JAMA Ophthalmology | Original Investigation

Effect of Oral Valproic Acid vs Placebo for Vision Loss in Patients With Autosomal Dominant Retinitis Pigmentosa
A Randomized Phase 2 Multicenter Placebo-Controlled Clinical Trial

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IMPORTANCE There are no approved drug treatments for autosomal dominant retinitis pigmentosa, a relentlessly progressive cause of adult and childhood blindness.

OBJECTIVES To evaluate the potential efficacy and assess the safety of orally administered valproic acid (VPA) in the treatment of autosomal dominant retinitis pigmentosa.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, phase 2, prospective, interventional, placebo-controlled, double-masked randomized clinical trial. The study took place in 6 US academic retinal degeneration centers. Individuals with genetically characterized autosomal dominant retinitis pigmentosa were randomly assigned to receive treatment or placebo for 12 months. Analyses were intention-to-treat.

INTERVENTIONS Oral VPA 500 mg to 1000 mg daily for 12 months or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome measure was determined prior to study initiation as the change in visual field area (assessed by the III4e isopter, semiautomated kinetic perimetry) between baseline and month 12.

RESULTS The mean (SD) age of the 90 participants was 50.4 (11.6) years. Forty-four (48.9%) were women, 87 (96.7%) were white, and 79 (87.8%) were non-Hispanic. Seventy-nine participants (87.8%) completed the study (42 [95.5%] received placebo and 37 [80.4%] received VPA). Forty-two (46.7%) had a rhodopsin mutation. Most adverse events were mild, although 7 serious adverse events unrelated to VPA were reported. The difference between the VPA and placebo arms for mean change in the primary outcome was −150.43 degree^2 (95% CI, −290.5 to −10.03; P = .035).

CONCLUSIONS AND RELEVANCE This negative value indicates that the VPA arm had worse outcomes than the placebo group. This study brings to light the key methodological considerations that should be applied to the rigorous evaluation of treatments for these conditions. This study does not provide support for the use of VPA in the treatment of autosomal dominant retinitis pigmentosa.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT01233609

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Supplemental content

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JAMA Ophthalmol. 2018;136(8):849-856. doi:10.1001/jamaophthalmol.2018.1171
Published online June 7, 2018.

Retinitis pigmentosa (RP) is a group of inherited disorders of the retina characterized by the gradual progressive loss of rod, and subsequently cone, photoreceptors, resulting in vision loss. Photoreceptor loss is accompanied by inner retinal reorganization and atrophy of the retinal pigment epithelium.[1] Affected individuals typically first experience defective dark adaptation or nyctalopia (night blindness), followed by progressive bilateral reduction of the peripheral vision field. As field loss progresses into the macula, central vision is lost together with acuity.[2,3] Autosomal recessive and X-linked forms of inheritance progress most rapidly.[4-6] The more slowly progressing autosomal dominant retinitis pigmentosa (ADRP) accounts for 15% to 20% of all cases and is caused by approximately 30 genes, of which the proline-to-histidine mutation at codon 23 missense rhodopsin (*RHO*) gene mutation is most prevalent in the United States.[2,7] There is no approved medical treatment for RP. For the most advanced cases, the Argus II Retinal Prosthesis System (Second Sight)[8,9] may afford some functional improvement.

Valproic acid (VPA) has been an approved drug since the 1970s for epilepsy, bipolar disorder, migraine headache, and pain management. Adverse effects include hepatic failure, birth defects, pancreatitis, encephalopathy, suicidal behavior, and bleeding disorders. Valproic acid carries a black box warning reserved for drugs that have high risk of serious adverse events (without careful dose monitoring) (eFigure 1 in Supplement 3). Fetal exposure carries an increased risk of teratogenicity manifesting as spina bifida, facial dysmorphism, and heart, genital, and dental abnormalities.[10,11]

The antiepileptic activity of VPA is thought to arise from its ability to stimulate transmission of brain γ-aminobutyric acid.[12] Valproic acid is also a histone deacetylase inhibitor,[13] a drug class that upregulates growth factor gene expression. In the retina, this has been shown to enhance ganglion cell survival by increasing levels of brain-derived neurotrophic factor and nerve growth factor.[14] Additional functions include chaperone, antioxidant, and anti-inflammatory activity and complement downregulation.[15] Collectively, these findings support a hypothesis that VPA could exert efficacy in ADRP mutations that result in protein misfolding and aberrant subcellular localization,[16,17] Indeed, recently, VPA was shown to have ameliorative effects in a *Xenopus* model of the proline-to-histidine mutation at codon 23 *RHO* mutation but exerted apparently negative effects in other mutations.[18]

In a small uncontrolled study, 7 patients with RP (all genetic types) received 2 to 6 months of 500 mg to 750 mg VPA daily,[19,20] and 9 of 13 eyes showed improvement in visual field, while 4 showed stable or decreased field sensitivity. The effect size was modest (approximately >10%) and, when compared with expected visual field decline, statistically significant ($P < .02$). Based in part on this clinical data, the Foundation Fighting Blindness decided to sponsor a randomized clinical trial of VPA in ADRP. During the course of this study, other publications contributed to our understanding of the potential role of VPA. An uncontrolled short-term study of 29 participants showed improvements in acuity and field.[21] However, a retrospective analysis of longer-term use (approximately 10 months) suggested a more complex association with some individuals worsening and leading the authors to recommend "that VPA may not be an appropriate treatment for all retinal dystrophies."[22] In this article, we present the results of the primary and key secondary outcome results of the VPA study and provide methodological and logistical information to aid the design of future trials. We seek to determine whether participants who receive VPA experience improvement in visual function.

Key Points

Question Does oral valproic acid treat vision loss in patients with autosomal dominant retinitis pigmentosa?

Findings This multicenter randomized clinical trial analyzed oral valproic acid in 90 participants with autosomal dominant retinitis pigmentosa. The primary outcome measure (change in visual field area between baseline and 12 months) showed a small but statistically significantly worse outcome for the valproic acid group vs the placebo group, with a difference between arms of −150.43 degree^2.

Meaning This study did not meet its primary end point at 12 months and does not provide support for the use of valproic acid to improve visual function in individuals with autosomal dominant retinitis pigmentosa.

Methods

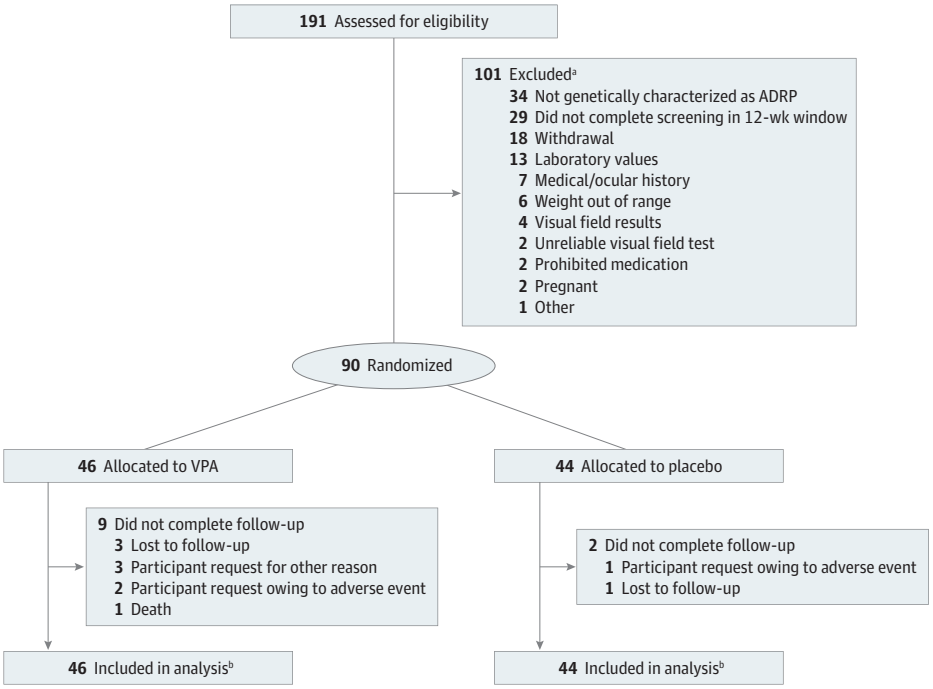
This trial was a prospective, placebo-controlled, double-masked study in which 90 participants were randomized to receive 12 months of VPA or placebo. Institutional review board approval was received from the University of Miami, Oregon Health & Science University, University of Tennessee Health Science Center, University of Michigan, University of Utah, and Western Institutional Review Board. The study began in March 2011 and was completed in December 2015. Final analyses began on March 9, 2016. Participants provided written informed consent. There were no instances of unmasking. The full trial protocol is available in Supplement 1, and the statistical analysis plan is available in Supplement 2.

The study population (**Figure 1**) comprised men and women 18 years or older with genetically defined ADRP. Eligibility criteria are shown in eTable 1 in Supplement 3. Participants were enrolled at 6 US clinical sites: Bascom Palmer Eye Institute (University of Miami), Casey Eye Institute (Oregon Health & Science University), Hamilton Eye Institute (University of Tennessee Health Science Center), Kellogg Eye Center (University of Michigan), Moran Eye Center (University of Utah), and Retina Foundation of the Southwest. Eligible participants were randomized (stratified by site) in a 1:1 fashion to treatment with VPA or placebo using a computer-generated schedule with random block sizes (eTable 2 in Supplement 3).

Study Procedures and Visit Schedule

Eligible individuals returned within 12 weeks of screening for baseline assessment and randomization. Study visits were at 8,

Figure 1. CONSORT Flow Diagram for the Valproic Acid (VPA) Study



ADRP indicates autosomal dominant retinitis pigmentosa.

[a] Participants may not have passed more than 1 eligibility criterion.

[b] All valid data collected at baseline, week 26, and week 52 were included in the analysis regardless of whether the participant was missing data at 1 or more visits.

26, 39, 52, and 65 weeks. Dose was selected based on proof-of-concept studies, and known tolerability of VPA and was 500 mg to 1000 mg daily by baseline weight (not to exceed 500 mg in women of childbearing age) (eTables 3 and 4 in Supplement 3).

The primary outcome measure was the change in (semi-automated) kinetic perimetry (KP) visual field area (VFA) between baseline and week 52 as assessed by the III4e isopter. The III4e isopter was chosen because, compared with the V4e isopter, it provides greater sensitivity to detect short-term change in RP.[23] Additionally, the stimulus size and intensity have been used in several randomized clinical trials and studies of the condition.[24-30] Further justification is provided in eMethods in Supplement 3.

Secondary outcomes included the change in VFA between baseline and week 52 (I4e and V4e isopters) and static perimetry (SP) volumetric measurements of the full field and the central 30° field. Safety outcomes were incidence of adverse events, best-corrected visual acuity (using the Electronic Visual Acuity test and the Early Treatment Diabetic Retinopathy Study testing method), and clinical chemistry (liver/pancreatic function, serum ammonia, and VPA levels). Other outcomes collected included central macular thickness/volume/cystoid macula edema (spectral domain optical coherence tomography), vision-related quality of life (National Eye Institute Visual Function Questionnaire 25-item scale), fundus appearances, color contrast sensitivity (Chroma Test), and electroretinography.

Kinetic Perimetry Test Strategy

Test vectors originating 10° outside the age-correlated normal isopter were presented every 15° with 4° per second angular velocity. Six reaction-time (RT) vectors were presented within seeing areas, with 1 repetition horizontally, vertically, and diagonally, originating from 10° and 30° eccentricity. Scotomas were mapped at 2° per second angular velocity originating from the assumed center and using at least 12 vectors. Blind spots were mapped with the I4e stimulus, or the smallest and least bright stimulus seen, at 2° per second angular velocity with a minimum of 8 vectors originating from the assumed center.

Static Perimetry Testing

Full-field automated SP was performed using the German Adaptive Thresholding Estimation[30] strategy and a 164-point centrally condensed radial grid extending 79° temporally, 67° inferiorly, and 54.8° nasally and superiorly (eFigure 2 in Supplement 3).[23] The grid included paired sentinel test loci, both along the nasal step to monitor for glaucoma field defects and along the vertical radius superiorly to monitor for chiasmic and hemianopic neurologic loss. On-site training and certification were performed for SP and KP.

Perimetry Data Analysis

The Octopus perimetry software calculated areas (in degree^2) for each isopter automatically. For SP, data were exported to the Visual Field Monitoring and Analysis to calculate both full-field (ie, VTOT) and central 30° sensitivity volumes (ie, V30).[31] These volumes, with units of decibel steradian, characterize the quantity of function present in the hill of vision, which Visual Field Modeling and Analysis represents with thin-plate spline interpolation of the raw sensitivity values.

Safety Assessments

Treatment emergent adverse events were defined as those that occurred between the first dose of study drug and the last dose

Table 1. Summary of Baseline Demographics and Ocular Conditions by Treatment Arm

Characteristic	Treatment Arm, No. (%)	
	Placebo (n = 44)	VPA (n = 46)
Sex		
Male	24 (54.5)	22 (47.8)
Women of childbearing age	9 (20.5)	8 (17.4)
Women of nonchildbearing age	11 (25.0)	16 (34.8)
Age at randomization, mean (SD), y	51.6 (10.9)	49.3 (12.3)
Age at randomization, y		
<18	0	0
18-25	0	1 (2.2)
25-35	1 (2.3)	4 (8.7)
35-45	11 (25.0)	11 (23.9)
45-55	13 (29.5)	13 (28.3)
55-65	13 (29.5)	14 (30.4)
65-75	6 (13.6)	2 (4.3)
>75	0	1 (2.2)
Ethnicity		
Not Hispanic or Latino	38 (86.4)	41 (89.1)
Hispanic or Latino	6 (13.6)	5 (10.9)
Race		
American Indian or Alaska Native	0	0
Asian	0	0
Black or African American	0	1 (2.2)
Native Hawaiian or Pacific Islander	0	0
White	43 (97.7)	44 (95.7)
Other	1 (2.3)	0
Multiracial	0	1 (2.2)
Condition		
Cataract	13 (29.5)	12 (26.1)
Cataract surgery/pseudophakia	23 (52.3)	15 (32.6)
Cystoid macular edema	6 (13.6)	10 (21.7)
Dry eye	5 (11.4)	9 (19.6)
Strabismus	1 (2.3)	1 (2.2)
Corneal scar	1 (2.3)	0
Keratoconus	1 (2.3)	0
Myopic degeneration	0	1 (2.2)
Other ocular condition	6 (13.6)	3 (6.5)

Abbreviation: VPA indicates valproic acid.

of study drug, plus 7 days. Study stopping rules were defined but were never met during the study. Serum VPA measurements commenced 9 months after protocol initiation. The delay in implementation resulted in 16 participants not having VPA serum levels measured at 39 visits because those visits were conducted before clinical sites were in a position to collect samples.

Statistical Considerations

The analysis of the primary end point tested for significance of a VPA-placebo treatment effect based on change in KP VFA from baseline to week 52 using a linear mixed model, which accounted for the variability related to site, participant, eye within participant (right and left), and the replicates measured on each eye at each visit.[32] This model uses maximum likelihood methodology to estimate the means, variances, and covariances given the sample data.[33] This methodology is appropriate to account for missing data in the sample under a missing-at-random assumption.[32] This mixed-model approach was also used for the analysis of the KP I4e and V4e isopters and the SP parameters. In the KP analyses, for baseline visits in which 3 testing sessions were performed, the 2 most reliable sessions as determined by the Reading Center were used. For the SP analyses, only baseline sessions that were deemed reliable by the Reading Center were used.

All analyses followed the intent-to-treat principle with all randomized participants included and analyzed according to their treatment assignment regardless of amount or type of treatment received. All valid data collected at baseline, week 26, and week 52 visits were included in the analysis, regardless of whether the participant was missing data at 1 or more visits. The primary outcome results are presented using a *P* value and 95% confidence interval. For the secondary outcomes, the focus is on describing the uncertainty in the treatment effect estimates, thus 95% confidence intervals are provided to describe the results. Confidence intervals are unadjusted for multiplicity as planned a priori. Thus, inferences from the results of secondary outcomes should be interpreted with caution. The sample size chosen provided an 80% power to detect an improvement in visual field at 12 months (see eMethods in Supplement 3).

Results

Study Eligibility and Screen Failures

A total of 191 potential participants signed informed consent and entered into screening. Of the 191 individuals, 90 (47.1%) were randomized and 101 (52.9%) did not pass screening (eTable 5 in Supplement 3). The most common reason for screen failure was the absence of a molecularly confirmed ADRP mutation (34 [33.7%]).

Baseline Characteristics

Ninety participants were enrolled in the study (mean [SD] age, 50.4 [11.6] years). Eighty-seven participants (96.7%) were white, 79 (87.8%) were non-Hispanic/Latino, 46 (51.1%) were men, 44 (48.9%) were women, and 17 (18.9%) were women of childbearing age. Overall, 46 participants (51.1%) were randomized to receive VPA and 44 (48.9%) to placebo. Baseline demographic information was similar between the 2 treatment arms (**Table 1**).

Genetic Basis of ADRP in Randomized Participants

Of 90 participants, 41 (45.6%) had a mutation in the *RHO* gene, 14 (15.6%) in *PRPF31* (2 participants had 2 mutations), and 13 (14.4%) in *RP1*; 4 (4.4%) each had mutations in *PRPF8* and *PRPH2*, 2 (2.2%) each in *NR2E3*, *PRPF3*, *SNRNP200*/*ASCC3L1*, and *TOPORS*; and 1 (1.1%) each had *IMPDH1* or *KLHL7* mutations. Four other participants (4.4%) had 2 ADRP mutations: 2 (2.2%) with *RHO* and *PRPH2* mutations, 1 (1.1%) with

NR2E3 and *TOPORS*, and 1 (1.1%) with *RHO* and *ROM1* mutations. Mutations were distributed reasonably evenly between treatment arms (eTable 6 in Supplement 3).

Ocular Findings at Baseline

All participants had RP, 25 (27.8%) had cataract, 38 (42.2%) had pseudophakia (23 [52.3%] in placebo and 15 [32.6%] in VPA treatment arm), and 16 (17.8%) had cystoid macular edema (Table 1). Kinetic visual field area measurements are presented for each eye by treatment arm in eTable 7 in Supplement 3.

Distribution of Participants by Clinical Site

Enrollment occurred between March 2011 and September 2014 (3.5 years), and follow-up was completed in December 2015. The mean number of participants enrolled per site was 15 (range, 9-33).

Treatment Exposure and Compliance

Participants received treatment for a mean (SD) of 349.2 (62.6) days in the placebo arm and 325.5 (92.8) days in the VPA arm. No participants in either arm had detectable levels of VPA at baseline. In the placebo arm, no participants had detectable VPA during the study. No participants had critically high VPA serum levels (>130 µg/mL). As study drug dosing ended at week 52, all participants who had a week-65 visit had undetectable VPA serum levels (eResults in Supplement 3).

Primary Outcome: Assessment of Efficacy

For the placebo arm, the mean (SD) change between baseline and week 52 in KP VFA averaged over replicate measures was −122.9 (543.6) degree^2 and −112.0 (584.6) degree^2 for OD and OS, respectively. For the VPA arm, the mean (SD) change between baseline and week 52 averaged over replicate measures was −293.7 (736.6) degree^2 and −237.1 (691.8) degree^2 for OD and OS, respectively. A negative change from baseline reflects a worsening of the visual field. The results of the analysis from the linear mixed model show that the difference between the VPA and the placebo arms for mean change in KP VFA for the III4e isopter was −150.43 degree^2 (95% CI, −290.5 to −10.03; P = .04). This negative value indicates that the VPA arm significantly worsened compared with the placebo arm. To verify that the difference in baseline values between treatment arms did not affect the results, the analysis was repeated including the baseline value as a covariate in the model. The estimate of the treatment effect was −148.17 degree^2 and thus remains similar between the 2 models with no significant difference observed between the arms (P = .10; 95% CI, −325.15 to 28.8).

Secondary Efficacy Outcome Measures

A similar pattern is seen in the KP I4e isopter VFA in which the difference between the VPA and placebo arms for mean change was −83.40 degree^2 (95% CI, −211.3 to 44.5). This contrasts with the V4e findings in which the difference between the 2 arms was positive at 199.03 degree^2 (95% CI, 14.5 to 383.5; P = .04). **Table 2** summarizes the analysis of the kinetic visual field I4e, III4e, and V4e isopters, and **Figure 2** provides a graphical representation of the changes from baseline, averaged over both eyes at weeks 26 and 52.

Table 2. Analysis of Kinetic and Static Visual Fields

Characteristic	Estimate (SE)	(95% CI)
Kinetic perimetry		
I4e isopter	−83.40 (65.14)	(−211.3 to 44.5)
III4e isopter[a,b]	−150.43 (71.37)	(−290.5 to −10.3)
V4e isopter	199.03 (94.00)	(14.5 to 383.5)
Static perimetry		
VTOT	0.52 (0.63)	(−0.72 to 1.77)
V30	0.14 (0.11)	(−0.09 to 0.36)

Abbreviations: V30, central 30° sensitivity volume; VTOT, full-field sensitivity.

[a] P value for comparing VPA and placebo arms = .04.

[b] Primary outcome.

Static perimetry outcomes (**Figure 3**) were measured by assessing VTOT and V30. For VTOT, the difference between the VPA and placebo arms for mean change from baseline was 0.52 decibel steradian (95% CI, −0.72 to 1.77). For V30, the difference between the arms was 0.14 decibel steradian (95% CI, −0.09 to 0.36) (Table 2). eFigure 3 in Supplement 3 shows the spectrum of visual field changes eligible for participation in this study.

Effect of ADRP Genotype

The only genotype prevalent enough in the study for meaningful subanalysis was *RHO* (including 1 participant who also had a *ROM1* mutation). Analyses were performed to assess whether VPA affected the magnitude of field loss in patients with mutations in this gene. No significant difference between arms was seen for the primary outcome in this subgroup. Although 95% confidence intervals for the secondary outcomes were broad, there was no indication of a treatment effect.

Safety Assessments

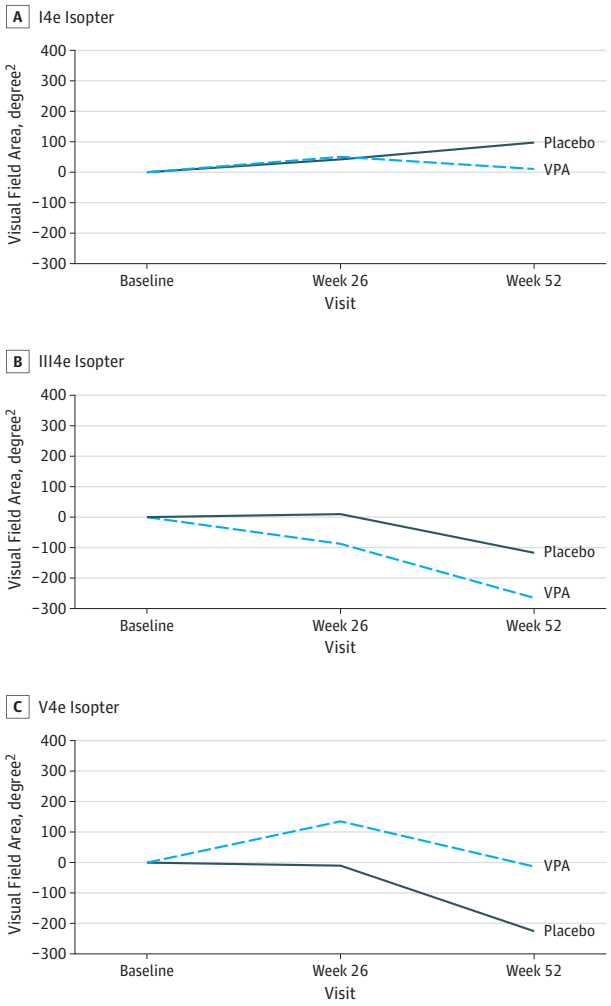
Safety was monitored throughout the study by a combination of clinical, ocular, and systemic evaluations, including clinical chemistry (eTable 8 in Supplement 3). No study stopping rules were met, and no pregnancies occurred.

Discussion

The scientific premise for this study was that VPA could ameliorate the molecular defects in ADRP. A proof-of-concept clinical study had suggested a biological effect (improved visual field size).[19] There was also concern that patients with RP were taking off-label VPA without adequate monitoring.

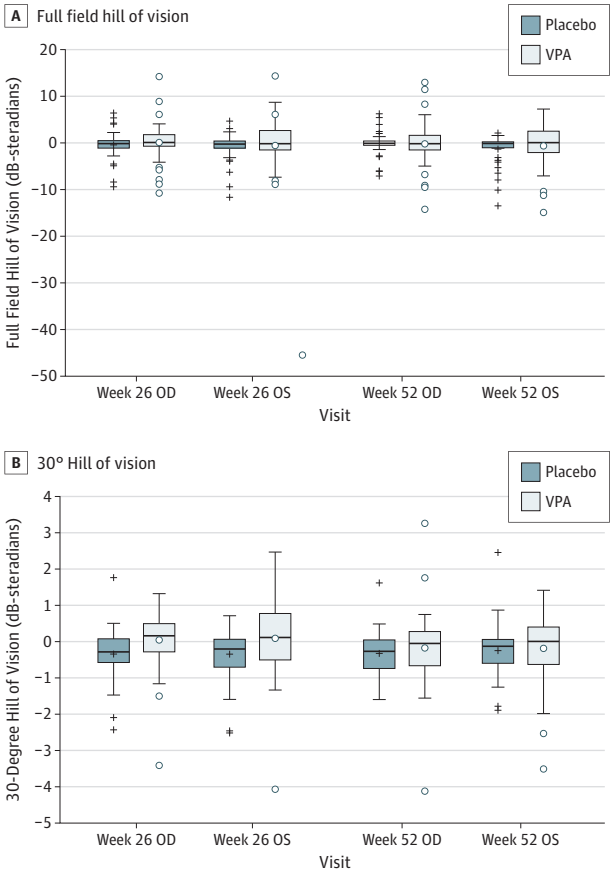
Valproic acid has been marketed for many years. Accordingly, it was concluded that the best evaluation of VPA as a treatment for ADRP would be a phase 2 randomized clinical trial. Given the orphan disease status of RP, the huge unmet medical need and the lack of other therapies, a positive result from the study might lead to a modified label for the drug to include the treatment of ADRP or spur the initiation of further trials to optimize dosage and target population. Following the observation of potential visual improvement, manifesting as

Figure 2. Change in Kinetic Visual Field From Baseline by Treatment Arm



VPA indicates valproic acid.

Figure 3. Change in Static Visual Field From Baseline by Treatment Arm



VPA indicates valproic acid.

an increase in visual field size[19] and remaining cognizant of the enrollment challenges in rare disease, the VPA study was statistically powered to detect improvement rather than to detect a slowing of the rate of degeneration.

Designing RP clinical trials to detect efficacy is difficult. Acuity does not deteriorate until advanced RP and its measurement is frequently confounded by cystoid macular edema. Visual field testing is disadvantaged by intrinsic variability, and the deterioration is slow. Anatomical biomarkers of disease progression, such as the ellipsoid zone[4,7,34-36] or fundus autofluorescence[37-40] and their correlation with visual field,[31,41-44] were unknown at study inception. Recent advances in perimetry include better equipment, analytical methods, and faster test algorithms, which led the study design team to choose kinetic perimetry as the primary end point. The Octopus 900 perimeter (Haag Streit) affords 2 major advances in visual field testing: (1) semiautomated KP testing and (2) the German Adaptive Thresholding Estimation fast-thresholding strategy, which allows rapid acquisition and duplicate testing, further reducing intertest variability.[45,46]

While initial clinical reports suggested a rapid improvement in the visual field from administration of VPA, the primary end point for the current trial was chosen to be 12 months, reflecting disease progression rate and yet reasonable assessment of durability. Before randomization, all participants were genotyped to confirm at the molecular level that they met the inclusion criteria. This approach should be considered for future trials, as almost half of those who showed interest in the study did not have a valid molecular diagnosis.

Despite broad eligibility criteria, a well-connected patient group, the support of a patient advocacy foundation, and all clinical sites being major research centers for inherited retinal disease, enrollment took 3.5 years. We suggest early engagement with patient groups, use of patient registries, databases, online resources, social media, and a larger number of clinical sites.

The eligibility criteria of this study allowed the enrollment of a participant group that adequately reflected a typical clinic population with a reasonably broad spectrum of ADRP. This study, however, failed to meet the primary end point. Indeed, those receiving VPA showed a statistically significant worsening of the KP III4e isopter at month 12, with the results from the analyses of the other KP and SP secondary outcomes providing little clarity as to the effect of VPA, with the estimates exhibiting a large amount of variability.

Limitations

The limitations of this study were 3-fold. In retrospect, because the study was powered to detect an improvement in visual function as predicted by prior studies, the trial was inadequately powered to detect a slowing of the degenerative process, and therefore such an effect may have been overlooked. For practical reasons, the study's primary end point was 12 months. Conceivably, a longer time frame may have been needed to show a small effect size. Although the study was limited to individuals with autosomal dominant retinitis pigmentosa, there was still significant genetic heterogeneity that may have masked any specific genotype-specific effect of valproic acid.

Conclusions

We conclude that 12-month oral VPA failed to show clinical benefit in participants with ADRP. There was minimal visual field change in the placebo group over 12 months, making it difficult to demonstrate a slowing of the decline in retinal function in ADRP. In the analysis plan, it was contemplated that VPA might have an effect that was genotype-specific. Only the *RHO* subgroup of individuals was large enough for analysis; no treatment effects were detected. This study prospectively assessed the use of VPA in ADRP but found no efficacy.

ARTICLE INFORMATION

Accepted for Publication: February 25, 2018.

Published Online: June 7, 2018. doi:10.1001/jamaophthalmol.2018.1171

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Obtained funding: Rose, Zilliox.
Administrative, technical, or material support: Birch, Lam, Heckenlively, Winthrop, Jayasundera, Hughbanks-Wheaton, Warner, Yang, Teske, Sklaver, Erker, Chegarnov, Smith, VanVeldhuisen, McCormack, Rose, Francis, Weleber.
Study supervision: Birch, Iannacone, Pennesi, Heckenlively, Csaky, Zilliox, Weleber.

Funding/Support: This research was supported by the Foundation Fighting Blindness and the Department of Defense, Human Research Protection Office, US Army Medical Research and Materiel Command.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Pennesi serves on advisory boards for the Foundation Fighting Blindness, an organization providing funding for this research. Dr Yang reports receiving support from the National Institutes of Health (grant NIH K08EY026650) and the Foundation Fighting Blindness Career Development Award (grant CD-NMT-0714-0648). Dr Francis reports personal fees from Foundation Fighting Blindness during the conduct of the study. Dr Weleber holds US patent no. 8657446, Method and apparatus for visual field monitoring, also known as Visual Field Modeling and Analysis; has served as principal investigator for clinical trials supported by Sanofi; and serves on advisory boards for Applied Genetic Technologies Corporation and the Foundation Fighting Blindness.

Additional Contributions: We thank Catherine L Schlechter, MS, MBI, Casey Eye Institute, Oregon Health & Science University, for assistance in genetic counseling and coordination of trial participants and who was compensated for her work; Joycelyn Niimi, OD, Casey Eye Institute, Oregon Health & Science University, for assistance with coordination of trial participants, perimetry and visual acuity testing and who was compensated for her work; Darius Liseckas, COT, Casey Eye Institute, Oregon Health & Science University for assistance with visual field perimetry testing and who was compensated for his work; Paula K Rauch, CRC, OT, Casey Eye Institute, Oregon Health & Science University, for assistance with visual field perimetry testing and who was compensated for her work; Peter Steinkamp, MS, Casey Reading Center, Oregon Health & Science University, for assistance with OCT and fundus photography quality control and who was compensated for his work; Maria Parker, MD, Casey Reading Center, Oregon Health & Science University, for assistance with OCT and fundus photography reading and who was compensated for her work; Edye Parker, MA, Casey Reading Center, Oregon Health & Science University, for assistance with data and information technology management and who was compensated for her work; Melissa Krahmer, MS, Casey Reading Center, Oregon Health & Science University for assistance with ERG quality control and reading and who was compensated for her work; Dagmar Salazar, MS, Emmes, for assistance with data management and protocol monitoring and who was compensated for her work; Maria June Figueroa, MBA, Emmes, for assistance with project management and clinical operations and who was compensated for her work; Gaurav Sharma, PhD, Emmes, for assistance with the statistical analysis and interpretation of results and who was compensated for his work; Neal Oden, PhD, Emmes, for assistance with the formulation and interpretation of the statistical model and who was compensated for his work; Kirsten Locke, RN, Retina Foundation of the Southwest, for assistance with study coordination and clinical testing and who was compensated for her work; Martin Klein, MS, Retina Foundation of the Southwest, for assistance with study coordination and clinical testing who was compensated for his work; Jorge Calzada, MD, University of Tennessee Health Science Center, for assistance with enrollment and clinical evaluation; and Barbara J. Jennings, OD, MA, for assistance with study coordination, clinical testing, data entry, compliance and who was compensated for her work.

Additional Information: Coauthor Steven Bramer, PhD, died.

REFERENCES

1. Jones BW, Pfeiffer RL, Ferrell WD, Watt CB, Marmor M, Marc RE. Retinal remodeling in human retinitis pigmentosa. *Exp Eye Res*. 2016;150:149-165.

2. Daiger SP, Bowne SJ, Sullivan LS. Genes and mutations causing autosomal dominant retinitis pigmentosa. *Cold Spring Harb Perspect Med*. 2014;5(10):a017129.

3. Chizzolini M, Galan A, Milan E, Sebastiani A, Costagliola C, Parmeggiani F. Good epidemiologic practice in retinitis pigmentosa: from phenotyping to biobanking. *Curr Genomics*. 2011;12(4):260-266.

4. Birch DG, Locke KG, Wen Y, Locke KI, Hoffman DR, Hood DC. Spectral-domain optical coherence tomography measures of outer segment layer progression in patients with X-linked retinitis pigmentosa. *JAMA Ophthalmol*. 2013;131(9):1143-1150.

5. Sandberg MA, Rosner B, Weigel-DiFranco C, Dryja TP, Berson EL. Disease course of patients with

X-linked retinitis pigmentosa due to RPGR gene mutations. *Invest Ophthalmol Vis Sci*. 2007;48(3):1298-1304.

6. Berson EL, Sandberg MA, Rosner B, Birch DG, Hanson AH. Natural course of retinitis pigmentosa over a three-year interval. *Am J Ophthalmol*. 1985;99(3):240-251.

7. Sullivan LS, Bowne SJ, Birch DG, et al. Prevalence of disease-causing mutations in families with autosomal dominant retinitis pigmentosa: a screen of known genes in 200 families. *Invest Ophthalmol Vis Sci*. 2006;47(7):3052-3064.

8. Cheng DL, Greenberg PB, Borton DA. Advances in retinal prosthetic research: a systematic review of engineering and clinical characteristics of current prosthetic initiatives. *Curr Eye Res*. 2017;42(3):334-347.

9. Caspi A, Roy A, Dorn JD, Greenberg RJ. Retinotopic to spatiotopic mapping in blind patients implanted with the Argus II retinal prosthesis. *Invest Ophthalmol Vis Sci*. 2017;58(1):119-127.

10. Güveli BT, Rosti RÖ, Güzeltaş A, et al. Teratogenicity of antiepileptic drugs. *Clin Psychopharmacol Neurosci*. 2017;15(1):19-27.

11. Casassus B. France steps up warning measures for valproate drugs. *Lancet*. 2016;387(10024):1148.

12. Chiu CT, Wang Z, Hunsberger JG, Chuang DM. Therapeutic potential of mood stabilizers lithium and valproic acid: beyond bipolar disorder. *Pharmacol Rev*. 2013;65(1):105-142.

13. Göttlicher M. Valproic acid: an old drug newly discovered as inhibitor of histone deacetylases. *Ann Hematol*. 2004;83(suppl 1):S91-S92.

14. Kimura A, Namekata K, Guo X, Noro T, Harada C, Harada T. Valproic acid prevents NMDA-induced retinal ganglion cell death via stimulation of neuronal TrkB receptor signaling. *Am J Pathol*. 2015;185(3):756-764.

15. Kimura A, Namekata K, Guo X, Harada C, Harada T. Neuroprotection, growth factors and BDNF-TrkB signalling in retinal degeneration. *Int J Mol Sci*. 2016;17(9):E1584.

16. Iannaccone A, Man D, Waseem N, et al. Retinitis pigmentosa associated with rhodopsin mutations: correlation between phenotypic variability and molecular effects. *Vision Res*. 2006;46(27):4556-4567.

17. Felline A, Seeber M, Rao F, Fanelli F. Computational screening of rhodopsin mutations associated with retinitis pigmentosa. *J Chem Theory Comput*. 2009;5(9):2472-2485.

18. Vent-Schmidt RYJ, Wen RH, Zong Z, et al. Opposing effects of valproic acid treatment mediated by histone deacetylase inhibitor activity in four Transgenic*X. laevis* models of retinitis pigmentosa. *J Neurosci*. 2017;37(4):1039-1054.

19. Clemson CM, Tzekov R, Krebs M, Checchi JM, Bigelow C, Kaushal S. Therapeutic potential of valproic acid for retinitis pigmentosa. *Br J Ophthalmol*. 2011;95(1):89-93.

20. Tzekov R, Bigelow C, Clemson C, Checchi J, Krebs M, Kaushal S. Authors' response. *Br J Ophthalmol*. 2011;95(8):1177-1179.

21. Iraha S, Hirami Y, Ota S, et al. Efficacy of valproic acid for retinitis pigmentosa patients: a pilot study. *Clin Ophthalmol*. 2016;10:1375-1384.

22. Bhalla S, Joshi D, Bhullar S, Kasuga D, Park Y, Kay CN. Long-term follow-up for efficacy and safety of treatment of retinitis pigmentosa with valproic acid. *Br J Ophthalmol*. 2013;97(7):895-899.

23. Swanson WH, Felius J, Birch DG. Effect of stimulus size on static visual fields in patients with retinitis pigmentosa. *Ophthalmology*. 2000;107(10):1950-1954.

24. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment. *Arch Ophthalmol*. 2004;122(9):1297-1305.

25. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. *Arch Ophthalmol*. 2010;128(4):403-411.

26. Birch DG, Weleber RG, Duncan JL, Jaffe GJ, Tao W; Ciliary Neurotrophic Factor Retinitis Pigmentosa Study Groups. Randomized trial of ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for retinitis pigmentosa. *Am J Ophthalmol*. 2013;156(2):283-292.

27. Birch DG, Bennett LD, Duncan JL, Weleber RG, Pennesi ME. Long-term follow-up of patients with retinitis pigmentosa receiving intraocular ciliary neurotrophic factor implants. *Am J Ophthalmol*. 2016;170:10-14.

28. Hoffman DR, Hughbanks-Wheaton DK, Spencer R, et al. Docosahexaenoic acid slows visual field progression in X-linked retinitis pigmentosa: ancillary outcomes of the DHAX Trial. *Invest Ophthalmol Vis Sci*. 2015;56(11):6646-6653.

29. McGuigan DB III, Roman AJ, Cideciyan AV, et al. Automated light- and dark-adapted perimetry for evaluating retinitis pigmentosa: filling a need to accommodate multicenter clinical trials. *Invest Ophthalmol Vis Sci*. 2016;57(7):3118-3128.

30. Kim LS, McAnany JJ, Alexander KR, Fishman GA. Intersession repeatability of humphrey perimetry measurements in patients with retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2007;48(10):4720-4724.

31. Schiefer U, Pascual JP, Edmunds B, et al. Comparison of the new perimetric GATE strategy with conventional full-threshold and SITA standard strategies. *Invest Ophthalmol Vis Sci*. 2009;50(1):488-494.

32. Ibrahim JG, Molenberghs G. Missing data methods in longitudinal studies: a review. *Test (Madr)*. 2009;18(1):1-43.

33. Kackar R, Harville D. Approximations for standard errors of estimators of fixed and random effect in mixed linear models. *J Am Stat Assoc*. 1984;79(388):853-862.

34. Cai CX, Locke KG, Ramachandran R, Birch DG, Hood DC. A comparison of progressive loss of the ellipsoid zone (EZ) band in autosomal dominant and X-linked retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2014;55(11):7417-7422.

35. Hariri AH, Zhang HY, Ho A, et al; Trial of Oral Valproic Acid for Retinitis Pigmentosa Group. Quantification of ellipsoid zone changes in retinitis pigmentosa using en face spectral domain-optical coherence tomography. *JAMA Ophthalmol*. 2016;134(6):628-635.

36. Ramachandran R, X Cai C, Lee D, et al. Reliability of a manual procedure for marking the EZ endpoint location in patients with retinitis pigmentosa. *Transl Vis Sci Technol*. 2016;5(3):6.

37. Oishi A, Ogino K, Makiyama Y, Nakagawa S, Kurimoto M, Yoshimura N. Wide-field fundus autofluorescence imaging of retinitis pigmentosa. *Ophthalmology*. 2013;120(9):1827-1834.

38. Oishi A, Oishi M, Ogino K, Morooka S, Yoshimura N. Wide-field fundus autofluorescence for retinitis pigmentosa and cone/cone-rod dystrophy. *Adv Exp Med Biol*. 2016;854:307-313.

39. Audo I, Manes G, Mohand-Saïd S, et al. Spectrum of rhodopsin mutations in French autosomal dominant rod-cone dystrophy patients. *Invest Ophthalmol Vis Sci*. 2010;51(7):3687-3700.

40. Robson AG, Michaelides M, Saihan Z, et al. Functional characteristics of patients with retinal dystrophy that manifest abnormal parafoveal annuli of high density fundus autofluorescence; a review and update. *Doc Ophthalmol*. 2008;116(2):79-89.

41. Weleber RG, Smith TB, Peters D, et al. VFMA: topographic analysis of sensitivity data from full-field static perimetry. *Transl Vis Sci Technol*. 2015;4(2):14.

42. Smith TB, Parker M, Steinkamp PN, Weleber RG, Smith N, Wilson DJ; VPA Clinical Trial Study Group; EZ Working Group. Structure-function modeling of optical coherence tomography and standard automated perimetry in the retina of patients with autosomal dominant retinitis pigmentosa. *PLoS One*. 2016;11(2):e0148022.

43. Hood DC, Ramachandran R, Holopigian K, Lazow M, Birch DG, Greenstein VC. Method for deriving visual field boundaries from OCT scans of patients with retinitis pigmentosa. *Biomed Opt Express*. 2011;2(5):1106-1114.

44. Rangaswamy NV, Patel HM, Locke KG, Hood DC, Birch DG. A comparison of visual field sensitivity to photoreceptor thickness in retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2010;51(8):4213-4219.

45. Parker MA, Choi D, Erker LR, et al. Test-retest variability of functional and structural parameters in patients with stargardt disease participating in the SAR422459 Gene Therapy Trial. *Transl Vis Sci Technol*. 2016;5(5):10.

46. Jeffrey BG, Cukras CA, Vitale S, Turriff A, Bowles K, Sieving PA. Test-retest intervisit variability of functional and structural parameters in X-linked retinoschisis. *Transl Vis Sci Technol*. 2014;3(5):5.