.

Source: Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2013 Mar. Extract of Dossier Assessment No. A12-19.

Excerpt: The aim of this report is to assess the added benefit of aflibercept compared with ranibizumab as appropriate comparator therapy (ACT) in adult patients with wet age-related macular degeneration (AMD). The assessment was based on patient-relevant outcomes. No relevant study was identified where the ACT ranibizumab was used according to its approval status. Other analyses presented by the company could not be used for the benefit assessment as they did not allow to compare the benefit of aflibercept and ranibizumab. These analyses include an unpublished mathematical simulation by the manufacturer of ranibizumab from an assessment report of the European Medicines Agency (EMA), as well as extrapolations made by the company on the risk of an ocular adverse event (AE) of each intravitreal injection, and an analysis called "descriptive indirect comparison".

PMID: 27905747

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Eye (Lond). 2016 Dec 2. [Epub ahead of print]

Treatment patterns of ranibizumab intravitreal injection and dexamethasone intravitreal implant for retinal vein occlusion in the USA.

Nghiem-Buffet S, Baillif S, Regnier S, Skelly A, Yu N, Sodi A.

Purpose: Ranibizumab, an anti-vascular endothelial growth factor, and dexamethasone, a corticosteroid, have been shown to be effective in treating macular oedema secondary to retinal vein occlusion (RVO) (central RVO (CRVO) and branch RVO (BRVO)). Their real-world usage, however, has yet to be compared. We therefore evaluated ophthalmology visits for both drugs using US patient-level data.

Methods: The IMS Health Real-World Data Medical Claims database was used to identify treatment-naive patients receiving ranibizumab intravitreal injections or dexamethasone intravitreal implants between June 2010 and February 2014 who had 12 months of follow-up data. The primary outcome measure was the mean number of all ophthalmology visits for the two drugs in patients with CRVO and BRVO. Secondary outcome measures included a comparison of treatment visits, non-treatment visits, and time intervals between visits.

Results: Overall, 2822 patients received ranibizumab injections (CRVO, 1178; BRVO, 1644) and 365 received dexamethasone implants (CRVO, 191; BRVO, 174). The mean number (SD) of all ophthalmology

visits was higher for patients receiving ranibizumab injections than for those receiving dexamethasone implants (CRVO: 7.2 (3.6) vs 6.2 (3.1), P<0.001; BRVO: 7.1 (3.4) vs 6.3 (3.1), P=0.016).

Conclusions: Patients with RVO receiving ranibizumab injections had a mean of approximately one more visit to their ophthalmologist in the first 12 months of treatment than those treated with dexamethasone implants. The visit burden is therefore not substantially different and physicians should focus on the clinical benefits of these drugs when evaluating treatment options for RVO.

[PubMed - as supplied by publisher]

Ocul Immunol Inflamm. 2016 Nov 28:1-4. [Epub ahead of print]

Choroidal Neovascularization Associated with Multiple Evanescent White Dot Syndrome Treated with Intravitreal Ranibizumab.

Parodi MB, Iacono P, Zucchiatti I, Bandello F.

PURPOSE: To describe the clinical outcomes of intravitreal ranibizumab treatment for subfoveal choroidal neovascularization (CNV) associated with multiple evanescent white dot syndrome (MEWDS).

METHODS: This is a prospective, interventional, case series. All recruited patients underwent a baseline intravitreal ranibizumab injection and were monitored monthly over a 12-month follow-up, following a pro-re-nata regimen.

RESULTS: Four patients (four eyes) were included in the study. Mean best-corrected visual acuity (BCVA) changed from 0.60 ± 0.20 at baseline to 0.07 ± 0.05 logMAR at 12-month examination. Baseline central macular thickness reduced from 330 ± 32 µm to the final value of 228 ± 14 µm at the 1-year follow-up. Overall, a mean number of 2.2 ranibizumab injections were administered at the end of 12 months.

CONCLUSIONS: Intravitreal ranibizumab treatment represents a valuable therapeutic option for the management of CNV associated with MEWDS.

PMID: 27892746

Handb Exp Pharmacol. 2016 Nov 30. [Epub ahead of print]

Dry Age-Related Macular Degeneration Pharmacology.

Wright CB, Ambati J.

Abstract: Age-related macular degeneration (AMD), the most common form of irreversible blindness in the industrially developed world, can present years before a patient begins to lose vision. For most of these patients, AMD never progresses past its early stages to the advanced forms that are principally responsible for the vast majority of vision loss. Advanced AMD can manifest as either an advanced avascular form known as geographic atrophy (GA) marked by regional retinal pigment epithelium (RPE) cell death or as an advanced form known as neovascular AMD marked by the intrusion of fragile new blood vessels into the normally avascular retina. Physicians have several therapeutic interventions available to combat neovascular AMD, but GA has no approved effective therapies as of yet. In this chapter, we will discuss the current strategies for limiting dry AMD in patients. We will also discuss previous attempts at pharmacological intervention that were tested in a clinical setting and consider reasons why these putative therapeutics did not perform successfully in large-scale trials. Despite the number of unsuccessful past trials, new pharmacological interventions may succeed. These future therapies may aid millions of AMD patients worldwide.

PMID: 27900609

Am J Ophthalmol. 2016 Nov 25. [Epub ahead of print]

Real-World Outcomes of Ranibizumab Treatment for Diabetic Macular Edema in a United Kingdom National Health Service Setting.

Călugăru D, Călugăru M.

PMID: 27894510

Other treatment & diagnosis

Eye (Lond). 2016 Dec 2. [Epub ahead of print]

Impact of optical coherence tomography scanning density on quantitative analyses in neovascular age-related macular degeneration.

Velaga SB, Nittala MG, Konduru RK, Heussen F, Keane PA, Sadda SR.

Purpose: To assess the influence of varying B-scan frame-sampling densities on retinal thickness and volume measurements from spectral domain optical coherence tomography (OCT) in eyes with neovascular age-related macular degeneration (AMD).

Methods: Volume OCT data (512 × 128 macular cube over 6 × 6 mm) were collected from 39 eyes with neovascular AMD. All 128 B-scans in each image set were manually segmented, allowing quantification of the neurosensory retina, subretinal fluid (SRF), subretinal hyperreflective material (SRHM), and pigment epithelium detachment (PED). Thickness maps were generated for less dense subsets of scans, ranging from every other (64 B-scans) to every 64th (2 B-scans). For each less dense subset, foveal central subfield thickness and total macular volume (TMV) were compared with values obtained using all 128 scans (considered the reference).

Results: For each parameter, the mean absolute difference compared with the reference increased with reducing B-scan density. However, these differences did not reach statistical significance until frame-sampling density was reduced to every eighth scan (ie, 16 B-scans spaced 375 μm apart) for neurosensory retina, and every fourth scan (ie, 32 B-scans spaced 188 μm apart) for SRF, SRHM, and PED. For neurosensory retina, the mean (% error) and maximum (% error) absolute differences in TMV were 0.02 mm3 (0.24%) and 0.06 mm3 (0.79%), respectively. Similarly, at a density of 32 B-scans, mean and maximum differences for SRF were 0.004 mm3 (3.47%) and 0.02 mm3 (22.22%), respectively. The mean differences for SRHM and PED were 0.01 mm3 (8.03%) and 0.01 mm3 (4.04%), respectively.

Conclusions: A minimum of 16 equally spaced B-scans, covering a 6 × 6 mm area, appears necessary to generate retinal thickness measurements similar to those obtained using all 128 B-scans in eyes with choroidal neovascularization (CNV). When considering other CNV lesion features, a minimum of 16 B-scans for SRF and PED, and 32 B-scans for SRHM are required to generate volume maps similar to ground-truth values. These findings may have implications for the design of acquisition and grading protocols for clinical trials using OCT in neovascular AMD.Eye advance online publication, 2 December 2016; doi:10.1038/eye.2016.260.

PMID: 27911444

Ophthalmologe. 2016 Dec 1. [Epub ahead of print]

[Clinical, morphological and molecular biological characteristics of the aging eye]. [Article in German]

Böhm MR, Thomasen H, Parnitzke F, Steuhl KP.

BACKGROUND: The physiological aging of the eye is associated with loss of visual function. Age-related changes of the eye can result in ophthalmological diseases. The aim of this article is to display morphological, histological and molecular biological alterations of the aging eye.

MATERIAL AND METHODS: A web-based search and review of the literature for aging of the visual system including cornea, lens, vitreous humor, retina, retinal pigment epithelium (RPE), choroidea and optic nerve were carried out. The most important results related to morphological, histological and molecular biological changes are summarized.

RESULTS: Age-related, morphological alterations can be found in preretinal structures, e. g. cornea, lens and vitreous humor, as well as neuronal structures, such as the retina. In addition to negligible clinical signs of the aging eye, there are clinically relevant changes which can develop into pathological ophthalmological diseases. These transitions from age-related alterations to relevant ophthalmological diseases, e. g. age-related macular degeneration and glaucoma are continuous.

CONCLUSION: An understanding of aging could provide predictive factors to detect the conversion of physiological aging into pathological conditions. The derivation of physiological markers or new approaches to detection and treatment of disease-related entities associated with the risk factor aging are desirable. Translational approaches in clinical and basic science are necessary to provide new therapeutic options for relevant ophthalmological diseases in the future.

PMID: 27909796

Expert Review of Ophthalmology, 2016 Nov 4 [Epub ahead of print]

Salient features and management options of macular telangiectasia type 2: a review and update

Vaze A, Gillies M

Introduction: Initially thought to be a retinal vasculopathy macular telangiectasia (MacTel) type 2 is now believed to be a primary neuroglial disorder with secondary vascular changes. To date there is no evidence for an effective treatment of nonproliferative MacTel type 2. Patients with proliferative MacTel type 2 with decreasing visual function may benefit from intravitreal injection of vascular endothelial growth factor inhibitors.

Areas covered: A medline search using Pubmed and google scholar was conducted to identify research studies providing an overview of epidemiology, clinical features, imaging characteristics and structure-function correlation, with an emphasis on currently available treatment options for MacTel type 2.

Expert commentary: The nature of the initiating event in MacTel type 2 remains obscure. Identification of a genetic basis would be a great advance but has so far been elusive. It is likely that derangement of outer retinal metabolism plays a major role.

Invest Ophthalmol Vis Sci. 2016 Nov 1;57(14):6440-6446.

Choroidal Thickness Influences Near-Infrared Reflectance Intensity in Eyes With Geographic Atrophy Due To Age-Related Macular Degeneration.

Dolz-Marco R, Gal-Or O, Freund KB.

PURPOSE: To evaluate the effects of retinal and choroidal thickness on near-infrared reflectance (NIR) scanning laser ophthalmoscopy in eyes with geographic atrophy (GA) secondary to non-neovascular age-related macular degeneration (AMD).

METHODS: This was a cross-sectional review of the clinical records and multimodal imaging data of eyes diagnosed with GA secondary to non-neovascular AMD. Imaging modalities included color fundus photography, fundus autofluorescence, NIR, and structural spectral-domain optical coherence tomography (SD-OCT). On SD-OCT images, the foveal retina thickness and the subfoveal choroidal thickness were

measured by two independent readers. Near-infrared reflectance intensity within areas of GA was subjectively graded as hyperreflective, isoreflective, or hyporeflective and objectively estimated by using ImageJ to calculate the mean gray scale value within each GA area. A linear regression analysis was performed to model the relationship between mean NIR gray scale value and retinal and choroidal thickness.

RESULTS: One hundred four eyes of 104 patients with a mean age of 81.3 years (SD: ±8.3) were included. The area of GA was hyperreflective on NIR in 88 eyes (85%), isoreflective in 13 eyes (12%), and hyporeflective in 3 eyes (3%). The mean foveal retinal thickness was 101.5 μm (SD: ±54) showing no significant relationship with mean NIR (P = 0.464); and the mean subfoveal choroidal thickness was 172.6 μm (SD: ±114.7) showing a statistically significant relationship with mean NIR intensity in the linear regression analysis (r = 0.590; r2 = 0.348; P < 0.00001).

CONCLUSIONS: Variations in choroidal thickness appear to influence NIR intensity in areas of GA and have the potential to affect image interpretation. The recognition of this relationship may provide useful information regarding choroidal thickness.

PMID: 27893108

Exp Eye Res. 2016 Nov 24. [Epub ahead of print]

Slowed dark adaptation in older eyes; Effect of location.

Tahir HJ, Rodrigo-Diaz E, Parry NR, Kelly JM, Carden D, Murray IJ.

PURPOSE: The rate of rod sensitivity recovery following a photobleach is a basic measure of the integrity of the outer retina. Rods are selectively impaired in aging and many disorders of the retina, notably Age-Related Macular Degeneration (AMD). It is not known for certain whether the age-related deficit is a pan-retinal effect or if there are localised regions of impaired rod function. To address this important issue a dual arc stimulus was developed that samples sensitivity recovery in two retinal locations.

METHODS: Arc-shaped stimuli were presented on a black CRT screen at two locations, 6° and 11° in the inferior visual field. Following a bleach, which was localised to the stimuli, recovery of sensitivity was measured using a modified method of adjustment technique. Neutral density filters were used to extend the luminance range of the CRT. Sensitivity recovery functions were fitted by non-linear regression to a seven-parameter model.

RESULTS: Pairs of sensitivity recovery functions were generated from the stimuli. The cone phases of these functions were identical. The slopes of the S2 sections of the curves were steeper for the outer (11°) stimuli for both young ($p < 0.001$) and older ($p = 0.003$) observers. The difference between the two was the same for the two groups. The α point was reached slightly earlier for the young observers and with the outer (11°) stimulus but neither of these effects reached statistical significance. The β point occurred earlier for the outer stimuli and this effect was statistically significant only for the older group.

CONCLUSIONS: The method places minimal demands on observers. The fact that rod sensitivity recovery is slowed in the older normal eye to the same extent in the two locations suggests that this deficit may be uniform across the retina. As there are localised losses in scotopic function in AMD, the technique is ideally suited to distinguishing impaired recovery dynamics due to normal ageing from those caused by disease.

PMID: 27890475

Pathogenesis

Proc Natl Acad Sci U S A. 2016 Dec 1. [Epub ahead of print]

Reductive carboxylation is a major metabolic pathway in the retinal pigment epithelium.

Du J, Yanagida A, Knight K, Engel AL, Vo AH, Jankowski C, Sadilek M, Tran VT, Manson MA, Ramakrishnan A, Hurley JB, Chao JR.

Abstract: The retinal pigment epithelium (RPE) is a monolayer of pigmented cells that requires an active metabolism to maintain outer retinal homeostasis and compensate for oxidative stress. Using 13C metabolic flux analysis in human RPE cells, we found that RPE has an exceptionally high capacity for reductive carboxylation, a metabolic pathway that has recently garnered significant interest because of its role in cancer cell survival. The capacity for reductive carboxylation in RPE exceeds that of all other cells tested, including retina, neural tissue, glial cells, and a cancer cell line. Loss of reductive carboxylation disrupts redox balance and increases RPE sensitivity to oxidative damage, suggesting that deficiencies of reductive carboxylation may contribute to RPE cell death. Supporting reductive carboxylation by supplementation with an NAD+ precursor or its substrate α-ketoglutarate or treatment with a poly(ADP ribose) polymerase inhibitor protects reductive carboxylation and RPE viability from excessive oxidative stress. The ability of these treatments to rescue RPE could be the basis for an effective strategy to treat blinding diseases caused by RPE dysfunction.

PMID: 27911769

Vestn Oftalmol. 2016;132(5):5-14.

[Role of immunological factors in the development of myopic choroidal neovascularization]. [Article in Russian]

Shchuko AG, Zaitseva NV, Yur'eva TN, Chernykh ER, Mikhalevich IM, Grigor'eva AV.

AIM: To study the concentration of cytokines in the aqueous humor of the anterior chamber in patients with myopic choroidal neovascularization (mCNV) and to compare the results to their ophthalmic status.

MATERIAL AND METHODS: A total of 19 patients (19 eyes) with mCNV treated with intravitreal ranibizumab were included in the study. The control group consisted of 15 patients (15 eyes) with myopia who had cataract surgery. Age, sex, and refractive error distribution were similar to that in the study group. All patients underwent a detailed ophthalmic examination as well as immunological study of the aqueous humor for cytokines concentrations using flow fluorometry (Bio-Plex Pro Human Cytokine Panel, 27-Plex, Bio-Rad Laboratories, USA).

RESULTS: Significant differences in concentrations of 10 cytokines were found between the mCNV and study groups. Vascular endothelial growth factor (VEGF) level was twice as low in patients with mCNV as that in the controls (191.15±142.3 pg/ml and 320.06±170.05 pg/ml, respectively) ($p<0.05$). The other 9 cytokines were higher in mCNV, namely, platelet-derived growth factor (PDGF-BB), inflammatory and anti-inflammatory cytokines (IL-2, IL-15, IL-17A and IL-5, IL-13, respectively), tumor necrosis factor (TNFα), and chemokines (IL-8, RANTES). The degree of myopia as well as morphological and functional changes in the macular zone were shown to be in close correlation with cytokines involved in inflammation and VEGF. VEGF level appeared to be negatively related to axial eye length, refractive error, and three cytokines: IL-13, INF-γ, and RANTES. At the same time, numerous (6, 8 and more) close correlations were established between inflammatory and anti-inflammatory cytokines, chemokines, and growth factors.

CONCLUSION: Patients with mCNV have been found to have higher than usual levels of inflammatory and anti-inflammatory cytokines, chemokines, and growth factors as well as a significantly decreased VEGF concentration. Immunological status of these patients differs from that in other ocular neovascular diseases suggesting possible involvement of alternative pathogenetic mechanisms.

PMID: 27911420

Sci Rep. 2016 Dec 2;6:38342.

Analysis of the Serum Lipid Profile in Polypoidal Choroidal Vasculopathy.

Li M, Zhang X, Liao N, Ye B, Peng Y, Ji Y, Wen F.

Abstract: Polypoidal choroidal vasculopathy (PCV), the predominant subtype of neovascular age-related macular degeneration in the Asian population, is associated with genetic polymorphism of lipid metabolism. In this study, we performed the untargeted lipidomics approach of ultra-performance liquid chromatography coupled with mass spectrometry (UPLC-MS) to reveal the potential discriminating lipid profile of PCV patients in serum (21 PCV patients and 19 age-matched controls). Unsupervised principal component, supervised orthogonal partial least squares analysis, correlation analysis, and heatmap analysis were performed with the data obtained by UPLC-MS. Forty-one discriminating metabolites were identified. Receiver operating characteristic curve analysis, pathway analysis and functional analysis were performed subsequently, and platelet-activating factor (PAF) was further selected as the key indicator of the distinct lipid metabolism in PCV patients. Finally, the serum level of PAF was validated by enzyme-linked immunosorbent assay, which is significantly higher in PCV patients compared to controls (65 PCV patients and 63 age-matched controls, $p < 0.0001$), consistent with the UPLC-MS analysis. Our results suggested that PAF is considered as the major indicator of the distinct lipid metabolism in PCV patients.

PMID: 27910906

Sci Rep. 2016 Dec 1;6:37298.

In silico Mapping of Protein Unfolding Mutations for Inherited Disease.

McCafferty CL, Sergeev YV.

Abstract: The effect of disease-causing missense mutations on protein folding is difficult to evaluate. To understand this relationship, we developed the unfolding mutation screen (UMS) for in silico evaluation of the severity of genetic perturbations at the atomic level of protein structure. The program takes into account the protein-unfolding curve and generates propensities using calculated free energy changes for every possible missense mutation at once. These results are presented in a series of unfolding heat maps and a colored protein 3D structure to show the residues critical to the protein folding and are available for quick reference. UMS was tested with 16 crystal structures to evaluate the unfolding for 1391 mutations from the ProTherm database. Our results showed that the computational accuracy of the unfolding calculations was similar to the accuracy of previously published free energy changes but provided a better scale. Our residue identity control helps to improve protein homology models. The unfolding predictions for proteins involved in age-related macular degeneration, retinitis pigmentosa, and Leber's congenital amaurosis matched well with data from previous studies. These results suggest that UMS could be a useful tool in the analysis of genotype-to-phenotype associations and next-generation sequencing data for inherited diseases.

PMID: 27905547

Retina. 2016 Nov 29. [Epub ahead of print]

THE PATHOPHYSIOLOGY OF GEOGRAPHIC ATROPHY SECONDARY TO AGE-RELATED MACULAR DEGENERATION AND THE COMPLEMENT PATHWAY AS A THERAPEUTIC TARGET.

Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C.

PURPOSE: Geographic atrophy (GA) is an advanced, vision-threatening form of age-related macular degeneration (AMD) affecting approximately five million individuals worldwide. To date, there are no approved therapeutics for GA treatment; however, several are in clinical trials. This review focuses on the pathophysiology of GA, particularly the role of complement cascade dysregulation and emerging therapies targeting the complement cascade.

METHODS: Primary literature search on PubMed for GA, complement cascade in age-related macular degeneration. ClinicalTrials.gov was searched for natural history studies in GA and clinical trials of drugs

targeting the complement cascade for GA.

RESULTS: Cumulative damage to the retina by aging, environmental stress, and other factors triggers inflammation via multiple pathways, including the complement cascade. When regulatory components in these pathways are compromised, as with several GA-linked genetic risk factors in the complement cascade, chronic inflammation can ultimately lead to the retinal cell death characteristic of GA. Complement inhibition has been identified as a key candidate for therapeutic intervention, and drugs targeting the complement pathway are currently in clinical trials.

CONCLUSION: The complement cascade is a strategic target for GA therapy. Further research, including on natural history and genetics, is crucial to expand the understanding of GA pathophysiology and identify effective therapeutic targets.

PMID: 27902638

Retin Cases Brief Rep. 2016 Nov 29. [Epub ahead of print]

CYSTOID MACULAR EDEMA AND CYSTOID MACULAR DEGENERATION AS A RESULT OF MULTIPLE PATHOGENIC FACTORS IN THE SETTING OF CENTRAL SEROUS CHORIORETINOPATHY.

Astroz P, Balaratnasingam C, Yannuzzi LA.

PURPOSE: To report the pathogenic factors that account for cystoid macular edema and cystoid macular degeneration in chronic central serous chorioretinopathy (CSC).

METHODS: The clinical course and multimodal imaging findings, including fundus color photography, fundus autofluorescence, spectral-domain optical coherence tomography, and fluorescein angiography, of one eye with cystoid macular edema due to chronic CSC was documented.

RESULTS: A 44-year old woman with a history of chronic CSC presented with progressive visual decline in the right eye. Best-corrected visual acuity was 20/40. Funduscopic examination revealed diffuse retinal pigment epithelial changes and macular edema. Fluorescein angiography demonstrated perifoveal microaneurysms and leakage in a petaloid configuration. Spectral-domain optical coherence tomography demonstrated cysts at the level of the inner nuclear layer, an epiretinal membrane, vitreomacular traction, and an attenuated retinal pigment epithelial band. Central subfield thickness was 486 µm. Three intravitreal injections of aflibercept were administered over 16 weeks following which there was resolution of leakage, release of vitreomacular traction, and resolution of microaneurysms. Central subfield thickness reduced to 379 µm, but persistent intraretinal cysts were observed. There was subjective improvement in visual symptoms, but Snellen acuity remained at 20/40.

CONCLUSION: Intraretinal cystic changes in chronic CSC may be the result of multifactorial pathogenic factors and may represent the coexistence of cystoid macular edema and cystoid macular degeneration. Anti-vascular endothelial growth factor may play an important role in the treatment of cystoid macular edema caused by CSC.

PMID: 27902539

[PubMed - as supplied by publisher]

Cell Biol Toxicol. 2016 Nov 29. [Epub ahead of print]

Autophagy regulates death of retinal pigment epithelium cells in age-related macular degeneration.

Kaarniranta K, Tokarz P, Koskela A, Paterno J, Blasiak J.

Abstract: Age-related macular degeneration (AMD) is an eye disease underlined by the degradation of retinal pigment epithelium (RPE) cells, photoreceptors, and choriocapillares, but the exact mechanism of cell death in AMD is not completely clear. This mechanism is important for prevention of and therapeutic intervention in AMD, which is a hardly curable disease. Present reports suggest that both apoptosis and pyroptosis (cell death dependent on caspase-1) as well as necroptosis (regulated necrosis dependent on the proteins RIPK3 and MLKL, caspase-independent) can be involved in the AMD-related death of RPE cells. Autophagy, a cellular clearing system, plays an important role in AMD pathogenesis, and this role is closely associated with the activation of the NLRP3 inflammasome, a central event for advanced AMD. Autophagy can play a role in apoptosis, pyroptosis, and necroptosis, but its contribution to AMD-specific cell death is not completely clear. Autophagy can be involved in the regulation of proteins important for cellular antioxidative defense, including Nrf2, which can interact with p62/SQSTM, a protein essential for autophagy. As oxidative stress is implicated in AMD pathogenesis, autophagy can contribute to this disease by deregulation of cellular defense against the stress. However, these and other interactions do not explain the mechanisms of RPE cell death in AMD. In this review, we present basic mechanisms of autophagy and its involvement in AMD pathogenesis and try to show a regulatory role of autophagy in RPE cell death. This can result in considering the genes and proteins of autophagy as molecular targets in AMD prevention and therapy.

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Retinal Pre-Conditioning by CD59a Knockout Protects against Light-Induced Photoreceptor Degeneration.

Song D, Wilson B, Zhao L, Bhuyan R, Bandyopadhyay M, Lyubarsky A, Yu C, Li Y, Kanu L, Miwa T, Song WC, Finnemann SC, Rohrer B, Dunaief JL.

Abstract: Complement dysregulation plays a key role in the pathogenesis of age-related macular degeneration (AMD), but the specific mechanisms are incompletely understood. Complement also potentiates retinal degeneration in the murine light damage model. To test the retinal function of CD59a, a complement inhibitor, CD59a knockout (KO) mice were used for light damage (LD) experiments. Retinal degeneration and function were compared in WT versus KO mice following light damage. Gene expression changes, endoplasmic reticulum (ER) stress, and glial cell activation were also compared. At baseline, the ERG responses and rhodopsin levels were lower in CD59aKO compared to wild-type (WT) mice. Following LD, the ERG responses were better preserved in CD59aKO compared to WT mice. Correspondingly, the number of photoreceptors was higher in CD59aKO retinas than WT controls after LD. Under normal light conditions, CD59aKO mice had higher levels than WT for GFAP immunostaining in Müller cells, mRNA and protein levels of two ER-stress markers, and neurotrophic factors. The reduction in photon capture, together with the neurotrophic factor upregulation, may explain the structural and functional protection against LD in the CD59aKO.

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Epidemiology

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The Age-Related Macular Degeneration Complex: Linking Epidemiology and Histopathology Using the Minnesota Grading System (The Inaugural Frederick C. Blodi Lecture).

Olsen TW, Bottini AR, Mendoza P, Grossniklausk HE.

PURPOSE: To describe the histopathologic findings of the four stages of age-related macular degeneration (AMD) as defined by the Age-Related Eye Disease Study (AREDS) using the Minnesota grading system (MGS).

CLINICAL RELEVANCE: There are no animal models for AMD. Eye banks enable access to human tissue with AMD. The level of AMD (grades 1 through 4) as defined by AREDS is determined ex vivo using the MGS. The AREDS has the largest collection to date of prospectively gathered data on the natural history of AMD. Since the MGS uses the same clinical criteria as AREDS, the addition of histopathologic findings of graded tissue confirms important pathophysiology at each stage of AMD.

METHODS: Four eye bank eyes were graded according to the MGS. Only the right eyes were dissected for phenotype grading. The fellow (left) eyes were fixed for histopathologic study. The eyes were serially sectioned (7 µm) through the macula. Individual slides were examined, and a two-dimensional reconstruction of the topography of the macula was created for each donor. Selected, unstained slides were used for immunohistochemical staining. In one donor, portions of tissue were obtained for transmission electron microscopic (TEM) processing.

RESULTS: Donor 1 had a rare hard, nodular druse (MGS1). Donor 2 had intermediate confluent drusen (MGS2). Donor 3 had numerous intermediate drusen (MGS3) in the right eye. Histopathology of the fellow left showed basal laminar deposits (BLamD), soft drusen, and an area of occult choroidal neovascularization underlying the retinal pigment epithelium (RPE) with endothelial cells (CD31-positive). Donor 4 also had MGS 3 along with reticular pseudodrusen (RPD). Histologic and TEM examination demonstrated diffuse BLamD, thickening of Bruch's membrane, hard drusen, and focal nodules underlying the RPE that corresponded to the RPD. EM examination demonstrated both BLamD and electron-dense material located just external to the elastic layer of Bruch's membrane.

CONCLUSION: Eye bank eyes graded using the MGS serve as an important link to the phenotypic and epidemiologic data from the AREDS. Thus, the MGS serves as a system to study the histopathology at each stage of AMD to better understand the relevant pathophysiologic changes in disease progression.

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Features of Age-Related Macular Degeneration in the General Adults and Their Dependency on Age, Sex, and Smoking: Results from the German KORA Study.

Brandl C, Breinlich V, Stark KJ, Enzinger S, Aßenmacher M, Olden M, Grassmann F, Graw J, Heier M, Peters A, Helbig H, Küchenhoff H, Weber BH, Heid IM.

Abstract: Age-related macular degeneration (AMD) is a vision impairing disease of the central retina characterized by early and late forms in individuals older than 50 years of age. However, there is little knowledge to what extent also younger adults are affected. We have thus set out to estimate the prevalence of early AMD features and late AMD in a general adult population by acquiring color fundus images in 2,840 individuals aged 25 to 74 years of the Cooperative Health Research in the Region of Augsburg project (KORA) in South Germany. Among the 2,546 participants with gradable images for each eye, 10.9% (n = 277) had early AMD features (applying the 9-step Age-Related Eye Disease Study Severity Scale), 0.2% (n = 6) had late AMD. Prevalence increased with age, reaching 26.3% for early AMD features and 1.9% for late AMD at the age 70+. However, signs of early AMD were found in subjects as young as 25 years, with the risk for early AMD features increasing linearly by years of age in men, and, less consistent with a linear increase, in women. Risk for early AMD features increased linearly by pack years of smoking in men, not in women, nor was there any association with other lifestyle or metabolic factors. By providing much sought-after prevalence estimates for AMD from Central Europe, our data underscores a substantial proportion of the adult population with signs of early AMD, including individuals younger than 50 years. This supports the notion that early AMD features in the young might be under-acknowledged.

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Genetics

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A decade of age-related macular degeneration risk models: What have we learned from them and where are we going?

Zhang M, Baird PN.

Abstract: The genomic revolution has revealed the complexity of multifactorial diseases, making the development of effective diagnostics extremely challenging. In turn, the prospect of precision medicine as applied through targeted therapeutic treatments continues to remain largely elusive. Age-related macular degeneration (AMD) as a complex disease falls under this category, despite it being one of the most well characterized multifactorial diseases. This reflects both the extent of identified genetic components and known environmental risk factors. Additional considerations in dissecting out the roles played by genetic and non-genetic risk factors arise through the rapid increase in prevalence of AMD with age and the varying time periods over which disease progression can occur, complicating efforts to discriminate between "progressors" and non-"progressors." As a consequence, extensive research into the aetiology of AMD is yet to realize a clinically acceptable predictive test. This review covers the current climate of risk models in late AMD but will focus mainly on genetic risk factors as well as the types of models that have currently been employed in the AMD modelling literature.

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GWAS study using DNA pooling strategy identifies association of variant rs4910623 in OR52B4 gene with anti-VEGF treatment response in age-related macular degeneration.

Riaz M, Lorés-Motta L, Richardson AJ, Lu Y, Montgomery G, Omar A, Koenekoop RK, Chen J, Muether P, Altay L, Schick T, Fauser S, Smailhodzic D, van Asten F, de Jong EK, Hoyng CB, Burdon KP, MacGregor S, Guymer RH, den Hollander AI, Baird PN.

Abstract: Pooled DNA based GWAS to determine genetic association of SNPs with visual acuity (VA) outcome in anti-vascular endothelial growth factor (anti-VEGF) treated neovascular age-related macular degeneration (nAMD) patients. We performed pooled DNA based GWAS on 285 anti-VEGF treated nAMD patients using high density Illumina 4.3 M array. Primary outcome was change in VA in Early Treatment Diabetic Retinopathy Study (ETDRS) letters after 6 months of anti-VEGF treatment (patients who lost ≥5 ETDRS letters classified as non-responders and all remaining classified as responders). GWAS analysis identified 44 SNPs of interest: 37 with strong evidence of association ($p < 9 \times 10\text{-}8$), 2 in drug resistance genes ($p < 5 \times 10\text{-}6$) and 5 nonsynonymous changes ($p < 1 \times 10\text{-}4$). In the validation phase, individual genotyping of 44 variants showed three SNPs (rs4910623 $p = 5.6 \times 10\text{-}5$, rs323085 $p = 6.5 \times 10\text{-}4$ and rs10198937 $p = 1.30 \times 10\text{-}3$) remained associated with VA response at 6 months. SNP rs4910623 also associated with treatment response at 3 months ($p = 1.5 \times 10\text{-}3$). Replication of these three SNPs in 376 patients revealed association of rs4910623 with poor VA response after 3 and 6 months of treatment ($p = 2.4 \times 10\text{-}3$ and $p = 3.5 \times 10\text{-}2$, respectively). Meta-analysis of both cohorts (673 samples) confirmed association of rs4910623 with poor VA response after 3 months ($p = 1.2 \times 10\text{-}5$) and 6 months ($p = 9.3 \times 10\text{-}6$) of treatment in nAMD patients.

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Diet, lifestyle and low vision

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Intake of key micronutrients and food groups in patients with late-stage age-related macular degeneration compared with age-sex-matched controls.

Gopinath B, Liew G, Russell J, Cosatto V, Burlutsky G, Mitchell P.

BACKGROUND: Knowledge of the risk factor profile of patients presenting with late-stage age-related macular degeneration (AMD) could help identify the most frequent modifiable AMD precursors among people who are referred for treatment. We aimed to assess dietary behaviours by comparing adjusted mean intakes of micronutrients and major food groups (fruits, vegetables, fish) among patients with AMD and a sample of age-sex-matched controls.

METHODS: Cross-sectional analysis of 480 late AMD cases and 518 population-based age-sex-matched controls with no AMD signs. AMD cases (aged 60+ years) were those presenting for treatment to a hospital eye clinic in Sydney, Australia, during 2012-2015. The comparator group were obtained from a cohort study (Blue Mountains Eye Study; Sydney, Australia) during 2002-2009. Dietary intake was assessed using a semiquantitative food-frequency questionnaire. AMD lesions were assessed from retinal photographs.

RESULTS: After multivariable adjustment, patients with late-stage AMD compared with controls had significantly lower intakes of vitamin E (7.4 vs 9.8 mg/day; p<0.0001), beta-carotene (6232 vs 7738 µg/day; p<0.0001), vitamin C (161 vs 184 mg/day; p=0.0002) and folate (498.3 vs 602 µg/day; p<0.0001); but had higher intakes of zinc (13.0 vs 11.9 mg/day; p<0.0001). A significantly lower proportion of patients with late AMD met the recommended intake of vegetables than controls: 52.9% versus 64.5%; p=0.0002.

CONCLUSIONS: This study showed significant differences in intakes of vitamins C and E, beta-carotene, folate and vegetables between patients with late-stage AMD and healthy controls, and thus has provided a better understanding of the nutritional intake of patients presenting with advanced AMD.

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The association of smokeless tobacco use and pack-years of smokeless tobacco with age-related macular degeneration in Indian population.

Srinivasan S, Swaminathan G, Kulothungan V, Sharma T, Raman R.

PURPOSE: To explore the association of use and the influence of pack-year use of smokeless tobacco versus no use with that of early and late age-related macular degeneration (AMD) in rural and urban south Indian population. We hypothesized that the use and pack-years of use would be significantly associated with both early and late AMD. We therefore sought to examine subjects who gave a history of using smokeless tobacco and we quantified the usage as pack-years, to examine the association with that of early and late AMD.

MATERIALS AND METHODS: This was part of Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular-genetics Study (SN-DREAMS II) that was conducted between 2007-2010. Subjects aged 60 years or older or those turned 60 in the calendar, with a history of using smokeless tobacco were noted along with duration and number of pack use per day. Smokeless tobacco was defined as chewed-tobacco (loose leaves) and/or snuff (finely chopped tobacco). Subjects underwent detailed ophthalmic evaluation including cataract grading using the Lens Opacities Classification System (LOCS III) and 45° 4-field stereoscopic fundus photography and AMD evaluation. Pack-years of smokeless tobacco use was stratified as <15, 15-34, and ≥35 years; the association of tobacco use and pack-years of use with that of early and late AMD was examined. A p-value of < 0.05 was considered statistically significant.

RESULTS: The number of smokeless tobacco users was significantly higher in rural (n = 767) than in urban groups (n = 281), p < 0.001. Of the 1048 users, 238 subjects (23%) provided details regarding quantification of use. There were no significant differences in the pack-years between rural and urban areas, p = 0.756 or that between AMD and no AMD, p = 0.562. Use of smokeless tobacco compared with no use was

significantly associated with late AMD, OR= 3.178, 95% CI: 1.095, 9.227, p = 0.033, when adjusted for age, gender, rural-urban differences, presence of diabetes, socioeconomic status, systolic and diastolic blood pressure, total cholesterol, low-density and high-density lipoprotein levels. The association was not significant for early AMD, p = 0.582. The pack-years of use did not show a statistically significant association with early or late AMD. Furthermore, out of the 1048 subjects, 547 reported as using areca nut. Of which, 415 (75.8%) subjects had no AMD, 119 (21.7%) showed evidence of early AMD, and 13 (2.4%) had late AMD. There was no significant association between the use of areca nut and early AMD, (X 2 (1, N = 930) =2.345, p = 0.126) or with that of late AMD (X2 (1, N = 761) =0.075, p = 0.785).

CONCLUSIONS: Smokeless tobacco use compared with no use, is associated with late AMD, regardless of the pack-years of use. Tobacco use is a modifiable risk factor. Efforts to reduce or stop the use of smokeless tobacco is indicated in an effort to prevent this vision loss in relation to late AMD.

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Functional Reading Independence (FRI) Index: A New Patient-Reported Outcome Measure for Patients With Geographic Atrophy.

Kimel M, Leidy NK, Tschosik E, Dolan C, Souied EH, Varma R, Bressler NM.

PURPOSE: To develop and validate the Functional Reading Independence (FRI) Index, a new patient-reported outcome measure assessing reading activities in individuals with geographic atrophy (GA) due to age-related macular degeneration.

METHODS: The Index was developed through expert consultation and qualitative patient interviews. Reliability, validity, and responsiveness were tested with data from the Mahalo study (NCT01229215) of lampalizumab in patients with GA.

RESULTS: Qualitative interviews (n = 40) yielded a 10-item FRI Index, which was refined to seven items in quantitative testing (n = 100). Strong internal consistency (marginal reliability = 0.90) and reproducibility (intraclass correlation coefficient = 0.86) were shown. Known-group validity testing for baseline mean FRI Index scores showed differences (mean [SD]) between patients with Minnesota Low-Vision Reading test reading speed ≥80 vs. <80 words per minute (3.0 [0.7] vs. 1.9 [0.7]; P < 0.001), and between patients above vs. below median values on the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25) score (2.9 [0.7] vs. 2.1 [0.8]; P < 0.001). Convergent validity with binocular measures was strong (Spearman's correlation = 0.66 for reading speed, 0.72 for NEI-VFQ-25). Analysis of sensitivity to change revealed mean FRI Index score changes for patients with GA lesion size growth ≥2.5 mm2/18 months of -0.41 (0.70) vs. -0.13 (0.61) for patients with lesion growth <2.5 mm2/18 months (P = 0.07).

CONCLUSIONS: The FRI Index demonstrated good reliability and validity in patients with GA. Further study in a broader GA population is warranted to confirm responsiveness.

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