FEATURED ARTICLE

Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy: Longitudinal Evaluation in Age-Related Macular Degeneration.

Opthamology 2022 Sep 11

Wu Z, Goh KL, Hodgson LAB, Guymer RH.

Purpose: To examine the association between incomplete retinal pigment epithelial and outer retinal atrophy (iRORA) on optical coherence tomography (OCT) imaging and the subsequent risk of developing geographic atrophy (GA) defined on conventional color fundus photography (CFP), and to compare this with the specific features that define nascent geographic atrophy (nGA). DESIGN: Retrospective analysis of data from a longitudinal study.

Participants: Two-hundred and eighty eyes from 140 participants with bilateral large drusen without specific nGA defining features or late AMD at baseline.

Methods: OCT imaging and CFP was performed at baseline and then at six-monthly intervals for up to 36 months. Eyes that developed neovascular AMD were censored at the day it was detected. OCT volume scans were graded for the presence of iRORA and nGA separately, and CFPs were graded for the presence of GA. MAIN OUTCOME MEASURES: Association with and variance explained in time to GA development.

Results: A total of 58 (21%) eyes from 46 (33%) participants had iRORA at baseline, and a further 87 (31%) eyes developed iRORA over the follow-up period. Time-to-event analyses demonstrated that prevalent or incident iRORA was associated with an increased rate of GA development (adjusted hazard ratio [HR] = 12.1; P = 0.021), as was incident nGA (adjusted HR = 78.6; P < 0.001). However, only the specific nGA features (adjusted P < 0.001) and not iRORA (adjusted P = 0.520) were associated with an increased rate of GA development when both features were included in the same multivariable model. The proportion of variance explained in the time to GA development by iRORA itself (R2 = 43%) was significantly lower than explained by nGA alone (R2 = 91%; P = 0.010).

Conclusions: In this cohort, iRORA is a significant risk factor for GA development, but its association with GA development appears to be accounted for by the development of the specific features that define nGA. Whilst requiring replication, these findings provide useful guidance on the relative utility of nGA and iRORA as risk factors for GA and as potential surrogate endpoints for future interventional studies in the early stages of AMD.

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DRUG TREATMENT

Characterising treatment outcomes of patients achieving quarterly aflibercept dosing for neovascular age-related macular degeneration: real-world clinical outcomes from a large tertiary care centre.

Eye (London, England) 2022 Sep 9

Fu DJ, Hanumunthadu D, Keenan TDL, Wagner S, Balsakas K, Keane PA, Patel PJ.

Background and objective: To evaluate the proportion of patients achieving a 12-week (q12) aflibercept dosing interval in patients with neovascular age-related macular degeneration (nAMD).

Patients and methods: Retrospective, comparative, non-randomised electronic medical record (EMR) database study of the Moorfields database of treatment-naïve nAMD eyes. Extraction criteria included at least 7 aflibercept injections in first year of treatment, AMD in the diagnosis field of EMR, and minimum of 1 year follow-up data.

Results: There were 2416 eyes of 2163 patients started on anti-vascular endothelial growth factor (anti-VEGF) between 01-11-2013 & 14-02-2020 who had received at least 7 aflibercept intravitreal injections (electronic database accessed March 2021). Of these, 1674 (68%) eyes of 1537 patients had at least one q12 dosing interval (>=84 and < =98 days between injections) during the first 2 years of treatment. This included 926 (61.8%) female patients and 856 (right eyes age at 1st injection), 936 (62.4%) Caucasian, and 32 (2.1%) Afro-Caribbean patients. The median time to the first q12 injection (95% confidence interval) was 1.76 years (1.70-1.86) with mean (±SD) of 11.8 (±6.0) injections. Visual acuity (ETDRS letters) of the eyes without q12 injection and eyes with a q12 injection was 57.9 ± 14.7 and 56.7 ± 14.8 respectively at baseline, 61.4 ± 18.1 and 63.0 ± 15.9 respectively at 12 months and 61.2 ± 20.1 and 61.1 ± 17.8 respectively at 24 months.

Conclusion: 68% of eyes were able to achieve a q12 injection dose within the first 2 years of treatment. Eyes achieving a q12 injection in the first 2 years achieved a similar visual acuity outcome at both 1 and 2-year follow-up to those unable to do so, with a fewer number of total injections.

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Difference in characteristics and lesion reactivation between type 3 macular neovascularization with and without subretinal fluid at baseline.

Graefe's archive for clinical and experimental ophthalmology 2022 Sep 16

Kim JH, Kim JW, Kim CG.

Purpose: To compare the characteristics and incidence rates of lesion reactivation after anti-vascular endothelial growth factor (VEGF) treatment in type 3 macular neovascularization (MNV) with and without subretinal fluid (SRF) at baseline.

Methods: This retrospective study included 95 patients diagnosed with type 3 MNV. After the initial loading injections, re-treatment was performed when lesion reactivation occurred defined as the re-accumulation of subretinal or intraretinal fluid or the new development of a retinal/subretinal hemorrhage. The differences in the baseline characteristics and the incidence rates of lesion reactivation were compared between patients with SRF (SRF group, n = 42) and those without SRF (non-SRF group, n = 53).

Results: At diagnosis, the mean visual acuity was worse (0.68 ± 0.41 vs 0.50 ± 0.36; P = 0.032), mean central retinal thickness was greater (515.4 ± 145.9 µm vs 383.8 ± 105.5 µm; P < 0.001), and the incidence of focal retinal hemorrhages was higher (90.5% vs 66.0%; P = 0.005) in the SRF group than in the non-SRF group. In the SRF group, the first lesion reactivation was noted in 89.7% at a mean of 5.8 ± 4.4 months after the third injection. In the non-SRF group, the first lesion reactivation was noted in 70.6% at a mean of 6.1 ± 3.8 months. There was a significant difference in lesion reactivation between the two groups (P = 0.019).

Conclusions: The difference in the baseline characteristics and incidence of lesion reactivation between type 3 MNV with and without SRF suggests that the presence of SRF may be indicative of more advanced disease with a high risk of visual deterioration. This result also suggests the need for more active treatment to preserve vision in patients with SRF.

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GENETICS

Systems genomics in age-related macular degeneration.

Experimental Eye Research 2022 Sep 12

den Hollander AI, Mullins RF, Orozco LD, Voigt AP, Chen HH, Strunz T, Grassmann F, Haines JL, Kuiper JJW, Tumminia SJ, Allikmets R, Hageman GS, Stambolian D, Klaver CCW, Boeke JD, Chen H, Honigberg L, Katti S, Frazer KA, Weber BHF, Gorin MB.

Genomic studies in age-related macular degeneration (AMD) have identified genetic variants that account for the majority of AMD risk. An important next step is to understand the functional consequences and downstream effects of the identified AMD-associated genetic variants. Instrumental for this next step are 'omics' technologies, which enable high-throughput characterization and quantification of biological molecules, and subsequent integration of genomics with these omics datasets, a field referred to as systems genomics. Single cell sequencing studies of the retina and choroid demonstrated that the majority of candidate AMD genes identified through genomic studies are expressed in non-neuronal cells, such as the retinal pigment epithelium (RPE), glia, myeloid and choroidal cells, highlighting that many different retinal and choroidal cell types contribute to the pathogenesis of AMD. Expression quantitative trait locus (eQTL) studies in retinal tissue have identified putative causal genes by demonstrating a genetic overlap between gene regulation and AMD risk. Linking genetic data to complement measurements in the systemic circulation has aided in understanding the effect of AMD-associated genetic variants in the complement system, and supports that protein QTL (pQTL) studies in plasma or serum samples may aid in understanding the effect of genetic variants and pinpointing causal genes in AMD. A recent epigenomic study fine-mapped AMD causal variants by determing regulatory regions in RPE cells differentiated from induced pluripotent stem cells (iPSC-RPE). Another approach that is being employed to pinpoint causal AMD genes is to produce synthetic DNA assemblons representing risk and protective haplotypes, which are then delivered to cellular or animal model systems. Pinpointing causal genes and understanding disease mechanisms is crucial for the next step towards clinical translation. Clinical trials targeting proteins encoded by the AMD-associated genomic loci C3, CFB, CFI, CFH, and ARMS2/HTRA1 are currently ongoing, and a phase III clinical trial for C3 inhibition recently showed a modest reduction of lesion growth in geographic atrophy. The EYERISK consortium recently developed a genetic test for AMD that allows genotyping of common and rare variants in AMD-associated genes. Polygenic risk scores (PRS) were applied to quantify AMD genetic risk, and may aid in predicting AMD progression. In conclusion, genomic studies represent a turning point in our exploration of AMD. The results of those studies now serve as a driving force for several clinical trials. Expanding to omics and systems genomics will further decipher function and causality from the associations that have been reported, and will enable the development of therapies that will lessen the burden of AMD.

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REVIEWS

Characterisation of macular neovascularisation subtypes in age-related macular degeneration to optimise treatment outcomes.

Eye (London, England) 2022 Sep 14

Mathis T, Holz FG, Sivaprasad S, Yoon YH, Eter N, Chen LJ, Koh A, Cunha de Souza E, Staurenghi G.

The aim of this review is to identify the common characteristics and prognoses of different subtypes of neovascular age-related macular degeneration (nAMD). We also propose recommendations on how to tailor treatments to the subtype of neovessels to optimise patient outcomes. The authors, selected members of the Vision Academy, met to discuss treatment outcomes in nAMD according to macular neovascularisation (MNV) subtypes, using evidence from a literature search conducted on the PubMed database (cut-off date: March 2019). This review article summarises the recommendations of the Vision Academy on how the characterisation of MNV subtypes can optimise treatment outcomes in nAMD. The identification of MNV subtypes has been facilitated by the advent of multimodal imaging. Findings from fluorescein angiography, indocyanine green angiography and spectral-domain optical coherence tomography collectively help refine and standardise the determination of the MNV subtype. To date, three subtypes have been described in the literature and have specific characteristics, as identified by imaging. Type 1 MNV is associated with better long-term outcomes but usually requires more intense anti-vascular endothelial growth factor dosing. Type 2 MNV typically responds quickly to treatment but is more prone to the development of fibrotic scars, which may be associated with poorer outcomes. Type 3 MNV tends to be highly sensitive to anti-vascular endothelial growth factor treatment but may be associated with a higher incidence of outer retinal atrophy, compared with other subtypes. Accurately assessing the MNV subtype provides information on prognosis and helps to optimise the management of patients with nAMD.

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Cystoid macular oedema without leakage in fluorescein angiography: a literature review.

Eye (London, England) 2022 Sep 10

Naseripour M, Hemmati S, Chaibakhsh S, Gordiz A, Miri L, Abdi F.

Cystoid macular oedema (CMO), which is defined as a macular thickening and cystic changes due to accumulation of fluid, could be asymptomatic and only diagnosed using paraclinical techniques. Fluorescein angiography (FA) and optical coherence tomography (OCT) are useful in detecting CMO in clinical practice. Non-leaking CMO, also known as angiographically silent CMO, is referred to as cases of CMO without leakage in fluorescein angiography. This type of CMO has been reported in some retinal dystrophies, in cases of maculopathy as a side effect of certain drugs, and also in some systemic disorders. The exact mechanism and treatment options for this type of CMO are still not clear. This literature review aims to discuss different causes of non-leaking CMO, proposed mechanisms, and management options. Three sections including drugs, retinal dystrophies, and systemic disorders are discussed in this review.

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NUTRITION AND LIFESTYLE

Potential roles of dietary zeaxanthin and lutein in macular health and function.

Nutrition Reviews 2022 Sep 12

Li X, Holt RR, Keen CL, Morse LS, Zivkovic AM, Yiu G, Hackman RM.

Lutein, zeaxanthin, and meso-zeaxanthin are three xanthophyll carotenoid pigments that selectively concentrate in the center of the retina. Humans cannot synthesize lutein and zeaxanthin, so these compounds must be obtained from the diet or supplements, with meso-zeaxanthin being converted from lutein in the macula. Xanthophylls are major components of macular pigments that protect the retina through the provision of oxidant defense and filtering of blue light. The accumulation of these three xanthophylls in the central macula can be quantified with non-invasive methods, such as macular pigment optical density (MPOD). MPOD serves as a useful tool for assessing risk for, and progression of, age-related macular degeneration, the third leading cause of blindness worldwide. Dietary surveys suggest that the dietary intakes of lutein and zeaxanthin are decreasing. In addition to low dietary intake, pregnancy and lactation may compromise the lutein and zeaxanthin status of both the mother and infant. Lutein is found in modest amounts in some orange- and yellow-colored vegetables, yellow corn products, and in egg yolks, but rich sources of zeaxanthin are not commonly consumed. Goji berries contain the highest known levels of zeaxanthin of any food, and regular intake of these bright red berries may help protect against the development of age-related macular degeneration through an increase in MPOD. The purpose of this review is to summarize the protective function of macular xanthophylls in the eye, speculate on the compounds' role in maternal and infant health, suggest the establishment of recommended dietary values for lutein and zeaxanthin, and introduce goji berries as a rich food source of zeaxanthin.

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RISK OF DISEASE

Risk Factors for Progression of Age-Related Macular Degeneration: Population-Based Amish Eye Study.

Journal of clinical medicine 2022 Aug 30

Nittala MG, Corvi F, Maram J, Velaga SB, Haines J, Pericak-Vance MA, Stambolian D, Sadda SR.

Objective: To evaluate the optical coherence tomography (OCT)-based risk factors for progression to late age-related macular degeneration (AMD) in a population-based study of elderly Amish.

Methods: A total of 1332 eyes of 666 consecutive subjects who completed a 2-year follow-up visit were included in this multicenter, prospective, longitudinal, observational study. Imaging features were correlated with 2-year incidence of late AMD development. Odds ratios for imaging features were estimated from logistic regression. Baseline OCT images were reviewed for the presence of drusen volume ≥0.03 mm3 in the central 3 mm ring, intraretinal hyperreflective foci (IHRF), hyporeflective drusen cores (hDC), subretinal drusenoid deposits (SDD), and drusenoid pigment epithelium detachment (PED). Subfoveal choroidal thickness, drusen area, and drusen volume within 3 and 5 mm circles centered on the fovea were also assessed.

Results: Twenty-one (1.5%) of 1332 eyes progressed to late AMD by 2 years. The mean age of the study subjects was 65 ± 10.17 (±SD) years and 410 subjects were female. Univariate logistic regression showed that drusen area and volume in both 3 mm and 5 mm circles, subfoveal choroidal thickness, drusen volume ≥ 0.03 mm3 in the 3 mm ring, SDD, IHRF, and hDC were all associated with an increased risk for development of late AMD. The multivariate regression model identified that drusen volume in the 3 mm ring (OR: 2.59, p = 0.049) and presence of IHRF (OR: 57.06, p < 0.001) remained as independent and significant risk factors for progression to late AMD.

Conclusions: This population-based study confirms previous findings from clinic-based studies that high central drusen volume and IHRF are associated with an increased risk of progression to late AMD. These findings may be of value in risk-stratifying patients in clinical practice or identifying subjects for early intervention clinical trials.

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PATIENT EXPERIENCE

Increased probability of mood disorders after age-related macular degeneration: a population-based cohort study.

Scientific reports 2022 Sep 8

Lee CY, Chen HC, Huang JY, Lai CC, Lin HY, Yang SF, Wu WC.

We aim to investigate the association of mood disorders with age-related macular degeneration (AMD). This retrospective cohort study used data from 2000 and 2016 from National Health Insurance Research Database (NHIRD) in Taiwan. Patients with AMD diagnosis formed the exposed group, and an age- and sex-matched group without AMD served as the nonexposed group. Main outcomes were the incidence of mood disorders including psychological counseling, behavior therapy, sleep or anxiety-related disorders, and major depressive disorders (MDDs) in the exposed and non-exposed groups. The Cox proportional hazard regression analysis was used to evaluate the incidence and adjusted hazard ratio (aHR) of mood disorders. A total of 5916 and 11,832 individuals with and without AMD were enrolled into the exposed and nonexposed groups. There were 1017 (17.19%) and 1366 (11.54%) episodes of mood disorders occurred in the exposed and nonexposed groups, respectively. The aHRs of any psychological counseling, behavioral therapy, sleep or anxiety-related disorders, and MDD were significantly higher in patients with AMD than in those without AMD (all P < 0.05). Besides, patients with dry-AMD, participants aged 50-70 years, and women with AMD had a higher incidence of mood disorders (all P < 0.05) than did non-AMD individuals, patients > 70 years, and women without AMD. In conclusion, AMD occurrence leads to an increased rate of mood disorders, particularly among those with dry-AMD, middle aged participants (aged 50-70), and women.

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ADVERSE DRUG EVENTS

A Literature Review of Ozanimod Therapy in Inflammatory Bowel Disease: From Concept to Practical Application.

Theraputics and clinical risk management 2022 Sep 8

Becher N, Swaminath A, Sultan K.

Inflammatory bowel disease (IBD), namely Ulcerative Colitis (UC) and Crohn's Disease (CD), is believed to be due to a dysregulation of the innate immune response. The complexity of the immune cascade offers both a challenge and an opportunity to researchers seeking out new treatments for IBD, as various points along the inflammatory pathways can be targeted for interruption. Sphinogosine-1-phosphate (S1P) is a phospholipid molecule with wide ranging biological effects caused by binding five known S1P receptor subtypes. Ozanimod is a small molecule drug that selectively targets S1P receptors 1 and 5 which play a crucial role in lymphocyte trafficking. In clinical trials for both UC and CD, it has been shown to induce a reversible lymphopenia which correlates with response to therapy. Reported adverse events include infection, anemia, and elevated liver enzymes. Rare instances of bradycardia, heart block, and macular edema were also reported. As a newly available therapy approved for UC patients, we aim to summarize ozanimod's novel mechanism of action, pre-clinical and clinical trial results, and to give context to this newly available drug that gastroenterologists may utilize in their treatment algorithm.

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