JOURNAL OF OCULAR PHARMACOLOGY AND THERAPEUTICS
Volume 30, Number 7, 2014

DOI: 10.1089/jop.2013.0166

Efficacy of Oral Valproic Acid in Patients with Retinitis Pigmentosa

Atul Kumar, Neha Midha, Varun Gogia, Shikha Gupta, Srivats Sehra, and Annu Chohan

Abstract

Purpose: To evaluate the efficacy of valproic acid (VPA) on visual function in patients with retinitis pigmentosa (RP).
Methods: Thirty patients (60 eyes) with typical RP were recruited for the study. Of these, 15 patients received oral VPA (500 mg once daily) for a period of 1 year (group 1) and the remaining 15 received no treatment (group 2) and served as controls. The effect of VPA on visual function was determined in terms of visual acuity, amplitude and implicit time in multifocal electroretinography (mfERG), and visual evoked response (VER) performed at presentation and at the third month, sixth month, and 1 year in both groups. Side effects of oral VPA were also monitored.
Results: At 1-year follow-up, 14 of 15 patients in group 1 had improvement in median best corrected visual acuity (BCVA) from 1.8 [Range (R) 1–3] at baseline to 1.3 (R, 0.6–1.3) ($P < 0.001$). In contrast, there was a slight decrease in median BCVA from 1.8 (0.8– 3) logarithm of the minimum angle of resolution (logMAR) at baseline to 1.83 ($P = 0.3$) in the control arm. There was also a statistically significant increase in improvement in amplitude and latency/implicit time in mfERG and VER in this group ($P < 0.001$). However, no such improvement was observed in the control arm.
Conclusions: Thus, VPA seems to have a positive effect on the visual functions in RP patients. Long-term studies evaluating the dose modifications, genetic analysis, and change in visual fields will add to our current knowledge.

Introduction

Retinitis pigmentosa (RP) is a retinal degenerative disease, involving photoreceptors, which is associated with night blindness, progressive peripheral visual field loss followed by reduction in central vision, and electroretinography (ERG) abnormalities.[1] It primarily affects the rods and later may involve the function of the cones also. Conventionally, full-field ERG has been used in the diagnosis and monitoring of RP, however, it measures retinal mass response and does not assess specifically the central retinal function. Multifocal ERG (mfERG) has been widely utilized to evaluate the central and regional variations of retinal dysfunction in RP patients.[2–5]

Currently there is no established treatment for RP. Various genes have been linked to the dominant and recessive forms of this disease making targeted gene therapy difficult. Furthermore, approaches, including nutritional supplementation, light reduction, and gene therapy,[6,7] have shown only modest benefits. Recently, experimental studies have documented the use of retinoid, valproic acid (VPA), and other molecules as pharmacological chaperones to increase the amount of properly folded RP mutant rhodopsins in heterologous cell culture.[5,7] Clemson et al.[8] had also previously shown benefits of VPA in terms of improvement in visual acuity in RP patients. VPA is FDA approved for use as a broad-spectrum anticonvulsant, as therapy for mania in bipolar disease and for migraine prophylaxis.[9,10] It acts as a potent inhibitor of histone deacetylase (HDAC) and inhibits the inflammatory response pathway through apoptosis of microglial cells.[11–14] A particularly exciting property of VPA has recently been documented suggesting that it has the unique ability to reverse photoreceptor damage and has been shown to stimulate glial cells to differentiate into photoreceptor-like cells.[11,15] In addition, it downregulates complement proteins and upregulates the levels of various neurotropic factors and, thus, shows a unique biological profile suitable for treating retinal diseases, including retinal dystrophies.[16,17] However, there is controversial evidence about the benefits of VPA therapy in RP.[18,19] To assess the effects of VPA in our population, we conducted this

Dr. Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India.

study wherein we used mfERG and change in visual acuity as objective parameters. mfERG allows independent and simultaneous stimulation of multiple retinal areas, thus recognizing localized areas of dysfunction. It gives a topographic analysis of focal retinal responses, which are displayed either in quadrants or in the form of concentric rings as in our study. Full-field ERG, on the other hand, tests the overall response to a stimulus and so will miss any localized area of retinal dysfunction.[20]

Methods

A pilot, prospective, single cohort interventional study was conducted at our tertiary care ophthalmic center (Dr. Rajendra Prasad Center for Ophthalmic Sciences). A diagnosis of RP was made in patients presenting to the vitreoretinal services at our center on the basis of history of night blindness and clinical signs like waxy pallor of the optic nerve, vascular attenuation, and/or the presence of intraretinal pigment. Patients with nonsyndromic RP, without any systemic association, cooperative for mfERG, and compliant for follow-up were included. Patients with atypical RP (e.g., sectoral, pericentral, or inverse), media opacities, cystoid macula edema (confirmed on ophthalmoscopy and optical coherence tomography), glaucoma, nystagmus, myopia greater than -6.00 diopter sphere (DS), or any systemic disease that could affect vision or their capacity to perform the tests were excluded. Patients with suspected liver or renal dysfunction, metabolic hereditary diseases or other urea cycle disorders, history of neurological disorders like epilepsy requiring any anticonvulsants, those with allergy to VPA or peanuts (peanut oil is an inactive ingredient in VPA capsules), pregnant women, and lactating mothers were excluded.

Based on the study by Clemson et al. and by keeping the power of the study to be 80%, the sample size was computed. The analysis, however, was done only on 60 eyes, for which complete follow-up data of 1 year were available. Thus, 60 eyes of 30 RP patients, which met above criteria, were included in this study. These were randomized (block randomization) into 2 groups, 15 patients (group 1) received VPA and 15 control subjects (group 2) did not receive any treatment. The evaluators were masked from the treatment and control group. Patients in group 1 were administered 500 mg/day ($\sim$10 mg/kg/day) of VPA every day (which is much lower than the anticonvulsant dose). Patient demographics, diagnosis, family history, best corrected visual acuity (BCVA), dosage of VPA, duration of treatment, blood chemistry included alanine aminotransferase, aspartate aminotransferase, serum urea, and ammonia, and electrolyte and blood cell panels included sodium, potassium, chloride, bicarbonate, creatinine, white blood cell count with differential red blood cell count and platelet count and reported side effects were recorded at baseline, 3 months, 6 months, and at 1 year. For each patient, baseline and follow-up mfERG (Vision monitor, Monpack 3; Metrovision) readings were recorded from each eye.

mfERG was recorded as per the guidelines issued by the International Society for Clinical Electrophysiology of Vision (ISCEV).[20] A patient was light adapted for at least 15 min in room light, pupils were fully dilated, an LCD screen was used to produce 61 regular hexagonal stimulus patterns with a viewing distance of 33 cm (corresponding to a field of $\pm 30°$ horizontally and $\pm 24°$ vertically) with a central fixation point, luminance of a bright hexagon was maintained at 100 cd/m^2, <1 cd/m^2 for dark hexagon, and 30 cd/m^2 for background cover. The stimulus frequency was set at 17 Hz. Recording was done monocularly using contact lens electrodes after anesthetizing the cornea with 1% proparacaine, with near refractive correction; fixation was monitored on a camera system. The total duration of pseudorandom stimulation was 5 min.

Visual acuity was recorded using a Snellen chart at a distance of 20 feet (6.1 m). Values were converted to the logarithm of the minimum angle of resolution (logMAR) score for statistical analysis. Statistical analysis was performed on SPSS 17 for Windows. In intragroup analysis, that is, pre- and post-treatment visual acuity, mfERG and, visual evoked response (VER) were compared in each group separately using the Wilcoxon signed-rank test. In intergroup analysis, the changes in the above-mentioned parameters over 1 year were compared between the groups using the Mann–Whitney U test. A P-value of <0.05 was considered as statistically significant. Continuous variables have been described as median (range, R: minimum–maximum).

The research followed the tenets of the Declaration of Helsinki and informed consent was obtained. The research was approved by the institutional review board and institutional ethics committee.

Results

Demography

We recruited 30 patients with bilateral RP. Group 1 comprised 10 males (66.6%) and 5 females, whereas in group 2, 12 were males (80%) and 3 were females. The median age of patients in both groups was 30 years (R, group 1: 15–47; group 2: 15–57 years). Both the groups were comparable in terms of age and baseline visual acuity (Table 1).

Visual acuity

The median logMAR BCVA improved from 1.8^{1-3} in group 1 at baseline to 1.3 (0.6–1.3) at 1-year follow-up in group 1 (30 eyes). This change was statistically significant ($P<0.001$). On the other hand, in controls (30 eyes), there was a slight decrease in median BCVA from 1.8 (0.8–3) logMAR at baseline to 1.83 at 1-year follow-up ($P=0.3$) (Fig. 1a, b). A statistically significant difference was also seen for change in visual acuity between the 2 groups at the end of 1 year ($P=0.000$).

mfERG results

Central ring ($\leq 2°$). In the central 2° in group 1, the median amplitude increased from 137.5 nV (0–560) at baseline to 314.75 nV (0–753) at 1 year and the median latency decreased from 47.75 ms (0–78.4) at baseline to 40.3 ms (0–57.3) at 1 year; both these changes were statistically significant ($P<0.001$ for both). In group 2, amplitude decreased from 232.1 nV (0–1,065) at baseline to 74.3 nV (0–1200) at 1 year ($P=0.46$) and latency decreased from 46.75 ms (0–67.2) to 33.4 ms (0–60.1) ($P=0.001$) (Fig. 2a, b). On intergroup analysis, there was a significant improvement in amplitude ($P<0.001$). However, the change in implicit time between 2 groups was not significant ($P=0.367$).

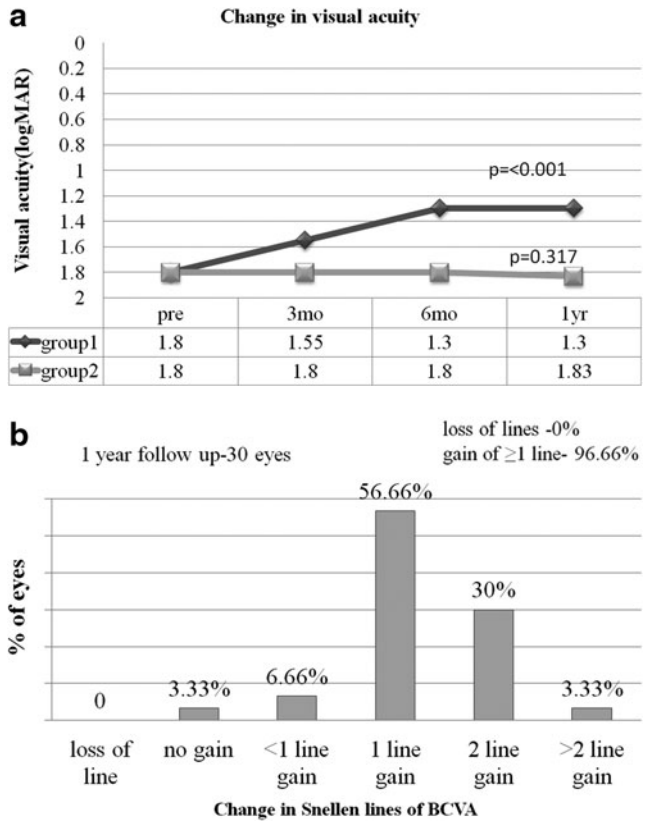

FIG. 1. **(a)** Graph depicting change in visual acuity in the 2 groups over 1 year. While there was a significant gain in visual acuity in group 1, no such change was observed in the control arm, reflecting natural disease progression. **(b)** Graph showing a gain in vision by at least 1 line in ~97% patients in group 1.

2°–5° ring. Median amplitude changed from 138 nV (0–567) at baseline to 272.5 nV (0–702) ($P < 0.001$) at 1 year and latency decreased from 55.6 ms (0–90.1) at baseline to 44.2 ms (0–77.3) at 1 year ($P = 0.009$) in group 1. On the contrary, in group 2, the median amplitude changed from 8.55 nV (0–388.1) at baseline to 132.1 nV (0–444.6) at 1-year follow-up ($P = 0.259$) and median latency changed from 55.6 (0–69.5) at baseline to 44.2 (0–77.1) at 1 year ($P = 0.009$; Wilcoxon signed-rank test) (Fig. 2c, d). Intergroup analysis also revealed significant improvement in amplitude and implicit time ($P < 0.001$).

5°–10° ring. Group 1 showed increase in the median amplitude from 107.5 nV (0–312) at baseline to 184.5 nV (0–423) at 1 year and the median latency decreased from 52.95 ms (0–76.8) at baseline to 41.4 ms (0–61.2) at 1 year; these changes were found to be statistically significant in both ($P < 0.001$). In group 2, the median amplitude changed from 135 nV (0–987) at baseline to 85.65 nV (0–338.4) at 1 year ($P = 0.02$) and the median latency decreased from 42.25 ms (0–66.7) at baseline to 38.4 ms (0–85) ($P = 0.1$) (Fig. 2e, f). On intergroup analysis, there was significant improvement in amplitude ($P < 0.001$), while no change in implicit time was observed ($P = 0.416$).

10°–15° ring. In group 1, the median amplitude increased from 114 nV (0–424) at baseline to 257 nV (0–487) at 1 year and the median latency decreased from 51.85 ms (0–74.1) at baseline to 43.45 ms (0–52.7) at 1 year ($P < 0.001$ for both). In group 2, the change in median amplitude was from 56.6 nV (0–728.6) at baseline to 118 nV (0–393.6) at 1 year (p 0.9). The change in median latency was from baseline value of 38.15 ms (0–68.6) to 38.8 ms (0–65.6) at 1-year follow-up ($P = 0.2$) (Fig. 2g, h). While there was significant improvement in amplitude on intergroup analysis ($P < 0.017$), the change in implicit time did not reach significance ($P = 0.458$).

≥15° ring. In group 1 eyes, the median amplitude increased from 96.85 nV (0–783) at baseline to 199.5 nV (0–815) at 1 year and the median latency decreased from 52.2 ms (0–73.1) at baseline to 44 ms (0–63.2) at 1 year ($P < 0.001$ for both). In group 2, the change in amplitude was from 42.75 nV (0–444.3) at baseline to 47.9 nV (0–412) at 1 year ($P = 0.3$). The median latency changed from 23.65 ms (0–52.3) at baseline to 29.1 ms (0–48.1) at 1 year ($P = 0.5$) (Fig. 2i, j). Similar to all other rings, significance was seen in amplitude ($P < 0.001$) on intergroup analysis, while change in implicit time was not significant ($P = 0.382$).

VER results

In group 1 eyes, median amplitude increased from 3.99 μV (0–12) at baseline to 5.4 μV (0–13.1) at 1-year follow-up and median latency decreased from 129 ms (0–167) at baseline to 96.5 ms (0–136) at 1-year follow-up ($P < 0.001$ for both). In the control group, there was no change in the median amplitude value at 1-year follow-up, which was 3 μV (0–18) at baseline. Latency, however, changed from 87.5 ms (0–108) at baseline to 93.5 (0–170) at 1-year follow-up ($P = 0.5$ and 0.39, respectively) (Fig. 3a, b). On intergroup analysis, there was significant improvement in amplitude and latency ($P < 0.004$ and < 0.001, respectively).

None of the patients experienced any adverse side effects requiring termination of VPA therapy. However, 3 patients developed gastritis, which was managed with antihistamines. No derangement was noted in serum chemistry or liver function tests at each follow-up in any of the patients. Table 2 gives normal range for liver function parameters for our laboratory.

Discussion

In the absence of any standard protocol for restoration of visual functions in RP patients and past evidence of failed attempts to delay the progression of photoreceptor loss in RP patients with nutritional supplementation such as vitamin A[2–4] or hyperbaric oxygen therapy,[21] this study was conducted to evaluate the efficacy of VPA on central visual functions in RP patients.

VPA is widely used as an anticonvulsant and mood stabilizer and its efficacy in these capacities is probably mediated through its ability to affect gamma-aminobutyric acid (GABA) levels through glutamic acid decarboxylase and GABA transaminase modulation.[22,23] Recent evidence suggests that VPA may work at the cellular level for cell death protection or inflammatory mediation for its neuroprotective action.[24,25] It can down-regulate the photoreceptor-specific inflammatory response pathway through apoptosis of microglial cells.[12–14] Furthermore, VPA is known to be a potent inhibitor of HDAC, which is involved in epigenetic regulation of gene expression.[10] Data by Noorwez[5] showed that there was an increase in yield of

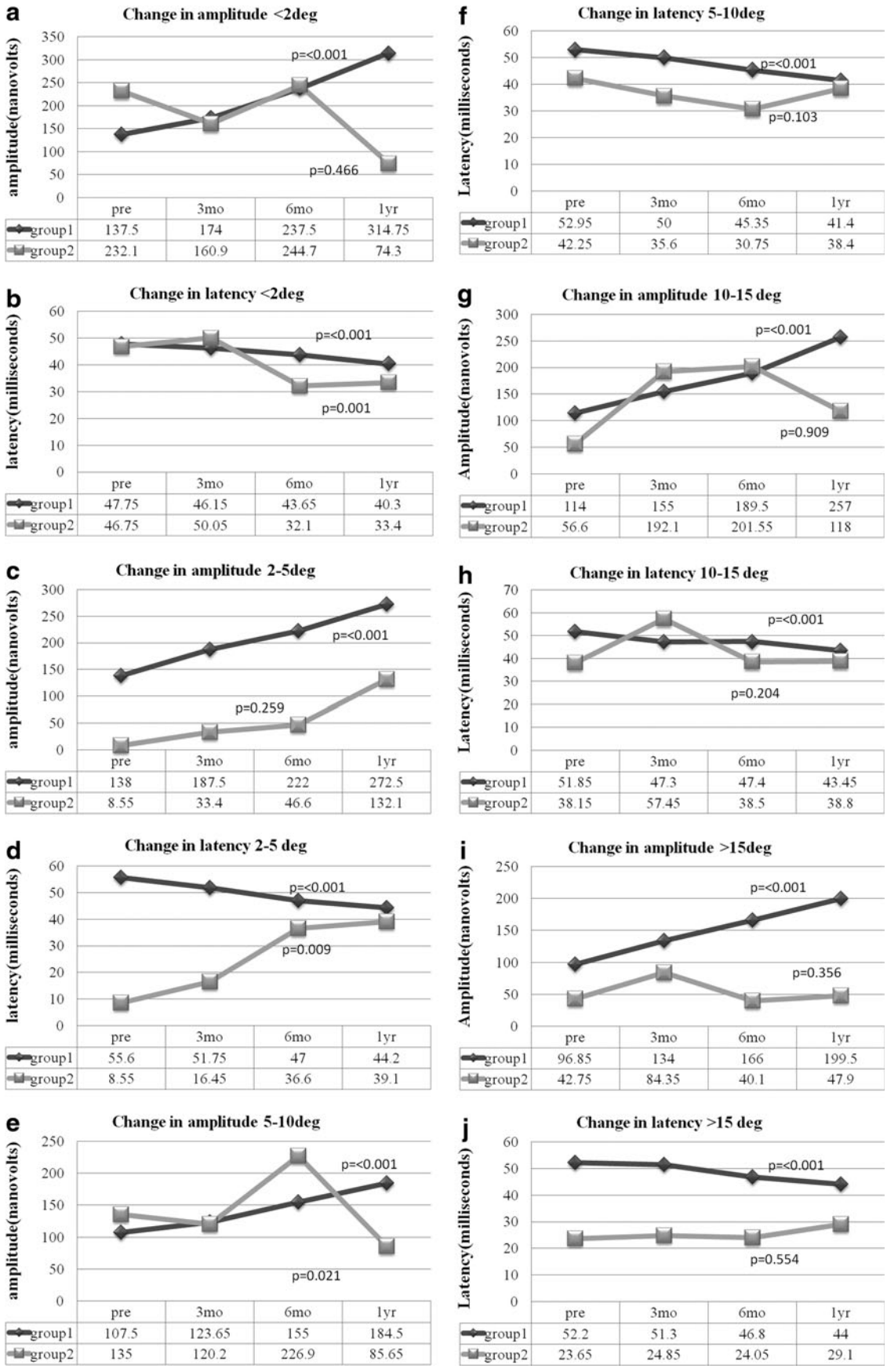

FIG. 2. **(a–j)** Graphs showing change in amplitude and latency in groups 1 and 2 over 1 year at different multifocal electroretinography rings, that is, $<2°$, $2°–5°$, $5°–10°$, $10°–15°$, and $>15°$.

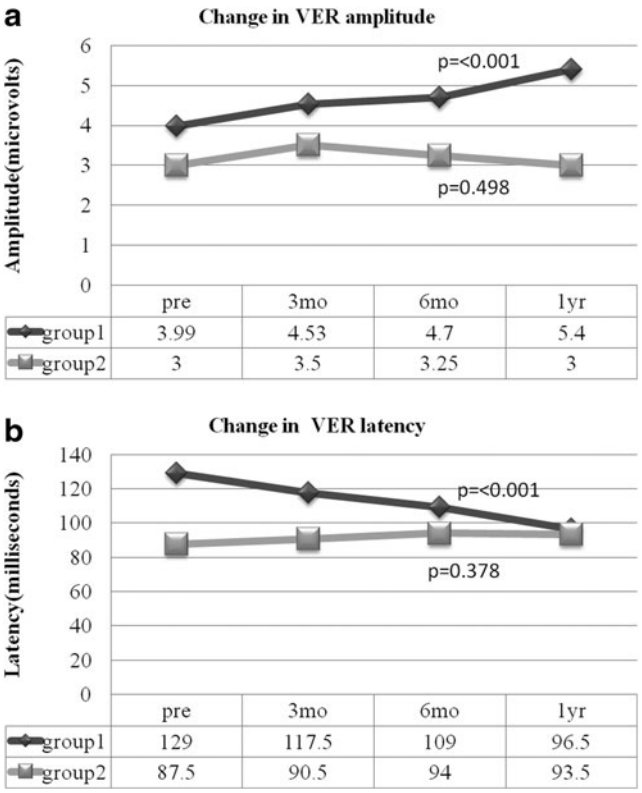

FIG. 3. Graphs showing significant increment in visual evoked response (VER) amplitude **(a)** and improvement in latency **(b)** in group 1 over time in contrast to the control arm.

properly folded RP mutant rhodopsins after treatment with oral VPA in heterologous cell cultures. This adds to the hypothesis that VPA has a potential role as a retinal therapeutic agent.

In our study, a statistically significant improvement in visual acuity in patients on VPA was observed at 1 year in comparison to the control group, which experienced no change in the visual acuity. The results described here add to the initial findings of Clemson et al.,[8] where they report therapeutic potential of VPA in RP. Change in visual acuity in our series, however, was much more as reported by them. We observed a fall in logMAR BCVA by 0.5 units, which correlates to a positive change from approximately 6/379 to 6/120 Snellen equivalent in comparison to their series that showed a logMAR change of 0.172 lines. We speculate that the difference resulted from different presenting median visual acuity in patient population as we recruited patients with lower baseline (1.8 in logMAR) median visual acuity. As a result, the improvement seen was much more in contrast to the above series. Because of lower baseline visual acuity of patients recruited, we were also unable to perform visual fields in most of our patients

mfERG provides an objective measurement of retinal function in RP and is used for assessing central retinal function in these patients. Holopigian et al. had demonstrated that the extent of visual field loss correlates significantly with cone-mediated mfERG amplitude as well as the implicit time.[26] Thus, mfERG results were analyzed over the follow-up to assess the role of VPA in preservation of vision in RP patients. Nagy et al. in their long-term follow-up of RP patients with mfERG have demonstrated that these patients are expected to show 6%–10% reduction in mfERG amplitudes annually.[1] However, we recorded a statistically significant increase in the mfERG amplitude and a decrease in the latency in all fields consistently in patients on oral VPA therapy, which also correlated well to the VER amplitude and latency, thus demonstrating the

TABLE 1. DEMOGRAPHY

Patient No.	*Group*	*Age (years)*	*Sex*	*Family history*
1	Case	15	M	No
2	Case	27	M	No
3	Case	20	M	No
4	Case	26	F	No
5	Case	30	F	No
6	Case	30	M	No
7	Case	29	M	Yes
8	Case	36	M	No
9	Case	28	F	No
10	Case	28	M	No
11	Case	38	M	Yes
12	Case	40	F	No
13	Case	30	M	Yes
14	Case	32	F	No
15	Case	47	M	No
16	Control	25	M	No
17	Control	28	F	No
18	Control	15	M	Yes
19	Control	25	M	No
20	Control	30	M	No
21	Control	30	M	No
22	Control	31	M	No
23	Control	37	F	No
24	Control	30	M	No
25	Control	22	M	No
26	Control	39	M	No
27	Control	41	M	No
28	Control	30	F	No
29	Control	27	M	No
30	Control	57	M	Yes

M, male; F, female.

TABLE 2. LIVER FUNCTION TESTS DONE AND THEIR NORMAL RANGE FOR OUR LABORATORY

Test	*Normal range*
Serum bilirubin (mg/dL) total	0.2–1.15
Direct	0.1–0.3
Indirect	0.2–0.9
SGOT (U/L)	15–37
SGPT (U/L)	15–65
Gamma GT (U/L)	5–85
ALP (U/L)	50–136
LDH (U/L)	81–234
Proteins (g/dL) total	6.4–8.2
Albumin	3.4–5.0
Globulin	1.5–3.6
A/G ratio	
Inorganic phosphorus (mg/dL)	2.5–4.9
Calcium (mg/dL)	8.5–10.1
Chloride (mmol/L)	96–110

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; Gamma GT, gamma glutamyl transferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; A/G, albumin/globulin.

positive protective effects of VPA on photoreceptors and therapeutic efficacy of the drug.

On the contrary, the control subjects experienced no change in BCVA over 1 year. This was also reflected on intergroup analysis where the groups that were comparable at baseline had a significant difference in final median visual acuity. A similar outcome was also seen on comparing VER in both the groups, the control group showing no change over the follow up. The mfERG responses displayed similar patterns of no change at most tested locations, except for attenuated latency at hexagons within 5° of macula. We hypothesize that this may be due to certain inherent limitations of mfERG recording such as an average variability of test–retest ranges from 10% to 20% of amplitude response.[27–29] Multifocal response variance has been found to be maximum in the central 2 rings.[30] Furthermore, sometimes the signal-to-noise ratio improves after the waveform responses are averaged. Other than these, some variants of RP are known to progress slowly.[31] The improvement in implicit time may also be related to seasonal variation of retinal sensitivity as demonstrated in ocular hypertension.[32]

We must say that our results differ from a few previously published reports. However, there are only 2 series with a relatively good number of patients as reported by Clemson et al. with 11 patients who demonstrated a favorable role of oral VPA in RP and the other by Bhalla et al. with 21 RP patients with conflicting results.[18] There is one other single report of 3 patients that is in agreement with Bhalla et al.[19] Since RP is a degenerative disease and the phenotype depends on genetic heterogeneity and inheritance, response to oral VPA may be varied in different populations. Moreover, we have kept a control group in our pilot study, which on intergroup analysis shows favorable results with oral VPA in RP patients, thus advocating its use. Based on a few reports, it is difficult to understand the exact role of this novel therapeutic agent for this blinding disease in the absence of any definitive treatment as yet.

VPA is known to cause a spectrum of side effects and can lead to central nervous system toxicity in higher doses and is contraindicated in various conditions as already described in Methods section. However, most of the side effects are dose related. We, however, observed no significant side effects in our patients on therapy with VPA, except for mild gastritis in 3 patients. The absence of significant side effects can be explained by the fact that the dosages used (10 mg/kg/day) were much less than actually prescribed for other indications like as an anticonvulsant (25–40 mg/kg/day).

Although we could assess the impact of VPA on macular function tests through central vision and mfERG testing, mid-peripheral retinal function using kinetic perimetry could not be evaluated. Another limitation includes that the patients were not genetically characterized, and genetic variation in RP might account for variability in the therapeutic response to VPA.[33] Despite these obvious limitations, our study offers useful information regarding the benefits of VPA as a potential therapy for RP, which currently has no established treatment modalities. VPA might alter the progression of this relentlessly progressive retinal degeneration.

Author Disclosure Statement

This is to certify that the article was not presented in any meeting. The authors did not receive any financial support from any public or private source. The authors have no financial or proprietary interest in a product, method, or material described herein. None of the authors has any conflicts of interest with the submission.

References

1. Nagy, D., Schonfisch, B, Zrenner, E., et al. Long-term follow-up of retinitis pigmentosa patients with multifocal electroretinography. *Invest. Ophthalmol. Vis. Sci.* 49:4664–4671, 2008.
2. Berson, E.L., Rosner, B., Sandberg, M.A., et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch. Ophthalmol.* 111:761–772, 1993.
3. Berson, E.L., Rosner, B., Sandberg, M.A., et al. Vitamin A supplementation for retinitis pigmentosa. *Arch. Ophthalmol.* 111:1456–1459, 1993.
4. Li, T., Sandberg, M.A., Pawlyk, B.S., et al. Effect of vitamin A supplementation on rhodopsin mutants threonine-17/methionine and proline-347/serine in transgenic mice and in cell cultures. *Proc. Natl. Acad. Sci. U. S. A.* 95: 11933–11938, 1998.
5. Noorwez, S.M., Ostrov, D.A., McDowell, J.H., et al. A high-throughput screening method for small-molecule pharmacologic chaperones of misfolded rhodopsin. *Invest. Ophthalmol. Vis. Sci.* 49:3224–3230, 2008.
6. Delyfer, M.N., Leveillard, T., Mohand-Said, et al. Inherited retinal degenerations: therapeutic prospects. *Biol. Cell* 96: 261–269, 2004.
7. Hartong, D.T., Berson, E.L., and Dryja, T.P. Retinitis pigmentosa. *Lancet*. 368:1795–1809, 2006.
8. Clemson, C.M., Tzekov, R., Krebs, M., et al. Therapeutic potential of valproic acid for retinitis pigmentosa. *Br. J. Ophthalmol.* 95:89–93, 2011.
9. Henry, T.R. The history of valproate in clinical neuroscience. *Psychopharmacol. Bull.* 37[Suppl 2]:5–16, 2003.
10. Monti, B., Polazzi, E., and Contestabile, A. Biochemical, molecular and epigenetic mechanisms of valproic acid neuroprotection. *Curr. Mol. Pharmacol.* 2:95–109, 2009.
11. Gottlicher, M., Minucci, S., Zhu, P., et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. *EMBO J.* 20:6969–6978, 2001.
12. Dragunow, M., Greenwood, J.M., and Cameron, R.E. Valproic acid induces caspase 3-mediated apoptosis in microglial cells. *Neuroscience.* 140:1149–1156, 2006.
13. Chen, P.S., Wang, C.C., and Bortner, C.D. Valproic acid and other histone deacetylase in hibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity. *Neuroscience.* 149:203–212, 2007.
14. Kim, H.J., Rowe, M., Ren, M., et al. Histone deacetylase inhibitors exhibit anti-inflammatory and neuroprotective effects in a rat permanent ischemic model of stroke: multiple mechanisms of action. *J. Pharmacol. Exp. Ther.* 321: 892–901, 2007.
15. Kubota, A., Nishida, K., Nakashima, K., et al. Conversion of mammalian Muller glial cells in to a neuronal line age by *in vitro* aggregate-culture. *Biochem. Biophys. Res. Commun.* 351:514 e 20, 2006.
16. Suuronen, T., Nuutinen, T., Ryhanen, T., et al. Epigenetic regulation of clusterin/apo lipoprotein J expression in retinal pigment epithelial cells. *Biochem. Biophys. Res. Commun.* 357:397–401, 2007.
17. Yasuda, S., Liang, M.H., Marinova, Z., et al. The mood stabilizers lithium and valproate selectively activate the

promoter IV of brain-derived neurotrophic factor in neurons. *Mol. Psychiatry.* 14:51–59, 2005.
18. Bhalla, S., Joshi, D., Bhullar, S., et al. Long-term follow-up for efficacy and safety of treatment of retinitis pigmentosa with valproic acid. *Br. J. Ophthalmol.* 97:895–899, 2013.
19. Sisk, R.A. Valproic acid treatment may be harmful in non-dominant forms of retinitis pigmentosa. *Br. J. Ophthalmol.* 96:1154–1155, 2012.
20. Hood, D.C., Bach, M., Brigell, M., et al. ISCEV standard for clinical multifocal electroretinography [mfERG] [2011 edition]. *Doc. Ophthalmol.* 124:1–13, 2012.
21. Vingolo, E.M., Rocco, M., Grenga, P., et al. Slowing the degenerative process, long lasting effect of hyperbaric oxygen therapy in retinitis pigmentosa. *Graefes Arch. Clin. Exp. Ophthalmol.* 246:93–98, 2008.
22. Chapma, N.A., Keane, P.E., Meldrum, B.S., et al. Mechanism of anticonvulsant action of valproate. *Prog. Neurobiol.* 19:315–359, 1982.
23. Mac Donald, R.L., and Bergey, G.K. Valproic acid augments GABA-mediated postsynaptic inhibition in cultured mammalian neurons. *Brain Res.* 170:558–562, 1979.
24. Feng, H.L., Leng, Y., Ma, C.H., et al. Combined lithium and valproate treatment delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model. *Neuroscience*. 155:567–572, 2008.
25. Leng, Y., Liang, M.H., Ren, M., et al. Synergistic neuroprotective effects of lithium and valproic acid or other histone deacetylase inhibitors in neurons: roles of glycogen synthase kinase-3 inhibition. *J. Neurosci.* 28:2576–2588, 2008.
26. Holopigian, K., Seiple, W., Greenstein, V.C., et al. Local cone and rod system function in progressive cone dystrophy. *Invest. Ophthalmol. Vis. Sci.* 43:2364–2373, 2002.
27. Seiple, W., Clemens, C.J., Greenstein, V.C., et al. Test-retest reliability of the multifocal electroretinogram and Humphrey visual fields in patients with retinitis pigmentosa. *Doc. Ophthalmol.* 109:255–272, 2004.
28. Bock, M., Andrassi, M., Belitsky, L., et al. A comparison of two multifocal ERG systems. *Doc. Ophthalmol.* 97:157–178, 1998–1999.
29. Marmor, F.M. Do you, doctor, take the mfERG for better or for worse. *Graefes Arch. Clin. Exp. Ophthalmol.* 240:241–243, 2002.
30. Maiti, A., Uparkar, M., Natarajan, S., et al. Principal components' analysis of multifocal electroretinogram in retinitis pigmentosa. *Indian J. Ophthalmol.* 59:353–357, 2011.
31. Choi, J.Y., Sandberg, M.A., and Berson, E.L. Natural course of ocular function in pigmented paravenous retinochoroidal atrophy. *Am. J. Ophthalmol.* 141:763–765, 2006.
32. Gardiner, S.K., Demirel, S., Gordon, M.O., et al. Seasonal changes in visual field sensitivity and intraocular pressure in the ocular hypertension treatment study. *Ophthalmology.* 120:724–730, 2013.
33. Birch, D.G., Anderson, J.L., and Fish, G.E. Yearly rates of rod and cone functional loss in retinitis pigmentosa and cone-rod dystrophy. *Ophthalmology.* 106:258–268, 1999.

Received: September 29, 2013
Accepted: April 25, 2014

Address correspondence to:
Dr. Neha Midha
Dr. Rajendra Prasad Center for Ophthalmic Sciences
All India Institute of Medical Sciences
Ansari Nagar
New Delhi 110029
India

E-mail: neha.midha1@gmail.com