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Vigabatrin for the Treatment of Infantile Spasms: Final Report of a Randomized Trial

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Abstract

A large randomized study was conducted in patients with newly diagnosed infantile spasms to compare 2 doses of vigabatrin in achieving spasm cessation. High (100-148 mg/kg/d) and low (18-36 mg/kg/d) oral doses of vigabatrin were evaluated in a randomized, single-blind study of 14 to 21 days with subsequent open-label treatment up to 3 years. Spasm cessation was defined as 7 consecutive days of spasm freedom beginning within the first 14 days, confirmed by video-electroencephalogram. A total of 221 subjects comprised the modified intent-to-treat cohort. More subjects in the high-dose group achieved spasm cessation compared with the low-dose vigabatrin group (15.9% [17/107] vs 7.0% [8/114]; $P = .0375$). During follow-up, 39 of 171 (23%) subjects relapsed; 28 of 39 (72%) regained spasm freedom. Adverse events were primarily mild to moderate in severity. Vigabatrin had a dose-dependent effect in spasm reduction. Spasm cessation occurred rapidly and was maintained in the majority of infants.

Keywords

vigabatrin, infantile spasms, epilepsy, anticonvulsant, clinical trial

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Vigabatrin is an analog of γ-aminobutyric acid (GABA) that selectively and irreversibly inhibits GABA-oxoglutarate aminotransferase, the principle enzyme responsible for GABA degradation.[1-4] Small controlled and uncontrolled studies provided initial support for vigabatrin as a potentially effective treatment for infantile spasms,[5-9] and it has been used outside the United States for more than 15 years for that purpose.[10] The current trial was conducted as a way to provide vigabatrin to patients with infantile spasms prior to regulatory approval and to obtain evidence concerning the efficacy and safety of the drug. At the request of the United States Food and Drug Administration, the study was conducted as a controlled clinical trial comparing 2 doses of vigabatrin.

The long-term developmental outcome of patients with infantile spasms is thought to benefit from rapid and complete control of the spasms.[11-14] Therefore, prolonged, placebo-controlled trials are not considered ethical in this population. The present study compared 2 doses of vigabatrin in a randomized, single-blind clinical study. Complete spasm cessation was defined by both clinical and electroencephalographic (EEG) criteria as a stringent outcome measure to evaluate the efficacy of vigabatrin in the treatment of infantile spasms. An interim analysis based on data collected through February 1999 from 142 evaluable subjects in this study has been previously published.[10] This report reviews the findings from the complete study population.

Methods

Participants

The design of this study has been previously published in detail.[10] The study was a multicenter, randomized, single-blind study of 14 to 21 days' duration followed by an open-label extension phase of up to 3 years' duration. All study sites were within the United States and obtained Institutional Review Board approval prior to enrolling study subjects. Parents or legal guardians were to have provided written

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informed consent prior to any study procedures. All subjects were to have a diagnosis of infantile spasms of less than 3 months' duration, were to be <2 years of age, were to weigh at least 3.5 kg, and could not have been treated with corticosteroids, adrenocorticotropic hormone, or valproic acid. Subjects could be on stable doses of non–infantile spasm antiepileptic drugs such as phenobarbital or clonzepam. The clinical diagnosis of infantile spasms was confirmed by findings of hypsarrhythmia, modified hypsarrhythmia, or multifocal spike wave discharges or by a video-EEG recording that captured an event confirming the diagnosis of infantile spasms. The study required a magnetic resonance imaging or a computed axial tomography scan of the brain within 12 months of the baseline visit to confirm the absence of a progressive lesion, as well as a normal ophthalmologic examination result or an abnormal examination finding documenting a static problem. Subjects were excluded from the study if they had a treatable or progressive cause of seizure, a currently active medical disorder that would interfere with the safe completion of the study, Lennox-Gastaut syndrome, a history of generalized tonic-clonic status epilepticus, poor medication compliance, or caregivers unable to keep accurate records of seizures.

This study was initially planned as a compassionate use study to allow physicians to distribute the study drug while a New Drug Application for vigabatrin was under review by the Food and Drug Administration. The trial subsequently became a controlled study comparing high-dose and low-dose vigabatrin, in cooperation with the Food and Drug Administration. While the original sample size was based on published reports of treatment effect[7] and spontaneous remission rates,[15] subsequent protocol amendments increased the enrollment up to 250 subjects to allow the investigators to provide more subjects with infantile spasms access to vigabatrin pending Food and Drug Administration approval. The increase was not based on considerations of statistical power. The randomization schedule was developed by a statistician in the Department of Clinical Research at Medical City Dallas Hospital. Site personnel contacted study staff at Medical City Dallas Hospital and were given a subject number and the predetermined dose assignment per the randomization schedule.

Subjects were randomized to receive high-dose (100-148 mg/kg/d) or low-dose (18-36 mg/kg/d) vigabatrin during the initial 14 days of the study. The dosing regimen was based on a review of data from previous studies evaluating the efficacy of vigabatrin in subjects with infantile spasms who had failed at least 1 standard antiepileptic drug therapy[5,7,15,16] and studies investigating vigabatrin monotherapy for infantile spasms.[6,8,9] High-dose group subjects had their dose escalated over 7 days. Vigabatrin was administered orally twice daily in the form of open-label 500-mg scored tablets unless the total daily dose was 250 mg/d or less, in which case it was administered once a day. Tablets could be crushed and administered with juice or applesauce.

Caregivers and non–investigator electroencephalographers were blinded to treatment assignment. Medications considered necessary by the investigator could be continued provided that the patients were on stable doses at study entry. Dosage adjustments of concomitant antiepileptic drugs were not allowed during the initial 21 days of the study. After 21 days, adjustments or withdrawal could be made at the investigator's discretion. Adrenocorticotropic hormone, corticosteroids, valproic acid, felbamate, or any investigational drugs other than vigabatrin were not allowed during the first 14 days of the study. Subjects achieving spasm freedom within the first 14 days remained on randomized therapy an additional 7 days before entering the open-label phase. Subjects not achieving spasm freedom within the first 14 days entered the open-label phase after day 14. In the open-label phase, the investigators were allowed to make vigabatrin dosage adjustments to clinical effect but could not make a change greater than 25 to 50 mg/kg/d each week and were not to exceed 200 mg/kg/d. Concomitant antiepileptic drugs were allowed in the open-label phase.

The primary outcome measure required that subjects be spasm free by caregiver observation for 7 consecutive days beginning within the first 14 days of the study, and if this were achieved, closed-circuit television EEG (video-EEG) was to be performed within 3 days of the seventh day of the 7-day period. During an 8-hour recording that included at least 1 sleep-wake-sleep period, a subject was considered spasm free if the video-EEG showed no indication of spasms or hypsarrhythmia; EEGs were interpreted locally by experienced encephalographers. A number of protocol-defined secondary analyses were conducted. One assessed spasm freedom based solely on caregiver assessment in response to direct questioning regarding spasm frequency or as recorded in the seizure diary, without the use of video-EEG. Other end points included the number of spasms per subject, time to spasm cessation by subgroup, physician and caregiver global assessments, and spasm freedom and relapse at various times during the study. The physician and caregivers used the following global assessment scale to report qualitative changes from baseline: 1 = marked deterioration; 2 = moderate deterioration; 3 = mild deterioration; 4 = no change; 5 = mild improvement; 6 = moderate improvement; and 7 = marked improvement.

Statistical Methods

Analysis of the primary efficacy variable was conducted on the modified intent-to-treat population. A comparison of high- and low-dose vigabatrin used Pearson χ^2 test. Logistic regression was used to compare etiology groups adjusting for treatment and to compare treatments adjusting for baseline use of antiepileptic drugs. Time to spasm cessation was summarized with Kaplan-Meier estimates and compared between treatment groups or among etiology groups with the log-rank test. The comparisons of high- and low-dose vigabatrin with respect to the physician and caregiver global assessments over time used repeated measures analysis of variance. All analyses were conducted using SAS software version 8.2 (SAS Institute, Cary, North Carolina). Two interim analyses were conducted to fulfill regulatory agency requests; neither was performed with the intention of stopping the study or changing its conduct.

Results

Subjects

A total of 227 subjects were randomized between January 1996 and August 2001; the last subject completed in April 2002. The disposition of study subjects and protocol deviations are presented in Figure 1. The 221 subjects in the modified intent-to-treat cohort were evaluated for vigabatrin efficacy. One additional subject, who received an unknown dose level of vigabatrin and was excluded from efficacy analyses, was included in the safety population of 222 subjects. Eleven subjects were started on an incorrect dose and were included in the modified intent-to-treat group and analyzed according to their randomized dose. A total of 116 subjects (52.5%) were taking allowed antiepileptic drugs for other seizure types at baseline, the most prevalent being phenobarbital (60/221; 27.1%) and clonazepam (27/221; 12.2%). The mean (standard deviation) dose during days 1 to 14 was 84.7 (16.4) mg/kg/d in the

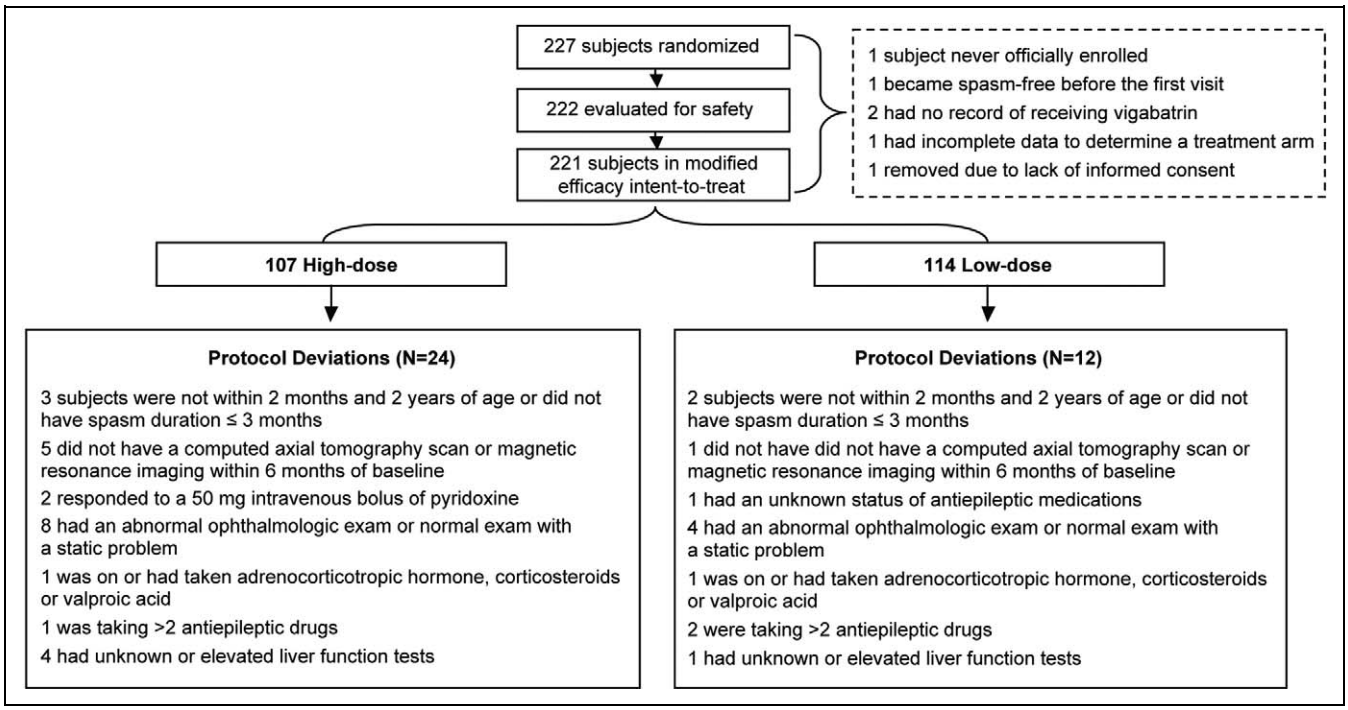

Figure 1. Subject disposition flow chart.

high-dose group and 29.0 (7.8) mg/kg/d in the low-dose group. The mean (standard deviation) maximum doses attained during the first 2 weeks of therapy were 115.3 (21.9) mg/kg/d in the high-dose group and 34.9 (18.6) mg/kg/d in the low-dose group. Mean doses in both groups increased in the open-label phase, with subjects in the low-dose group titrating more quickly than subjects in the high-dose group. Low-dose subjects increased from a mean of 35.0 mg/kg/d at the end of the randomization period to 105 mg/kg/d by day 30 of the open-label period, compared with an increase from 115.7 mg/kg/d to 138.8 mg/kg/d at day 30 in the high-dose group. During the open-label phase itself, there was little difference in vigabatrin dose between the 2 randomized treatment groups, with an observed mean (standard deviation) from study day 15 onward of 144.6 mg/kg/d (46.9) in the high-dose group versus 126.8 mg/kg/d (66.8) in the low-dose group.

Two subjects in the efficacy cohort were not followed through spasm freedom as they were noncompliant and discontinued from the study prior to 21 days; both subjects were included in the modified intent-to-treat efficacy analysis and analyzed as treatment failures. A majority of the subjects (183/221; 82.8%) were not followed for the entire 3 years. The mean (standard deviation) duration of vigabatrin exposure was 423.3 (317.2) days in the high-dose group and 512 (372.1) days in the low-dose group. The most frequent reasons for study discontinuation were lack of efficacy (49/221; 22.2%), other reasons (36/221; 16.3%), and administrative (35/221; 15.8%). An additional 19 subjects (8.6%) discontinued because of serious or severe adverse events. Baseline characteristics of the modified intent-to-treat efficacy cohort are presented in Table 1. The 2 groups were generally well matched; gender distribution was the only statistically significant difference.

Efficacy

Efficacy analyses are presented in Figure 2. Primary responders were defined as subjects who were spasm free and obtained a video-EEG within 3 days of the seventh day of spasm freedom that showed no indication of spasms or hypsarrhythmia. By this criterion, 11.3% (25/221) of the subjects overall were spasm free, with a statistically significant difference between treatment groups in the first 14 days of treatment. In the high-dose group, 15.9% (17/107) were spasm free versus 7.0% (8/114) in the low-dose group ($P = .0375$). During the course of the study, it became apparent that obtaining the video-EEG monitoring within 3 days of spasm cessation was not feasible for most subjects. Reasons included availability of video monitoring beds, transportation issues, family commitments, and a variety of other problems. A post hoc analysis was therefore performed relaxing the window of video-EEG. Post hoc criteria were defined as spasm free by both caregiver assessment and video-EEG confirmation during a subsequent visit. The total number of responders in each group, as well as the separation between high and low dose, increased as the visit window broadened from 3 to 9 days. When video-EEG was performed by any subsequent visit, the response rates were 30.8% (33/107) for high dose and 13.2% (15/114) for low dose ($P = .0014$).

One secondary efficacy analysis compared proportions of subjects in the 2 treatment groups who were free of spasms for

Table 1. Baseline Demographic Characteristics (Modified Intent-to-Treat Cohort)

Characteristic		Treatment Group: High Dose (n = 107)	Treatment Group: Low Dose (n = 114)	Total (n = 221)	*P* Value
Age,[a] y	n	102	112	214	
	Mean (standard deviation)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	.9184
Gender, n (%)	Male	45 (42.1)	63 (55.3)	108 (48.9)	.0491
	Female	61 (57.0)	50 (43.9)	111 (50.2)	
	Missing	1 (0.9)	1 (0.9)	2 (0.9)	
Race, n (%)	White	76 (71.0)	84 (73.7)	160 (72.4)	.1931[b]
	Black	15 (14.0)	11 (9.7)	26 (11.8)	
	Asian	3 (2.8)	0 (0)	3 (1.4)	
	Other	13 (12.2)	19 (16.7)	32 (14.5)	
Weight,[c] kg	n	106	112	218	.8521
	Mean (standard deviation)	7.9 (2.1)	8.0 (2.0)	8.0 (2.0)	
Etiology, n (%)	Symptomatic-other	60 (56.1)	66 (57.9)	126 (57.0)	.8490
	Cryptogenic	27 (25.2)	30 (26.3)	57 (25.8)	
	Symptomatic-tuberous sclerosis	20 (18.7)	18 (15.8)	38 (17.2)	

[a] Three subjects were excluded from age analysis because their age was >2 years; an additional 4 subjects did not have enough information to calculate their age.
[b] Fisher exact test was utilized because of low expected cell frequency.
[c] The 3 subjects >2 years of age were also excluded from the weight analysis.

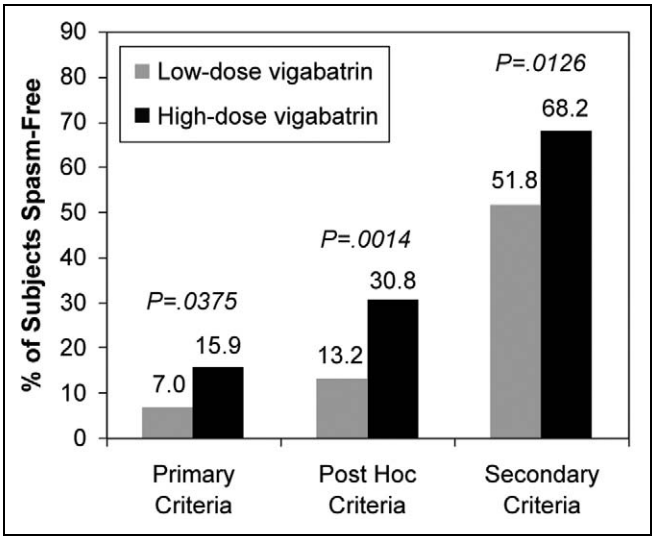

Figure 2. Vigabatrin effect on spasm cessation. The effect of high-dose vigabatrin is consistently greater than low-dose vigabatrin when different criteria for spasm cessation are applied. Primary criteria were defined as spasm free by both caregiver assessment and video-EEG confirmation within 3 days of the seventh day of spasm freedom. Post hoc criteria were defined as spasm free by both caregiver assessment and video-EEG confirmation during a subsequent visit. Secondary criteria were defined as spasm free for 7 consecutive days at any time during the study and remained spasm free for the duration of the study period based on caregiver assessment.

7 consecutive days at any time during the study and remained spasm free for the duration of the study based on caregiver assessment. A statistically significant greater number of subjects attained spasm freedom in the high-dose group (73/107; 68.2%) compared with 51.8% (59/114) in the low-dose group ($P = .0126$). The time-to-response analyses and Kaplan-Meier curves show a separation between treatment groups within 1 week of vigabatrin therapy initiation, with a greater response occurring in the high-dose treatment group ($P = .0016$) (Figure 3). The median time to spasm cessation was 6 weeks in the high-dose group and 13 weeks in the low-dose group.

By the primary outcome criteria, 21.1% (8/38) of subjects in the symptomatic-tuberous sclerosis complex group achieved spasm-free status, while 7.9% (10/126) of the symptomatic-other group and 12.3% (7/57) of the cryptogenic etiology group achieved spasm-free status. With respect to the primary end point, no statistically significant difference was observed among etiology groups when adjusting for treatment in the first 14 days ($P = .0736$). For each etiologic group, response rates were higher in the high-dose treatment group: symptomatic tuberous sclerosis (high dose, 25.0%; low dose, 16.7%); symptomatic other (high dose, 13.3%; low dose, 3.0%); and cryptogenic (high dose, 14.8%; low dose, 10.0%). The interaction between etiology and treatment was not statistically significant ($P = .5430$). Separation occurred in the Kaplan-Meier curves between the tuberous sclerosis and the other etiology groups beginning approximately 1 week after the initiation of vigabatrin treatment ($P < .001$) (Figure 4). Subjects with tuberous sclerosis responded more quickly. It is important to note that both Kaplan-Meier curves become progressively less representative of the randomized population after 12 weeks because of the high discontinuation rate during the open-label phase of the study.

In each treatment group, there were higher spasm cessation rates based on the primary efficacy outcome in subjects not using antiepileptic drugs at baseline ($P = .0505$), but the use of antiepileptic drugs at baseline did not modify the vigabatrin treatment effect (interaction P value = .9302). Spasm freedom

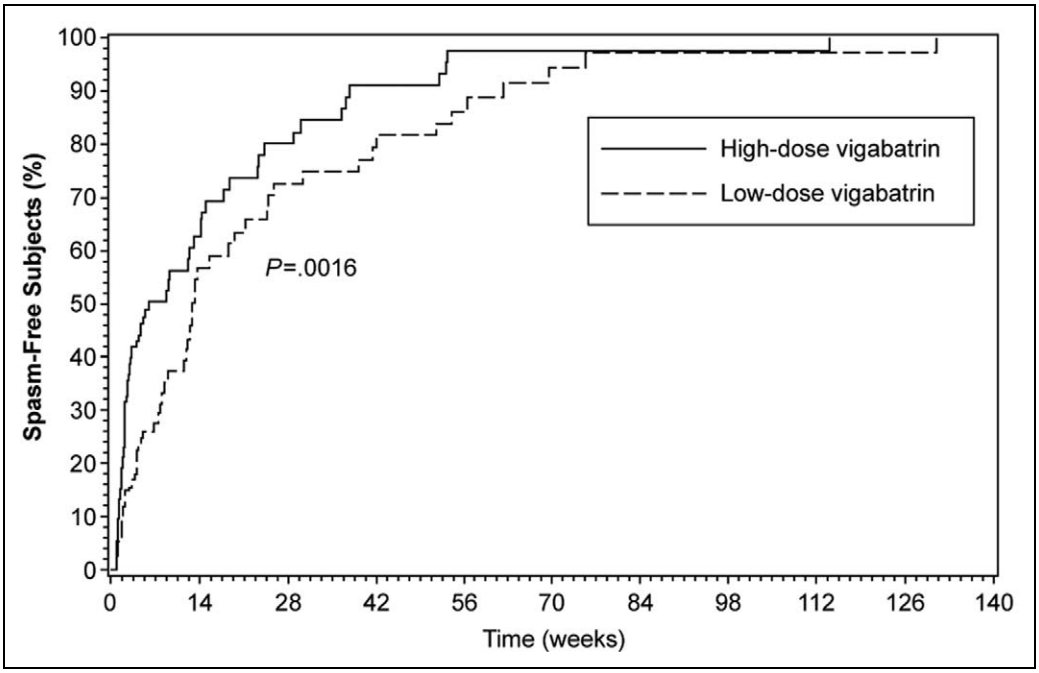

Figure 3. Comparison of treatment groups in time to spasm cessation using secondary criteria. The Kaplan-Meier curves show a clear separation between the high-dose curve (73 of 107 spasm-free subjects; median time = 6 weeks) and the low-dose curve (59 of 114 spasm-free subjects; median time = 13 weeks). The separation begins at the second week of vigabatrin treatment.

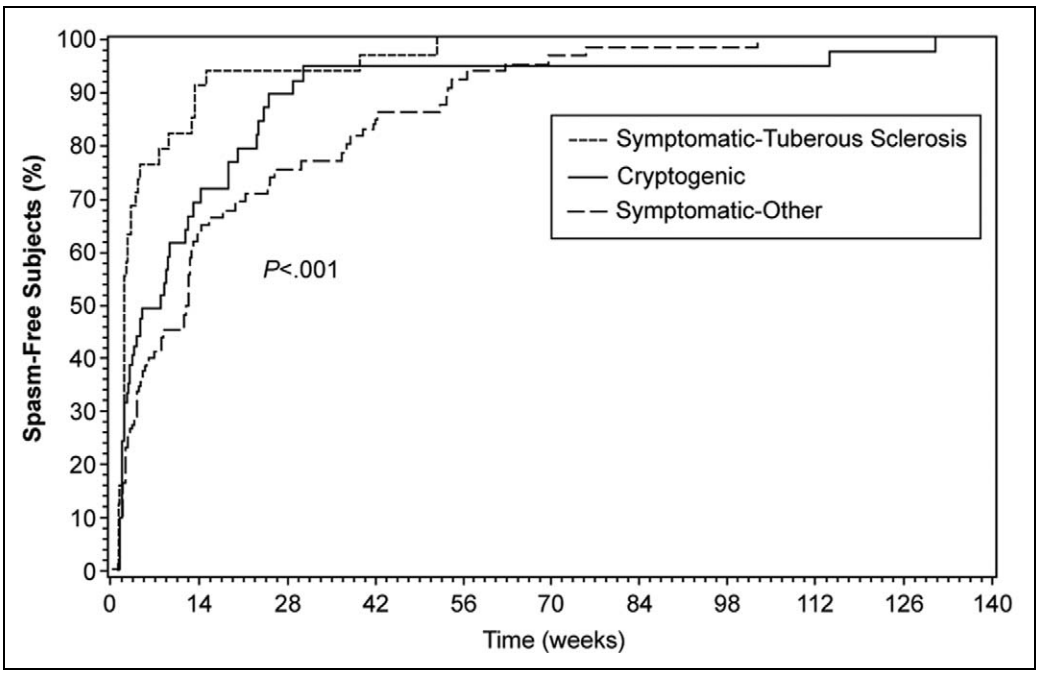

Figure 4. Comparison of etiology groups in time to spasm cessation using secondary criteria. The Kaplan-Meier curves illustrate a separation in the curves between the tuberous sclerosis complex etiology group (28 of 39 spasm-free subjects; median time = 3 weeks) and the cryptogenic (41 of 57 spasm-free subjects; median time = 9 weeks) and symptomatic-other etiology groups (63 of 126 spasm-free subjects; median time = 14 weeks). The separation begins approximately 1 week after vigabatrin treatment initiation.

during the flexible dosing phase was not affected by the use of antiepileptic drugs in that phase. The mean physician global assessment scores increased from "mild improvement" to "moderate improvement" over a 3-month period ($P = .0008$). At week 2, the high-dose group achieved a higher average score than the low-dose group, maintaining overall

higher scores throughout the study ($P = .0285$). The mean caregiver global assessment scores also increased from "mild improvement" to "moderate improvement" over a 3-month period ($P = .0018$). No significant difference between treatment groups was observed ($P = .0831$).

Relapses

According to the primary efficacy criteria, 25 subjects attained spasm freedom within the first 14 days with video-EEG confirmation within 3 days of the seventh day of spasm freedom. Of primary responders, 2 of 17 (11.8%) in the high-dose and 2 of 8 (25.0%) in the low-dose group relapsed. For primary responders, the mean time to relapse was 162 days (range, 53-270 days) in the high-dose group and 45 days (range, 31-58 days) in the low-dose group. Of the 171 subjects who became spasm free for 7 consecutive days, 39 (22.8%) relapsed, and 28 of 39 (71.8%) became spasm free again. A variety of methods were used by clinicians to address relapses, including vigabatrin dose adjustments, the addition of other medications, and modification of existing treatments. Twenty-two (78.6%) of the 28 subjects who regained spasm freedom again remained spasm free for the remainder of the follow-up period.

Safety

Throughout the study, 115 of 222 subjects (51.8%) experienced at least 1 adverse event considered to be related to vigabatrin. Of the 1587 unique adverse events reported, 219 (13.8%) were considered to be related to vigabatrin. Of these 219 unique adverse events, 5 (2.3%) were severe, 64 (29.2%) were moderate, 150 (68.5%) were mild, and 2 (0.9%) were unknown. The most common vigabatrin-related adverse events were sedation (n = 37; 16.7%), somnolence (n = 30; 13.5%), irritability (n = 22; 9.9%), insomnia (n = 14; 6.3%), sleep disorder (n = 10; 4.5%), constipation (n = 8; 3.6%), lethargy (n = 8; 3.6%), decreased appetite (n = 7; 3.2%), and hypotonia (n = 5; 2.3%). During the blinded phase, 52 of 108 (48.1%) in the high-dose group and 58 of 114 (50.9%) in the low-dose group experienced at least 1 adverse event. In the safety cohort, 5 of 222 subjects (2.3%) experienced at least 1 serious adverse event that was related to vigabatrin, and 5 of 156 (3.2%) distinct serious adverse events were considered related to vigabatrin treatment. Over the course of 3 years, 19 subjects discontinued therapy as a result of an adverse event or serious adverse event, with 5 considered related to vigabatrin therapy: vomiting (n = 1), infections (n = 2; pneumonia and respiratory tract infection), and nervous system disorders (n = 2; convulsion and infantile spasms). Three deaths occurred during the study; none was considered related to vigabatrin therapy.

Discussion

Treatment options for infantile spasms, a catastrophic form of childhood epilepsy, are limited in efficacy and safety. First-line therapy in the United States is often considered to be adrenocorticotropic hormone, although there are serious side effects that limit its use.[17,18] European studies have compared the efficacy of vigabatrin with hormone treatments such as adrenocorticotropic hormone and hydrocortisone and support the use of vigabatrin as a first-choice drug for treatment of infantile spasms.[8,9] The United Kingdom Infantile Spasms Study (UKISS) compared vigabatrin treatment with hormonal treatment, either oral prednisone or an injectable adrenocorticotropic hormone analog, tetracosactide. On average, hormonal treatment produced a more rapid response. Fourteen days after starting treatment, 73% of infants treated with steroids achieved spasm freedom (assessed by clinical observation), whereas 54% of vigabatrin-treated patients were spasm free.[19] At 14 months of age, however, there was no difference between the 2 groups in the proportion who were free of spasms: 75% for hormone treatment versus 76% for vigabatrin.[20] Follow-up at 4 years of age, published only in abstract form, demonstrated a modest benefit of corticosteroid treatment over vigabatrin in cognition.[21] A small (n = 40) randomized, placebo-controlled study of vigabatrin as first-line treatment for infantile spasms showed a 78% average reduction in spasms in patients treated with vigabatrin compared with 26% in patients treated with placebo after 5 days of treatment.[6]

The interim analysis of the first 142 subjects in this study indicated greater efficacy with high-dose vigabatrin than with low-dose vigabatrin. Using a similar outcome measure as applied in the current analysis, 36% of evaluable subjects in the high-dose group achieved spasm cessation within 14 days of starting treatment versus 11% in the low-dose arm. Nine patients had discontinued because of adverse events, and the most common adverse events were sedation, insomnia, and irritability, consistent with the overall findings.[10] In the final analysis, vigabatrin treatment also yielded an overall response rate that was greater in the high-dose group compared with the low-dose group according to the primary efficacy measure, although the more conservative responder analysis likely contributed to a lower response rate than previously reported.[10] In retrospect, the primary outcome measure was overly stringent in that video-EEG confirmation within a 3-day window of the spasm-free period was often impossible to obtain. While relaxing the video-EEG window increased the response rate in both groups, the dose effect also became stronger than when the more restrictive primary outcome criteria were employed.

To better compare the results of this study with those in the literature that did not require stringent video-EEG confirmation of spasm freedom, such as UKISS, secondary outcome measures were analyzed. The secondary end point of attaining spasm freedom for 7 consecutive days and maintaining spasm freedom also showed a statistically significant difference between high- and low-dose groups. As seen in the Kaplan-Meier curves, separation in response rates between the 2 groups initially occurred after 1 week of vigabatrin exposure and was maintained throughout the duration of the study despite the fact that the vigabatrin dose difference between the 2 groups was relatively minor during the open-label phase of the study. This secondary efficacy analysis shows a much larger response of

vigabatrin, albeit without the video-EEG confirmation, allowing for subjects who were unable to obtain confirmation of seizure freedom.

Rates of spasm freedom were higher in the high-dose group for all etiologies, and as seen in the lack of statistical interaction between treatment and etiology of infantile spasms, there was no etiologic-specific effect of high- versus low-dose vigabatrin. There were no statistically significant differences in the response rates among etiology groups in the primary end point analysis, but the highest observed response rate was in subjects with tuberous sclerosis complex. This and the shorter time to spasm-free status in infants with tuberous sclerosis complex suggest that they may achieve more predictable benefit from treatment with vigabatrin than other etiologic groups, an observation previously reported.[9,22] There were considerable differences in duration of treatment for subjects. Infants who tended to stay in the study longer were those responding to vigabatrin therapy with no other access to the drug.

Vigabatrin was safe and well tolerated in this study of subjects with newly diagnosed infantile spasms. The incidence of adverse events related to vigabatrin was low, with very few serious adverse events reported. Very few subjects discontinued from the study because of adverse events, and the rates of adverse events in each treatment group were comparable. Because this study was conducted prior to the recognition of vision loss or magnetic resonance imaging changes in infants as side effects of vigabatrin, the study design did not include assessments of vision or imaging.

The current study is the largest randomized trial conducted to date in patients with infantile spasms and has yielded valuable information in the treatment of this devastating disease. Responses to vigabatrin were obtained quickly and were significantly greater in the high-dose treatment group compared with the low-dose treatment group. Although all etiologies benefited from treatment, a trend toward a higher response rate and shorter time to response was observed in infants with tuberous sclerosis compared with other etiologies. The relapse rate in responders was lower in the high-dose group compared with the low-dose group, indicating that in addition to achieving spasm freedom more quickly, subjects who were treated with and responded to a higher dose of vigabatrin experienced lower rates of relapse.

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Declaration of Conflicting Interests

The authors declared a potential conflict of interest (eg, a financial relationship with the commercial organizations or products discussed in this article) as follows: Dr Elterman was a paid consultant to Ovation Pharmaceuticals Inc; Dr Shields was a paid consultant to Ovation Pharmaceuticals Inc and consults for Questcor Pharmaceuticals Inc; Dr Elterman and Dr Shields are officers of the Pediatric Epilepsy Research Foundation, a nonprofit organization that may receive royalty payments from the marketing of vigabatrin; Dr Bittman is a paid consultant to Lundbeck Inc and was formerly a paid consultant to Ovation Pharmaceuticals Inc; Ms Torri and Dr Sagar are employees of Lundbeck Inc; Dr Collins is an employee of NeuroTherapeutics Pharma Inc and was formerly employed by Ovation Pharmaceuticals Inc.

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