7/15/2022 09:10 am

Dry AMD 2 Symposium

Inhibition of C1q Protects Photoreceptor Synapses in a Light Damage Model and Is a Potential Treatment for Geographic Atrophy

- Patrick Williams, MD
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- Ellen Cahir-McFarland
- Ted Yednock
- Larry Mattheakis

Objective:
What is the role of C1q and the classical complement pathway in progression of geographic atrophy secondary to age-related macular degeneration?

Purpose:
To examine expression and tissue localization of complement proteins in mouse retina exposed to light damage and determine potential therapeutic benefit of classical complement inhibition in this model.

Methods:
Balb/c mice were exposed to white light to cause retinal damage and observed at Day 1, 3 and 7 post light exposure. Classical complement component levels were measured in retina lysates by ELISA. C1q expression in the tissue and microglia engulfment of synapses were assessed. To test the role of the classical complement pathway in photoreceptor cell damage, C1q activity was pharmacologically blocked by intravitreal injection of a C1q inhibitory antibody. Retina specimens from patients with GA (San Diego Eye Bank) were also evaluated to determine C1q deposition.

Results:
Progressive loss of photoreceptor synapses and cell bodies, as well as an increase in microglial cells across the outer plexiform (OPL, synapses) and outer nuclear layers (ONL, cell bodies), was observed in mice exposed to light damage. C1q expression was induced in microglia and was localized on photoreceptor synapses and cell bodies following light damage. Significant correlation between levels of C1q in the OPL and ONL and photoreceptor synapse and cell body loss was observed. C1q-tagged synapses were engulfed by microglial cells upon damage, suggesting a causal relationship. Treatment with a C1q inhibitory antibody normalized complement component levels. Preliminary evidence showed reduced photoreceptor synapse loss, reduced cell body loss, and reduced inflammation. C1q deposition on photoreceptor synapses was observed in human GA retinal tissue, suggesting that this mechanism may be operative in humans.

Conclusion:
We provide the first evidence of C1q deposition on photoreceptor synapses in a light exposure model of retinal damage in mice and human GA tissue. Preliminary results suggest that inhibiting C1q protects against photoreceptor neuron damage. A randomized, multi-center, Phase 2 trial of intravitreal ANX007 dosed monthly and every other month in patients with GA is underway.

IRB APPROVAL

7/15/2022 09:16 am

Dry AMD 2 Symposium

Platform for Screening Compounds for Treatment of AMD Using iPSC-derived human RPE: Examples Using Elamipretide and SBT-272

- Lucian Del Priore, MD, PhD
- Jie Gong
- Huey Cai
- Mark Fields, PhD

Objective:
To describe our platform for screening drugs effectve in inhibiting progression of AMD, RPE

Purpose:
Identification of compounds that may be of therapeutic benefit in inhibiting progression of AMD is limited by the absence of good animal models as well as a clear understanding of the biology of disease progression. Dysfunction of retinal pigment epithelial (RPE) cells is a key feature of AMD pathogenesis and likely occurs early in the disease. Somatic cells harvested from AMD patients can be reprogrammed to form RPE and thereby model patient-specific disease. We have reported previously that iPSC-derived RPE from AMD patients exhibit a retinal degenerative phenotype and a distinct transcriptome compared to controls. Here, we use an *in vitro* model of AMD to evaluate the therapeutic efficacy of elamipretide and SBT-272 on RPE derived from AMD patients.

Methods:
iPSC-derived RPE were generated from AMD patients and patients with no history of AMD. To test the therapeutic efficacy of elamipretide and SBT-272, cell viability was analyzed on nitrite-modified extracellular matrix (ECM), a typical modification of aged Bruch's membrane, for 48 hrs. DNA microarrays were used to elucidate gene expression in AMD-derived RPE cultured on nitrite-modified ECM.

Results:
AMD-derived RPE exhibited reduced ability to survive on nitrite-modified ECM. Treatment with both elamipretide and SBT-272 significantly improved cell viability on nitrite-modified ECM. Hierarchical clustering analysis reveals that the AMD-derived RPE segregate into two distinct clusters on nitrite-modified ECM vs. unmodified ECM. Nitration of ECM increases expression of complement component genes, complement C1R (C1R), complement component 3 (C3) and complement C4A (C4A), among others. Both compounds reverse this trend. Both drugs increase expression of complement regulatory genes including complement factor H-related protein 2 (CFHR2). Both drugs also alter the pattern of many mitochondrial-related genes such as glutaminase.

Conclusion:
Treatment with elamipretide and SBT-272 significantly improve the ability of AMD-derived RPE to survive on nitrite-modified ECM. Treatment with elamipretide and SBT-272 alter expression of mitochondrial and complement-related genes after nitration of ECM. Disease models using patient-derived iPSC-derived RPE may help pave the way for the development novel therapeutic strategies for AMD.

IRB APPROVAL

7/15/2022 09:22 am

Dry AMD 2 Symposium

Screening Mitochondrial-Targeted Drugs in iPSC-RPE from Patients With Dry Age-Related Macular Degeneration

- Sandra Montezuma, MD, FASRS
- Deborah Ferrington, BS, MEd, PhD
- James Dutton, PhD
- heidi roehrich, master
- Rebecca Kapphahn
- Madilyn Stahl
- Zhaohui Geng, PhD
- Mara Ebeling

Objective:
The purpose of this study is to screen drugs that could be used to prevent RPE loss in patients with dry AMD, using culture patient-specific iPSC-RPE approach.

Purpose:
The ability to generate and culture patient-specific iPSC-RPE provides a feasible platform for personalized testing of potential therapeutics.

Methods:
The severity of AMD was assessed by eye examination and fundus image analysis using the criteria established by the Age-related Eye Disease Study (AREDS). Conjunctival biopsies from five dry Age Related Macular Degeneration (AMD) patients were harvested, cultured, and reprogrammed to make induced pluripotent stem cell (iPSC). These iPSC were subsequently differentiated to generate iPSC-RPE lines, which were genotyped for two high-risk single nucleotide polymorphisms (SNPs) associated with AMD. Each patient iPSC-RPE line was used in a proof-of-concept drug screen that measured mitochondrial function following treatment with each of three drugs (AICAR (5-Aminoimidazole-4-carboxamide ribonucleotide), Metformin, trehalose) that target key processes in maintaining optimal mitochondrial function following acute (48 h) and extended (3 weeks) drug exposure.

Results:
The five patients (one male, four females) in this study ranged in age from 63 to 84 years. One patient exhibited early stages of AMD (MGS2), three patients had intermediate disease (MGS3), and one advanced stage (MGS4). Four out of five patients had high risk genotype for CFH (Y402H SNP) and five out of five had high risk genotype for ARMS2 (A69S SNP).

Following treatment with either AICAR or Metformin, the response was variable and patient specific. In general, a more robust response was elicited with the extended drug treatment. For trehelose, only one patient responded positively to treatment.

Conclusion:
A more targeted patient-specific approach is needed to find specific drugs that restore or improve RPE mitochondrial health in patients with dry AMD. Our results demonstrate the feasibility of using iPSC-RPE from AMD patients to develop a personalized drug treatment regimen and provide a roadmap for future clinical

use.

IRB APPROVAL Yes

7/15/2022 09:26 am

Dry AMD 2 Symposium

Association of Metformin and Other Antidiabetic Medication Use with Risk of Age-Related Macular Degeneration

- Dimitra Skondra, MD,PhD
- Lincoln Shaw, MD
- Max Hyman
- Andrea Blitzer
- Andrea Flores
- Sandra Ham

Objective:
To investigate the relationship of metformin and other antidiabetic medications with AMD using Big-Data.

Purpose:
The common antidiabetic drug metformin has been shown to have protective properties in multiple age-associated diseases and may have the potential to be protective for age-related macular degeneration (AMD). Purpose of this study was to investigate the relationship of metformin use and other antidiabetic medications with risk of development of AMD using Big-Data.

Methods:
Retrospective case-control study using large US health insurance claims database of 312, 404 subjects with newly diagnosed AMD from January 2008 to December 2017 and 312, 376 matched controls. Multivariate/adjusted regression models were used to identify risk of developing AMD and interactions among metformin and other commonly prescribed medications as insulin, sulfonylureas, glitazone, statins.

Results:
Metformin use was associated with reduced odds of developing AMD (odds ratio [OR], 0.94 [95%CI, 0.92-0.96]), with low to moderate doses of metformin showing the greatest potential benefit (1-270 g/2yr, OR, 0.91 [95%CI, 0.88-0.94]; 271-600 g/2, OR, 0.90 [95%CI, 0.87-0.93]). Doses > 1080 g /2 years did not have reduced odds of developing AMD. Both the reduction in OR and the dose-dependent response were preserved in diabetic patients only cohort. Metformin was associated with a decreased OR of AMD in diabetic patients without coexisting diabetic retinopathy (DR) (OR, 0.93 [95%CI, 0.91-0.95]) but not in the presence of DR (OR, 1.07 [95%CI, 1.01-1.15]).

Analysis within diabetic cohort revealed an independent protective effect against AMD development with the use of insulin (OR 0.92 [0.90-0.95], $p < 0.001$), and sulfonylureas (OR 0.94 [0.92-0.96], $p < 0.001$). When used in combination with metformin versus neither medication, insulin (OR 0.89 [CI 0.83-0.97], $p = 0.004$) and sulfonylureas (OR 0.91 [CI 0.84-0.98], $p = 0.01$) demonstrated a protective effect as well. Subjects taking insulin or sulfonylureas alone had a similar risk of developing AMD as those taking metformin alone (OR 0.96[CI 0.89-1.01] and OR 0.98 [CI 0.90-1.05), respectively). Those taking other diabetic medications (exenatide, sitagliptin, or pramlintide) were at higher risk of developing AMD (OR 1.08 [CI 1.05-1.11], $p < 0.001$), although when taken with metformin the increased risk was no longer demonstrated (OR 1.04 [CI 0.97-1.13]). Lastly, subjects taking sulfonylureas with metformin demonstrated a further decreased risk of AMD development compared to those taking metformin alone (OR 0.94 [CI 0.91-0.97], $p < 0.001$).

Conclusion:
These data suggest that metformin may be a novel AMD therapeutic strategy and provide the basis for future preclinical and clinical studies.

IRB APPROVAL No - exempt

7/15/2022 09:42 am

Dry AMD 2 Symposium

Retrospective Real-World Analysis of Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration Followed for 3 Years

- Ehsan Rahimy, MD
- M. Ali Khan, MD, FACS, FASRS
- Allen Ho, MD FASRS
- Ryan Corley, M Eng, BS
- Mark Gallivan, MPH
- Daniel Jones
- Ramiro Ribeiro, PhD
- Theodore Leng, MD, MS, FASRS
- Nancy Holekamp, MD, FASRS

Objective:
To report results from a retrospective analysis of clinical data, evaluating disease progression of patients with GA in 1 eye and either GA or choroidal neovascularization (CNV) in the other eye, over 3 years.

Purpose:
With the wide-ranging functional impact of GA, there is need for additional data from a large, real-world patient population that reflects the natural course of GA.

Methods:
Patients (125,743) with GA in ≥1 eye were identified from the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight) from January 2016 to March 2017. Patients were excluded if they had a history of CNV or active CNV in the study eye, a history of any other retinal condition, or <36 months of follow-up. Patients were grouped by fellow eye status: Cohort 1, GA:GA; Cohort 2, GA:CNV (study eye GA, fellow eye CNV). Subgroups were classified by lesion location: nonsubfoveal (NSF) or subfoveal. Main outcomes were study and fellow eye disease progression including visual acuity (VA) over 3 years.

Results:
Patients (36,817) met the inclusion criteria: Cohort 1: 21,789 (59.27%); Cohort 2: 14,976 (40.73%). In the GA:GA Cohort, NSF study eyes had a better mean VA at baseline (67.37 letters) than subfoveal eyes (62.33 letters). Mean 3-year VA changes from baseline were comparable for NSF (−10.38) and subfoveal (−9.31 letters) study eyes. Similar trends were observed in the GA:CNV Cohort: NSF study eyes had a better mean VA at baseline (65.80 letters) than subfoveal eyes (46.80 letters). Mean 3-year VA changes from baseline were similar for NSF (−8.53 letters) and subfoveal (−8.26 letters) study eyes. In GA:GA and GA:CNV Cohorts, NSF study eyes with a baseline VA of ≥20/40 lost a mean of −10.33 and −8.19 letters and subfoveal eyes lost a mean of −8.59 and −9.96 letters over 3 years, respectively (Figure). NSF study eyes with a baseline VA of <20/40 and ≥20/100 in GA:GA and GA:CNV Cohorts lost a mean of −12.09 and −11.44 letters vs −13.57 and −12.89 letters, respectively in subfoveal eyes over 3 years (Figure).

Conclusion:
GA caused substantial disease burden in this retrospective study of a large real-world database. Eyes with GA lost significant vision over a 3-year period, consistent with trends in the previously reported 2-year analysis. The rate of vision loss was numerically similar regardless of whether lesions were NSF or subfoveal at baseline. Eyes with good vision at baseline lost more letters over 3 years compared to eyes with poor vision.

IRB APPROVAL No - exempt

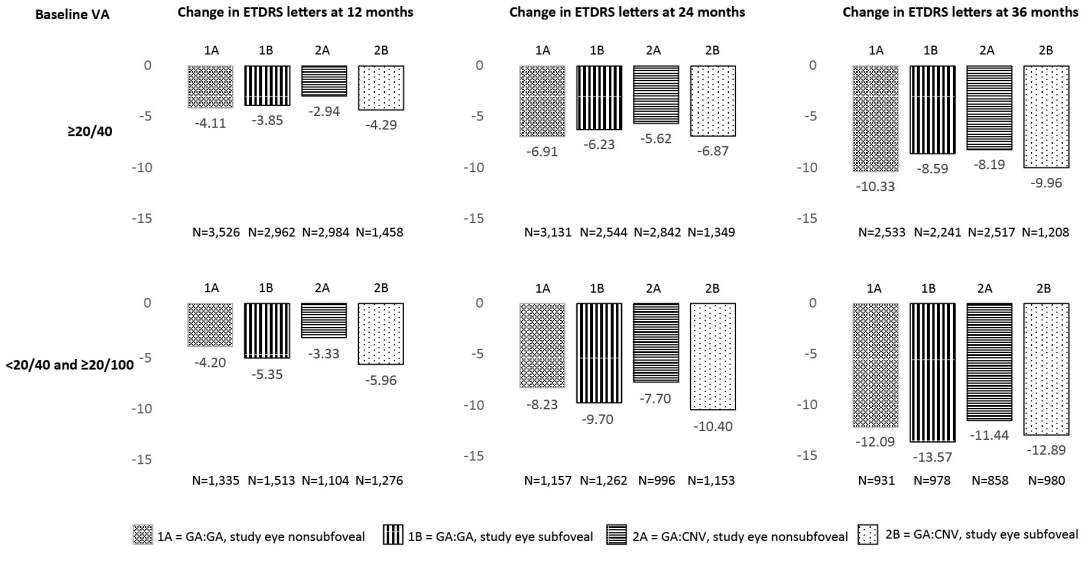

Figure. Mean study eye VA changes from baseline over time

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Dry AMD 2 Symposium

Characterizing Real-World Functional Outcomes in Patients with Geographic Atrophy: An IRIS Registry Analysis

- Durga Borkar, MD
- Meghan Hatfield, MPH
- Sonya Li
- Mark Gallivan, MPH
- Preeti Joshi
- Alex Mckeown, PhD, MBA
- Theodore Leng, MD, MS, FASRS

Objective:
To report results of a retrospective cohort analysis of patient notes to assess the feasibility of quantifying vision-related QoL (VR-QoL) and patient-reported outcomes (PRO) in GA.

Purpose:
Geographic atrophy (GA) impairs visual function and patient quality of life (QoL). However, real-world data (RWD) on correlations between GA progression and functional decline are lacking.

Methods:
Documentation of VR-QoL was assessed in a random sample of GA patient notes from the American Academy of Ophthalmology IRIS® Registry (Intelligent Research in Sight), a real-world electronic health record (EHR) dataset. Two cohorts were studied: (1) incident GA cases in 2019 analyzed on the date of diagnosis, and (2) prevalent GA cases first diagnosed in 2016 with notes at Year 3 of follow-up. Notes were searched for keywords associated with visual function, mental health, mobility, and independence. For frequently documented functional outcomes, clinical context was analyzed in 50 relevant notes per word.

Results:
The mean age of incident (n=101) and prevalent (n=97) GA patients was 80.6 years (standard deviation [SD]=7.5) and 81.9 years (SD=6.3), respectively. 54% of incident and 62% of prevalent patients had subfoveal GA; 27 – 39% had concomitant glaucoma or cataract. The majority of patients were managed by retina specialists. Functional outcomes were rarely documented in patient notes: keywords “reading” and “driving” were found in <10% of records. “Low vision” was mentioned in <3% of notes, while “anxiety / depression” was noted in <2%. “Mobility / independence / disability” were not found. 64% of driving-related notes discussed trouble driving or night driving; 44% of reading-related notes indicated impairment, while 32% discussed reading glasses or aids. 74% of low-vision-related notes recommended a low vision consultation.

Conclusion:
VR-QoL and PROs are infrequently documented in the EHR by ophthalmologists. Sparse documentation limits the use of standalone EHR note data for QoL/PRO assessment. Retina specialists often refer GA patients to low vision specialists, who may be more likely to monitor and document changes in VR-QoL. While regulatory agencies have advocated for the use of patient-centered outcomes in clinical trials, real-world assessment of PROs is lacking, necessitating improved tools to collect RWD on patient QoL.

IRB APPROVAL No - no IRB or exemption