7/30/19 12:55 PM

North Carolina Macular Dystrophy (NCMD/MCDR1) in a Turkish Family; A New Mutation for MCDR1 Involving PRDM13

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- Margaret A Pericak-Vance, PhD
- Jeffrey Vance, MD
- Andrea Vincent, MD
- Elfride De Baere, MD, PhD
- Karen Nuytemans, PhD
- Fadi Shaya, BS

OBJECTIVE A more limited promoter region of PRDM13 may be involved in overexpression earlier in embryonic development of the macula thus causing a more severe grade phenotype as seen in this family.

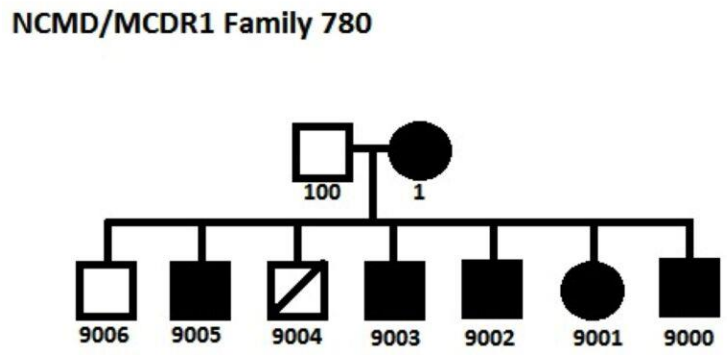
PURPOSE We report a new family with the NCMD phenotype from a new geographic region with a new mutation in MCDR1.

METHODS Clinical ophthalmic examinations were performed on eight members of a two-generation family from southern Turkey. Fundus photos and Spectral Domain Optical Coherence Tomography (SD-OCTs) were performed. Whole Genome Sequencing (WGS) was performed on two members. Sequencing across the break point was done on the other six members. Blood and saliva were collected from family members after IRB approved signed consent was obtained.

RESULTS The proband presented with lifelong bilateral vision impairment. The six children were subsequently examined. Four were found to have similar macular malformations suggesting an autosomal dominant inheritance pattern. The father was examined and was found to be normal. Copy number variant analysis of whole genome sequencing data of two of the affected family members showed a duplication in the MCDR1 chromosome 6 locus which involves PRDM13 (Chr6: g.99560265-99616492 (hg38)). Sequencing across the break point showed the duplication in the other four affected family members demonstrating segregation of the duplication within the family. All of the affected individuals in this family have large grade 3 coloboma-like lesions. The duplication is smaller than the previously reported duplications and it still involves PRDM13, as do all of the previously reported duplications on chromosome 6 (MCDR1).

CONCLUSION Although the family studied is only two generations with six affected individuals, the severity grades are not evenly distributed as seen in other NCMD families. Explaining this apparently unique feature of this family is difficult without definitively knowing the biological mechanisms as to how these duplications cause overexpression of PRDM13 and the disease phenotype NCMD.

HUMAN RESEARCH Yes: Approved by institutional review board



NCMD/MCDR1 Pedigree of Family 780

7/30/19 1:00 PM

Ocular Venous Air Embolism (OVAE)

- Robert Morris, MD
- Mathew R. Sapp, MD
- Matthew H. Oltmanns, OD, MD
- Ferenc Kuhn, MD, PhD

OBJECTIVE To ensure that ASRS members are aware of Ocular Venous Air Embolism and are thus enabled to prevent this potentially fatal complication of vitrectomy.

PURPOSE To review and analyze reported cases of ocular venous air embolism (OVAE) to develop a reliable clinical definition of OVAE and effective prevention strategies.

METHODS We reviewed all reports of suspected air embolism during vitrectomy published in PubMed since the introduction of pars plana vitrectomy, and 5 cases found elsewhere and separately reported concurrent with this review.

RESULTS OVAE is a precipitous drop in end-tidal CO2, a choroidal detachment, or a choroidal wound, followed by signs of impending or actual cardiovascular collapse, during vitrectomy air infusion. In each case meeting the above clinical definition, entrained air was found whenever it was sought (8/8, 100%), either by antemortem imaging or postmortem forensic investigations. Most OVAE cases were fatal (9/13, 69%), with 8 of 9 deaths (89%) occurring the day of surgery.

CONCLUSION OVAE is a rare but usually fatal complication of air infusion into the eye during vitrectomy. As of 2017, 80% of surveyed ASRS members were unaware of OVAE and thus remained susceptible to its occurrence. Because the effective response time to avoid a fatal OVAE outcome can be less than one minute, the use of preventive measures we discuss herein is critical.

HUMAN RESEARCH Yes: Exempt from approval

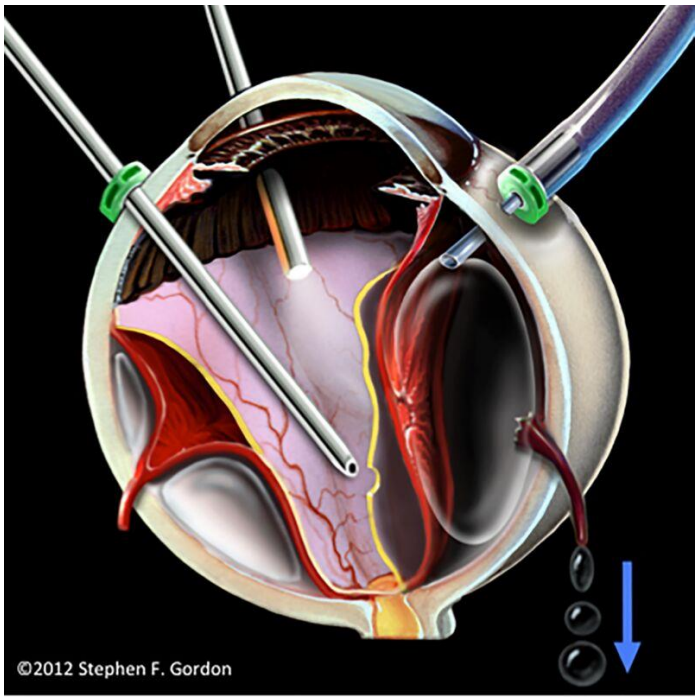
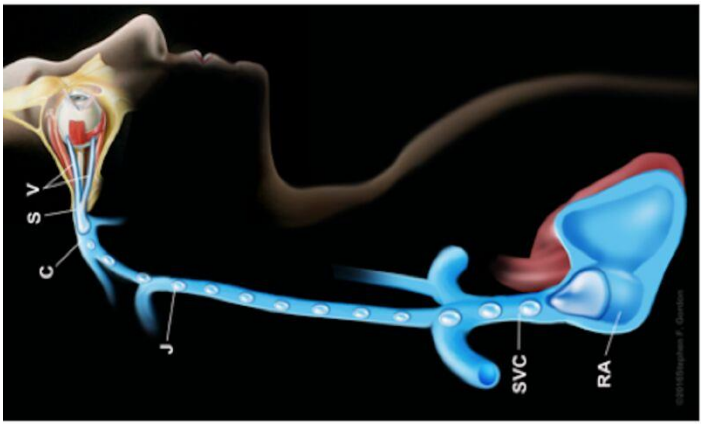


Illustration of pressurized air from a slipping, unsecured cannula causing accidental choroidal detachment, torn vortex vein ampullae and air entrainment through vortex veins (Image used with permission of the British Journal of Ophthalmology).



Artist's depiction of non-continuous air emboli leaving the eye through the vortex veins and entering the heart through the systemic venous circulation. V – vortex vein; C S – cavernous sinus; J – jugular vein; SVC – superior vena cava; RA – right atrium; RV - right ventricle.

7/30/19 1:05 PM

36-Month Outcomes of Injectable Fluocinolone Acetonide Intravitreal Insert on Recurrences of Non-infectious Posterior Segment Uveitis

- Quan Dong Nguyen, MD, MSc

OBJECTIVE To evaluate the 36-month safety and efficacy of a single fluocinolone acetonide intravitreal insert for treating non-infectious uveitis affecting the posterior segment (NIU-PS) of the eye.

PURPOSE Cumulative damage from repeat episodes of intermediate, posterior and panuveitis have been shown to contribute to vision morbidity. This study evaluated the hypothesis that a single administration of an injectable fluocinolone acetonide intravitreal insert (FAi) delivering daily microdoses for 36 months can reduce the rate of uveitic recurrence.

METHODS The index study was a controlled, prospective, double masked multi-center trial using a 2:1 blocked randomization based on therapy at study entry. Subjects who had experienced at least 2 separate recurrences of NIU-PS requiring ≥ 3 months of systemic therapy or ≥ 2 intra- or periocular steroid injections and with a > 1-year history of the disease, were randomized to treatment in one study eye with FAi (N=87) or sham (N=42) injection. The primary efficacy endpoint was NIU-PS recurrence. Visual acuity (VA) and macular thickness/edema were secondary efficacy outcomes. Safety results included rates of adverse events including, but not limited to, cataract and elevated IOP.

RESULTS Patients were enrolled at 33 sites in the US, Europe, Israel and India. During the 36M study, the recurrence rate in FAi treated eyes (56.3%) was significantly lower than in eyes randomized to sham (92.9%), $p<0.001$. Treatment of a recurrence was at each investigator's discretion. When possible, systemic therapy was used only if local therapy failed. Visual acuity

improvement of ≥3-lines was more common with FAi treatment (33% vs 15%) and VA loss was more common in the sham group (9% vs 1%) at the final visit. Eyes with baseline macular edema had an 85% resolution rate (34/40) at 36M when treated with FAi and 70% (16/23) when randomized to sham. During the 3-year study, 42% and 33% of FAi and sham subjects required IOP lowering medications, 6% (FAi) and 12% (sham) required IOP lowering surgery. Cataract surgery was performed on 74% and 24% of phakic study eyes in the FAi and sham groups respectively.

CONCLUSION Treatment with a single intravitreal injection of the FAi provided effective anti-inflammatory treatment for three years patients with NIU-PS. Recurrence rates were significantly reduced and side effects were manageable with clinical interventions.

HUMAN RESEARCH Yes: Approved by institutional review board

7/30/19 1:10 PM

Abicipar Phase 2 MAPLE Trial Supports Improved Safety for Patients with nAMD Following a Modified Manufacturing Process

- Raj K. Maturi, MD

OBJECTIVE The objective of this study was to evaluate the safety of abicipar in patients with neovascular age-related macular degeneration (nAMD).

PURPOSE MAPLE evaluated the safety of abicipar 2mg produced using a modified manufacturing process in patients with nAMD. Abicipar has the potential to be the first anti-VEGF therapy for nAMD patients with a fixed 12-week dosing regimen that could greatly reduce treatment burden for patients.

METHODS MAPLE is a Phase 2, multicenter, open-label, single-arm 28-week study. Enrolled patients (age ≥ 50, n=123) with nAMD were treatment-naïve (67.5% of subjects in this group) or had prior anti-VEGF treatments (32.5% of subjects in this group) and best-corrected visual acuity (BCVA) between 24 letters (20/320) and 78 letters (20/32) in the study eye. Patients who had prior treatment with abicipar, ocular anti-angiogenic therapy (within 1-2 months before baseline), macular laser treatment in the study eye or ocular/intraocular infection in either eye were excluded. Patient received abicipar 2 mg at baseline, Weeks 4, 8, 16 and 24. Safety was assessed at all visits.

RESULTS The overall incidence of treatment-related intraocular inflammation (IOI) was 8.9%. Most incidences of IOI were assessed as mild to moderate in severity. The incidence of severe

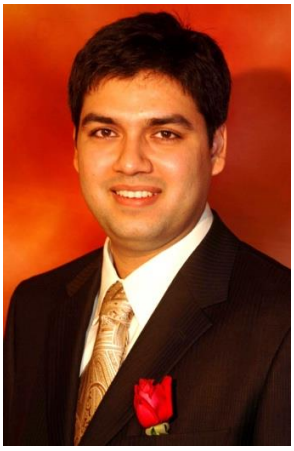
IOI was 1.6% with one reported case of iritis and one reported case of uveitis. Both cases were resolved and patients' vision recovered. There were no reported cases of endophthalmitis or retinal vasculitis in this study.

CONCLUSION Abicipar produced through a modified manufacturing process demonstrated an improved safety profile compared with the Phase 3 studies combined.

HUMAN RESEARCH Yes: Approved by institutional review board

7/30/19 1:15 PM

Outcomes of DRCR Network Treatment Regimen Starting with Observation for Eyes With Center-involved Diabetic Macular Edema and Good Visual Acuity



- Omar S. Punjabi, MD

OBJECTIVE To present the DRCR Retina Network approach and outcomes when managing eyes with center-involved DME and good visual acuity with initial observation and subsequent aflibercept only if VA worsens.

PURPOSE The DRCR Retina Network recently published clinical trial results showing no difference in 2-year VA loss with initial observation versus immediate aflibercept versus focal/grid laser for eyes with CI-DME and good VA. Since initial observation could reduce visits, cost, and side effects compared with immediate anti-VEGF treatment, understanding this approach is important for patient management.

METHODS Randomized clinical trial (Protocol V) performed at 91 US and Canadian sites among adults with type 1 or 2 diabetes (n = 236) who had one study eye with CI-DME and VA letter score ≥ 79 (Snellen equivalent ≥ 20/25). Eyes randomly assigned to initial observation were observed without aflibercept unless VA worsened from baseline by ≥ 10 letters (2 lines) at any visit or 5 to 9 letters (1 line) at 2 consecutive visits. Follow-up occurred every 8 weeks twice then every 16 weeks provided the eye remained stable. Once initiated, aflibercept was given every 4 weeks unless VA and optical coherence tomography (OCT) central subfield thickness (CST) were stable for at least 2 consecutive injections.

RESULTS Thirty-four percent of eyes (80/236) in the observation group received aflibercept. Eyes were more likely to receive aflibercept if baseline OCT CST was ≥300 µm (Zeiss-Stratus equivalent) versus < 300 µm (43% vs. 27%, P = .009) and if the non-study eye needed DME treatment within 4 months of randomization (52% vs 25%, P < .001). A 5 to 9-letter loss at any time was seen in 39% of eyes (92/236). Of these 92 eyes, 32% received aflibercept at the next visit for sustained VA loss, 22% received aflibercept at a subsequent visit, and 46% did not receive aflibercept.

CONCLUSION Eyes with greater baseline OCT CST or with a fellow eye receiving treatment were more likely to require anti-VEGF for VA loss. On average, VA outcomes with the DRCR Network observation strategy were not different than starting with aflibercept, indicating that observation can be considered a reasonable strategy for eyes with CI-DME and good VA.

HUMAN RESEARCH Yes: Approved by institutional review board

Table 1. Two-Year Outcomes by Receipt of Aflibercept During Follow-up.

	Did not receive aflibercept	Received aflibercept
2-Year Visit	**N = 132**	**N = 76**
Visual acuity, letter score		
Baseline		
Mean (SD)	85.4 (3.5)	84.8 (4.2)
Mean Snellen equivalent	20/20	20/20
Median (IQR)	85.0 (88.0-83.0)	84.0 (87.0-81.0)
Median Snellen equivalent (IQR)	20/20 (20/20-20/25)	20/20 (20/20-20/25)
20/20 or better (≥ 84 letters), no. (%)	90 (68)	43 (57)
2 years		
Mean (SD)	86.6 (5.2)	80.0 (14.4)
Mean Snellen equivalent	20/20	20/25
Median (IQR)	87.0 (90.0-83.5)	83.5 (87.0-78.5)
Median Snellen equivalent (IQR)	20/20 (20/16-20/25)	20/25 (20/20-20/32)
20/20 or better (≥ 84 letters), no. (%)	92 (70)	43 (57)
Change from baseline		
Mean (SD)	1.2 (4.5)	-3.0 (8.0)
Median (IQR)	1.5 (-1.0 to 5.0)	-2.0 (-6.0 to 1.0)
≥ 5-letter decrease, no. (%)	16 (12)	23 (30)
≥ 10-letter decrease, no. (%)	3 (2)	11 (14)
≥ 15-letter decrease, no. (%)	1 (<1)	7 (9)
OCT central subfield thickness (Zeiss Stratus equivalent), µm[a]		
Baseline		
Mean (SD)	308 (59)	332 (70)
Median (IQR)	292 (273-324)	312 (290-361)
2 years		
Mean (SD)	276 (69)	267 (79)
Median (IQR)	264 (229-306)	250 (218-315)
Change from baseline		
Mean (SD)	-30 (66)	-62 (86)
Median (IQR)	-33 (-68 to -1)	-53 (-117 to -14)
No center-involved diabetic macular edema[b] and ≥ 10% central subfield thickness decrease, no. (%)	41 (31)	33 (44)

Abbreviations: IQR, interquartile range; SD, standard deviation.
[a] Unavailable for 1 eye that received aflibercept.
[b] Defined by OCT machine and sex: Heidelberg Spectralis CST ≥ 305 µm in women and ≥ 320 µm in men; Zeiss Cirrus CST ≥ 290 µm in women and ≥ 305 µm in men.

Table 1: Two-Year Outcomes by Receipt of Aflibercept During Follow-up.

Figure 1. DRCR Algorithm for Eyes with Center-Involved DME and Good VA

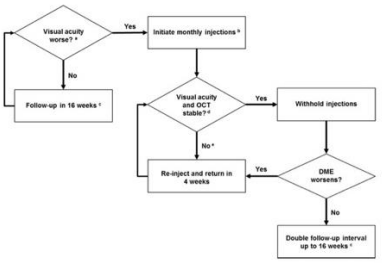


Figure 2. Cumulative Probability of Initiating Aflibercept Over Time by Indication.

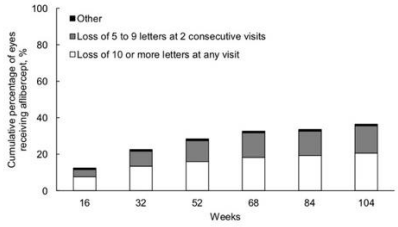
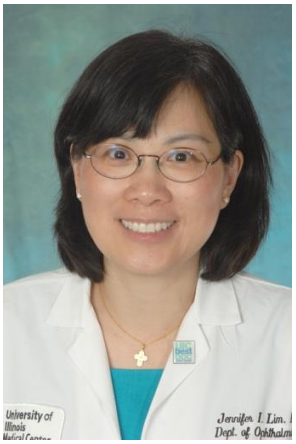


Figure 1. DRCR Retina Network Observation+ Treatment Algorithm for Eyes with Center-Involved DME and Good Visual Acuity.Figure 2. Cumulative Probability of Initiating Aflibercept Over Time by Indication: Eyes completing the 104-week visit (208 of 236 randomized, 90% excluding 4 deaths). “Other” injections were given for one case of proliferative diabetic retinopathy and one case of vision loss of 7 letters accompanied by a 150-µm increase in central subfield thickness.

7/30/19 1:20 PM

Artificial Intelligence Screening for Diabetic Retinopathy: Analysis from a Pivotal Multi-center Prospective Clinical Trial



- Jennifer I. Lim, MD
- Barbara A. Blodi, MD
- Carl D. Regillo, MD, FACS
- Srinivas Reddy Sadda, MD
- Bruce Bode, MD
- Eli Ipp, MD

OBJECTIVE To determine the sensitivity and specificity of an artificial intelligence system to detect referable diabetic retinopathy (moderate NPDR or CSDME).

PURPOSE To evaluate the sensitivity and specificity of an artificial intelligence (AI) system for diabetic retinopathy (DR) screening.

METHODS In this prospective study at 15 centers, patients underwent undilated 2-field, 45 degrees, fundus photography and then dilated 4-wide field stereoscopic fundus photography. The EyeArt system provided eye level results about referable DR (rDR), defined as moderate NPDR or higher per the International Clinical DR severity scale or CSDME. If the EyeArt system could not grade these images, the 2-field photos were repeated after dilation. Dilated wide field photographs were the reference standard and were graded by Wisconsin Fundus Photograph Reading Center graders using the ETDRS Severity Scale. Detection rates of rDR by the automated EyeArt system were compared with the reference standard.

RESULTS Of 1822 enrolled eyes (911 subjects), 1674 had both gradable 2-field and 4-field images. 310/ 1674 eyes were positive and 1364 eyes were negative for rDR. The sensitivity of the EyeArt system using only undilated images was 95.5% [95% CI: 92.4% - 98.5%], specificity was 86.0% [95% CI: 83.7% - 88.4%] and the gradability rate was 87.5% [95% CI: 85.4% - 89.7%]. Dilated 2-field photos were required for 214 eyes; 170 eyes were gradable and 44 (2.6% of 1718) remained ungradable per the EyeArt system. With this dilate-if-ungradable photography protocol, the gradability rate of the EyeArt system improved to 97.4% [95% CI: 96.4% - 98.5%]; sensitivity was 95.5% [95% CI: 92.6% - 98.4%], and specificity was 86.5% [95% CI: 84.3% - 88.7%]. Of 14 false negative rDR eyes, 14 had moderate ETDRS level 35 and 1 had CSDME. Of 184 false positive rDR eyes, 119 had mild DR and 20 had non-DR conditions (AMD, vein occlusion, ERM, vitreous opacities, optic disc edema, atrophy, scar and nevus).

CONCLUSION This AI system compared favorably with the clinical reference standard and has high enough sensitivity and specificity for the detection of referable DR in diabetic patients.

HUMAN RESEARCH Yes: Approved by institutional review board