7/29/2023 12:00 am

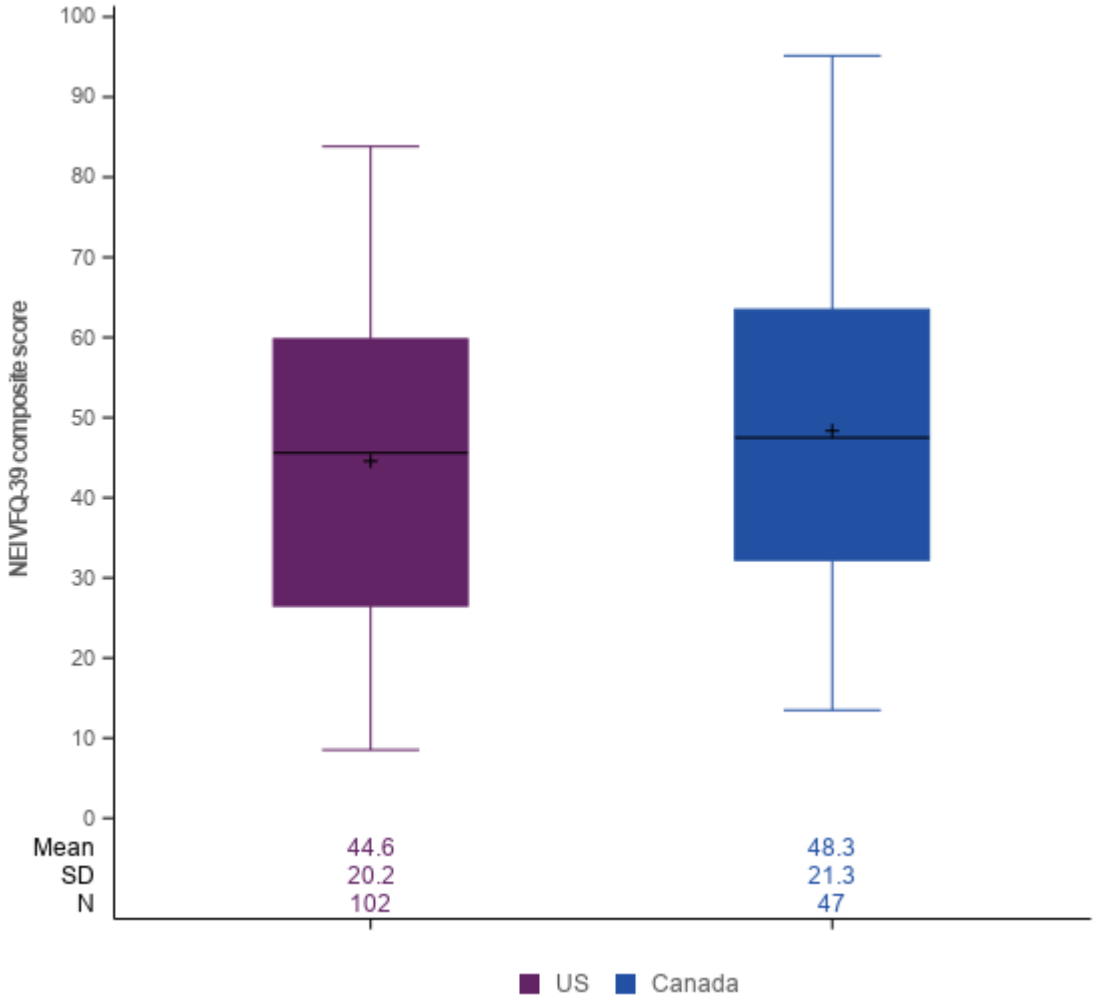
Dry AMD Symposium 1

The MOSAIC Study: A Clinical and Humanistic Burden of Illness Study of Patients With GA and Their Caregivers in the United States and Canada

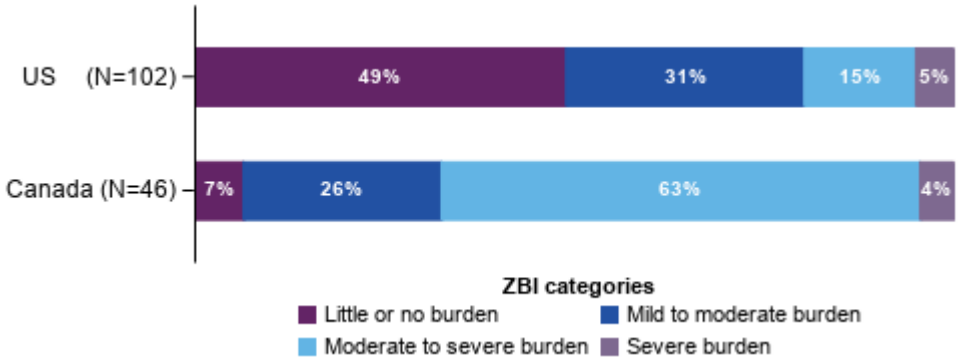
- Sophie Bakri, MD
- Jaclyn Quilantan
- Chris Réaume
- Winfried Amoaku
- Stéphane Quéré
- Manal M'Hari
- Julia Carpenter-Conlin
- Sujata Sarda, PhD, MS
- Daniel Jones
- Jared Nielsen

Objective: To what extent does the burden of Geographic Atrophy (GA) in patients and their caregivers differ between the United States (US) and Canada (CA)?
Purpose: To characterize and compare the burden of GA in patients and caregivers in the US and CA.
Methods: We conducted a survey in the US and CA with 149 GA patients (102 in the US, 47 in CA) and 148 unpaid caregivers of GA patients (102 in the US, 46 in CA).
Results: There was a higher proportion of male patients in CA than in the US (62% vs. 43%), and the mean (standard deviation [SD]) age was lower in the US (68 [4] years) than in CA (73 [5] years). Patients were mostly retired (77% in the US, 81% in CA). Mean (SD) time from GA diagnosis was 6.3 (5.2) and 5.3 (3.6) years in the US and CA, respectively. Visual changes due to GA were reported in both eyes by 43% of US patients and 47% of CA patients. Patients reported receiving help from children (41% in the US, 34% in CA), partners (39% in the US, 47% in CA), and/or other family members (39% in the US, 32% in CA). Mean (SD) 39-item National Eye Institute Visual Functioning Questionnaire (NEI-VFQ-39) composite scores were comparable in both countries (44.6 [20.2] in the US and 48.3 [21.3] in CA) (Fig. 1), indicating similar vision-related quality of life. More US patients reported needing daily help (68%) or a change in their living situation because of GA (38%) than did CA patients (38% and 28%, respectively). In total, 86% of US patients and 72% of CA patients did not drive; 95% and 97% of non-drivers gave up driving because of their eyesight in the US and CA, respectively.
There was a higher proportion of male caregivers in CA than in the US (61% vs. 47%), and the mean (SD) age was similar in both countries (46 [15] in the US; 44 [11] in CA). In the US, caregivers mostly reported caring for their partner (37%) or a parent (30%) whereas in CA they mostly reported caring for their parent (65%) or a grandparent (26%). In total, 63% of CA caregivers were categorized as having moderate to severe burden vs. only 15% of US caregivers (per Zarit Burden Interview [ZBI]) (Fig. 2). In total, 44% and 93% of US and CA caregivers were employed, respectively; time missed from work in the previous week due to caregiver responsibilities was similar (mean [SD] of 3 [6] in the US and 3 [3] hours in CA).
US dyad data (n=93) showed that the burden of patients and caregivers was moderately related, with a correlation of –0.63 between NEI-VFQ-39 composite score and ZBI score.
Conclusion: These results highlight the substantial burden of GA on patients and their caregivers in the US and CA.

IRB APPROVAL Yes



Distribution of NEI-VFQ-39 composite score among GA patients



Distribution of ZBI score among caregivers

7/29/2023 12:00 am

Dry AMD Symposium 1

Improving Vision in Dry AMD: Matching Mechanism With the Right Patient Population and Stage of Disease

- Baruch Kuppermann, MD, PhD, FASRS
- Justis Ehlers, MD, FASRS
- Eleonora Lad, MD, PhD
- Glenn Jaffe, MD

Objective: To determine factors (class of drugs, stage of disease, retina anatomical condition) associated with improvement of vision in patients with Dry AMD.

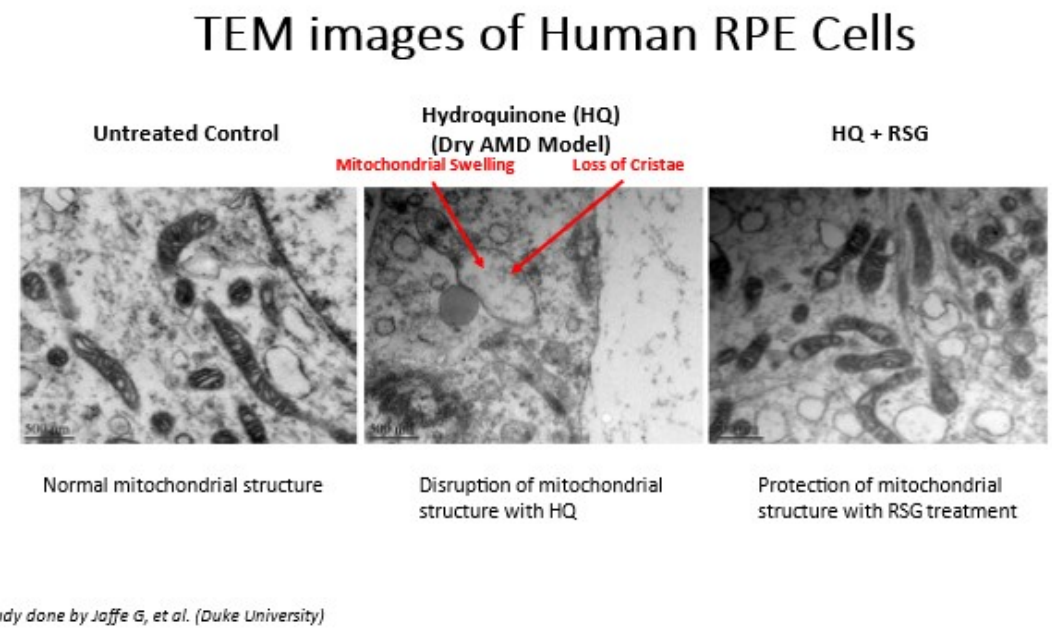
Purpose: In preclinical studies, risuteganib (RSG) preserved RPE mitochondrial structure, restored energy production, reduced inflammation and improved cell survival. The purpose of the present report is to evaluate the safety and effectiveness of RSG to reverse vision loss due to dAMD and to determine biomarkers that may predict response to the drug.

Methods: Prospective, randomized, controlled study in 40 eyes with intermediate dAMD. Subjects with BCVA of 20/40 - 20/200 were assigned to receive risuteganib (RSG) or sham IVT and followed for 32 weeks. Endpoints were percent of population with ≥ 8 (primary), 10 and 15 letters improvement (secondary) in ETDRS BCVA. Exploratory endpoints were change in microperimetry, color vision and OCT anatomy. Advanced OCT analysis was done using deep-learning enabled multi-layer segmentation with ellipsoid zone (EZ) integrity analysis.

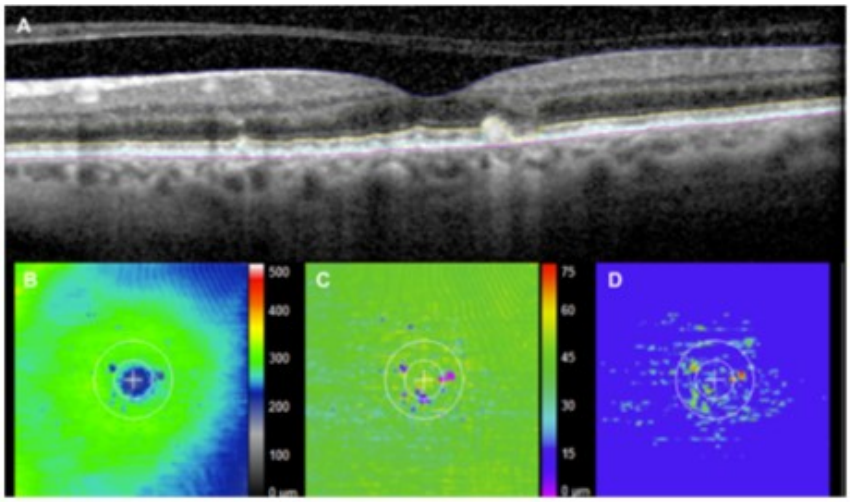
Results: 48%, 32% and 20% of the population in the RSG group improved by ≥ 8, 10 and 15 letters, respectively, versus 7%, 7% and 0% of the population in the sham group. Improvement in BCVA correlated strongly with improvement in microperimetry and color vision. 83% of responders (≥ 8 letters improvement) had ≥ 30µm EZ-RPE central subfield thickness at baseline versus 38% of non-responders, indicating a strong biomarker for RSG response. There was no detectable change in OCT anatomy over the 8-month study period. There were no drug-related SAE's.

Conclusion: Reversing vision loss in dAMD is potentially achievable with therapy that improves cellular function and survival, by targeting the mitochondria, in a patient population with a recoverable photoreceptor structure/function. Intervention is most fruitful during the earlier stage of the disease, when patients have discernible visual function loss (such as the loss of reading, driving, cooking vision), but before complete atrophy of the RPE and outer retina layers. Utilizing targeted enrollment for clinical trials using biomarkers, such as EZ integrity, may enable greater population enrichment and more efficient trial design.

IRB APPROVAL Yes



TEM Images of Human RPE Cells



Representative RSG responder OCT foveal B-scan with anatomic layer segmentation (A) with ILM-RPE thickness map (B), EZ-RPE thickness map (C), and RPE-BM thickness map (D). The color scale on the left applies to the ILM-RPE map, and the scale on the right applies to the EZ-RPE and RPE-BM maps. The maps and B-scan demonstrate mild anatomic perturbations. BM ¼ Bruch's membrane; EZ ¼ ellipsoid zone; ILM¼ internal limiting membrane; RPE¼ retinal pigment epithelium.

Representative RSG Responder

7/29/2023 12:00 am

Dry AMD Symposium 1

Use of Ellipsoid Zone Analysis As an Efficacy Endpoint in Clinical Trials for Geographic Atrophy

- Peter Kaiser, MD FASRS
- Justis Ehlers, MD, FASRS

Objective: To review the use of ellipsoid zone (EZ) analysis as an efficacy endpoint in clinical trials for geographic atrophy (GA) related to dry age-related macular degeneration (AMD).
Purpose: There is a need for more sensitive measures of disease progression to be used as efficacy endpoints in clinical trials for geographic atrophy (GA) related to age-related macular degeneration (AMD). The ellipsoid zone (EZ) is a mitochondrial-rich hyperreflective outer retinal band observed in optical coherence tomography. The quantification of progressive photoreceptor degeneration outside of the GA area suggests that EZ loss is indicative of cone and rod photoreceptor dysfunction and is significantly associated with GA progression.
Methods: A review of peer-reviewed manuscripts, available congress presentations, and indexed abstracts was performed. The inclusion criteria included publications originating from phase 2/3 interventional clinical trials in patients with GA where an EZ analysis was performed either as a prespecified endpoint or a post hoc analysis.
Results: In a post hoc analysis of the FILLY phase 2 trial with intravitreal C3 inhibitor pegcetacoplan compared to sham (283 μm ± 226), the mean change in square-root transformed EZ loss area (defined as axial photoreceptor thickness ≤ 4 μm) at month 12 was reduced with pegcetacoplan monthly (106 μm ± 400; P = 0.0014) and every other month (154 μm $\pm$ 249; P = 0.033). Another post hoc analysis examined the effect of intravitreal C5 inhibitor avacincaptad pegol (ACP) on EZ integrity change in the GATHER1 phase 2/3 trial. The progression in the percentage of macular total EZ attenuation (defined as the percentage of the macular cube with EZ-retinal pigment epithelium thickness = 0 μm) was reduced with ACP vs sham at month 12 (19% reduction; descriptive P = 0.049). The RECLAIM-2 phase 2 trial assessed the effect of subcutaneous elamipretide, a mitochondrial protective agent, in patients with GA. Prespecified trial endpoints showed that elamipretide at week 48 (month 12) was associated with a 43% reduction in the progression of total EZ attenuation vs placebo (P = 0.003).
Conclusion: There is growing evidence that EZ analysis is a suitable biomarker of photoreceptor degeneration and a predictor of future GA growth. Because it has been demonstrated that EZ loss or attenuation can predict areas of GA onset by 2 to years, quantification of EZ integrity could be useful as an endpoint in clinical trials for dry AMD patients. Albeit to varying degrees, it is encouraging that emerging therapies for GA can preserve photoreceptor integrity, a major correlate of visual function, and it suggests that earlier stages of dry AMD could show a greater benefit from treatment.

IRB APPROVAL No - no IRB

7/29/2023 12:00 am

Dry AMD Symposium 1

Modulation of Macrophages and Complement Dysfunction in Nonexudative AMD Using New Sialic Acid–Coated Nanoparticles

- Carl Regillo, MD
- David Callanan, MD
- Tarek Hassan, MD, FASRS
- Christopher Scott, PhD; Professor of Pharmaceuticals
- Anitha Krishnan, PhD
- Mohamed Genead, MD, MBA

Objective: Inhibition of the innate immune system with an engineered glycan (sialic-acid) nanoparticle is effective in reducing retinal degeneration in two animal models of age-related macular degeneration (AMD) without significant safety signals and a phase 2 clinical trial in geographic atrophy is planned.
Purpose: Both the cellular and non-cellular components of the innate immune system have been implicated in the pathophysiology of AMD. Inhibition of the complement system has been shown to decrease the rate of progression of geographic atrophy (GA) in randomized Phase 3 clinical trials. However, the therapeutic effect has been modest, and a significant number of patients have converted to the neovascular form of AMD. A novel therapeutic strategy to address chronic inflammation via the body's own self recognition system on immune cells was explored using an engineered glycan (sialic-acid) nanoparticle (Aviceda Therapeutics, Cambridge, MA) with dual therapeutic functions. It directly modulates the self-pattern recognition receptors on overly activated retina immune cells (macrophages & microglia) called Siglecs (**s**ialic-acid binding **i**mmuno**g**lobulin-like **lec**tins) thereby dampening the inflammatory activity of these immune cells and repolarizing them to the resolution state. It also enhances the activity of complement factor H, a key regulator for complement cascade, to downregulate the alternative complement cascade.
Methods: AVD-104 was injected intravitreally (IVT) in two doses in humanized Siglec- 11 transgenic mice to assess efficacy in both the bright light damage (BLD) model (n=15 eyes) and the laser-induced choroidal neovascularization (CNV) model (n=21 eyes). In the BLD model, animals were given an IVT injection of AVD-104 one day before bright light exposure and the outer nuclear layer (ONL) architecture and tumor necrosis factor-?? (TNF-??) levels in the retinal pigment epithelium (RPE)/choroid were examined 7 days later. In the laser CNV model, animals were given an IVT injection of AVD-104, lasered on the same day, and examined 8 days later.

Results: There was a dose dependent preservation of the ONL (*p value* < 0.01) and reduction in TNF-?? levels *(p* < 0.0001*)* in the BLD animals treated with AVD-104 compared to controls. In the laser CNV mice, there was a dose dependent reduction in the size of the CNV lesion and reduction of C5b-9 deposition (terminal membrane attack complex) with AVD-104 treatment compared to controls. The drug was well-tolerated in both studies and the safety profile was excellent at the two tested doses without any significant safety signals seen.

Conclusion: AVD-104, a novel sialic-acid coated nanoparticle, has shown a statistically significant beneficial effect in reducing inflammatory retinal damage in two different well-established ocular animal models of AMD and has previously been shown to be safe in 3 animal species, including non-human primates. A phase 2 human clinical trial for patients with AMD-related GA is planned to begin in Q1' 2023.

IRB APPROVAL