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High vigabatrin dosage is associated with lower risk of infantile spasms relapse among children with tuberous sclerosis complex

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Abstract

After initially successful treatment of infantile spasms, the long-term cumulative risk of relapse approaches 50%, and there is no established protocol to mitigate this risk. Although vigabatrin may be an effective means to prevent relapse, there is little guidance as to ideal duration and dosage. Using a cohort of children with infantile spasms and tuberous sclerosis complex (TSC), we evaluated the potential association of post-response VGB treatment and the rate of infantile spasms relapse. Patients with infantile spasms and clinical response to vigabatrin were identified among a multicenter prospective observational cohort of children with TSC. For each patient we recorded dates of infantile spasms onset, response to vigabatrin, relapse (if any), and quantified duration and dosage of vigabatrin after response. Time to relapse as a function of vigabatrin exposure was evaluated using survival analyses. We identified 50 children who responded to VGB. During a median follow-up of 16.6 months (IQR 10.3 – 22.9), 12 (24%) patients subsequently relapsed after a median of 7.8 months (IQR 3.1 — 9.6). Relapse occurred after VGB discontinuation in four patients, and during continued VGB treatment in the remaining eight cases. In survival analyses, risk of relapse was unaffected by the presence or absence of VGB treatment (HR 0.31, 95%CI 0.01 – 28.4, P= 0.61), but weighted-average dosage was associated with marked reduction in relapse risk: Each 50 mg/kg/d increment in dosage was associated with 61% reduction in risk (HR 0.39, 95%CI 0.17 – 0.90, P = 0.026). This study suggests that the risk of infantile spasms relapse in TSC may be reduced by high -dose vigabatrin treatment.

Keywords

West syndrome; epileptic spasms; secondary prevention

1. Introduction

Infantile spasms (IS) is the most common epilepsy syndrome with onset in the first year of life, affecting approximately 1 in 2,500 infants (Shields, 2006). IS presents in a distinctive fashion with clusters of brief seizures called epileptic spasms (Fisher et al., 2017), and a spectrum of severe electroencephalographic abnormalities that include hypsarrhythmia (Hrachovy et al., 1984). Onset is often heralded by neurodevelopmental arrest or regression (Shields, 2006). Despite its relatively high incidence and this unique clinical presentation, diagnostic confusion and treatment delay are common and potentially devastating (Hussain et al., 2017). Treatment delay is associated with reduced efficacy of first-line medications (O'Callaghan et al., 2017) as well as marked reductions in long-term neurodevelopmental outcomes.(O'Callaghan et al., 2011) First-line treatment options for IS include natural (Baram et al., 1996) and synthetic (Lux et al., 2004) adrenocorticotropic hormone (ACTH), prednisolone (Hussain et al., 2014) and vigabatrin (VGB) (Elterman et al., 2010). Although short-term response rates to these therapies are substantial (Knupp et al., 2016), the cumulative long-term risk of IS relapse approaches 50% (Hayashi et al., 2016; Rajaraman et al., 2016). As enduring freedom from IS appears to be a prerequisite for favorable long-term cognitive outcomes (Riikonen, 2010), an effective strategy to prevent relapse would be of great value. Unfortunately, no successful approach to relapse prevention has been established (Rajaraman et al., 2016).

Although the short-term efficacy of VGB is inferior to the hormonal therapies in general (Knupp et al., 2016; Lux et al., 2004), VGB appears to be especially effective in the treatment of IS among children with tuberous sclerosis complex (TSC) (Chiron et al., 1997). However, despite this established efficacy (Appleton et al., 1999; Elterman et al., 2001), the use of VGB has been limited by the threat of permanent peripheral visual field loss (Eke et al., 1997; Vanhatalo et al., 2002). MRI abnormalities (Dracopoulos et al., 2010; Hernández Vega Y et al., 2014; Pearl et al., 2009; Wheless et al., 2009). In particular, VGB has been linked to reversible—and usually asymptomatic—signal changes on T2-weighted and diffusion-weighted MRI, localized to the basal ganglia, thalami, brainstem tegmentum, and deep cerebellar nuclei. Although estimates of visual field loss vary substantially, risk appears to be lower among infants with treatment duration less than 12 months (Riikonen et al., 2015) and the risk of clinically meaningful vision loss is very low among children treated for infantile spasms (Schwarz et al., 2016). With regard to MRI abnormalities, the risk of toxicity is approximately 20–30% (Pearl et al., 2009; Wheless et al., 2009) and dependent on dose but not duration of therapy (Hussain et al., 2017).

Although there is consensus in the United States that vigabatrin is the first-line treatment of choice for TSC-associated IS, there is great variability in prescribed dosage and duration of therapy (Pellock et al., 2010). With the contemporary views that (1) risk of meaningful visual field loss is low, (2) risk of MRI abnormalities may be reduced by avoidance of high dosage, and (3) MRI abnormalities are reversible and usually asymptomatic, VGB may represent a reasonable treatment in the effort to prevent IS relapse. Accordingly, using a prospective cohort of children with TSC and IS—among whom long-term VGB therapy is common—we set out to determine whether ongoing VGB treatment is associated with lower risk of IS relapse.

2. Method

2.1 Standard protocol approvals

This study was approved by the institutional review boards at each center. All patients' guardians provided written informed consent prior to any study procedures.

2.2 Study design and procedures

We conducted a nested cohort analysis. The patients comprising the nested cohort were derived from two linked ongoing multicenter prospective observational studies (ClinicalTrials.gov: NCT01780441 and NCT02461459), which seek to identify genetic and electrophysiologic biomarkers of epilepsy, autism, and long-term neurodevelopmental outcomes in children with TSC. For the analyses in this study, we specifically identified the subset of patients with IS (based on seizure-diary) and response to VGB, as defined below, and as illustrated in Figure 1. Importantly, although the evaluation of a potential association between VGB exposure and IS relapse was not a specific aim of these studies, the data from these cohorts presented an opportunity to readily address this question. Our hypothesis was that risk to IS relapse would be lower among infants with longer duration and higher dosage of VGB.

Both parent studies enrolled infants with a clinical or genetic diagnosis of TSC, and all patients underwent serial in-person evaluations at ages 0–2, 3, 6, 9, 12, 18, 24, and 36 months (NTC01780441) and at ages 1.5, 3, 4.5, 6, 9, 12, 18, and 24 months (NTC02461459). At each visit, there was detailed accounting of seizure burden (via seizure diaries) with classification and quantification of each seizure type, and detailed tabulation of all medication exposures. In addition, serial outpatient video-EEGs (1 hour duration, awake and sleep) were performed at each visit and interpreted in a blinded fashion by a team of board-certified pediatric electroencephalograhers as follows: All studies were reviewed by at least MG and JMP. In the event of any inter-rater discrepancy, studies were then reviewed by JYW for adjudication. Although there was specific notation of the presence or absence of epileptic spasms and hypsarrhythmia at each visit, the video-EEGs performed in the course of this study were in addition to clinical EEGs obtained by treating physicians, and were not intended for verification of IS onset, response to therapy, or relapse on a clinical basis.

2.3 Definition of response and relapse

We defined response to VGB as the cessation of epileptic spasms (according to seizure diary and not contradicted by a study video-EEG demonstrating either epileptic spasms or hypsarrhythmia) for at least one month, and beginning not more than one month after VGB initiation. The date of response was defined as the first day of the interval of at least month duration without epileptic spasms. IS relapse was defined as the presence of either epileptic spasms (according seizure diary or study video-EEG) or hypsarrhythmia on any subsequent study video-EEG, at least 1 month after initial response.

2.4 Quantification of VGB exposure

Among VGB responders, VGB exposure was quantified from the date of initial response to (1) VGB discontinuation, (2) IS relapse, or (3) most recent study visit, whichever came first. Quantification was accomplished using dosages, dates of therapy, and patient weight, as recorded at each sequential study visit. For each patient, we determined (1) duration of VGB therapy, (2) weighted-average weight-based VGB dosage (mg/kg/day), and (3) peak weight-based VGB dosage (mg/kg/day). To determine weighted-average weight-based VGB dosage, each patient's exposure interval (time) was segmented into n subintervals of variable duration, t_i. The beginning and end of each subinterval was demarcated by any reported change in VGB dosage or patient weight. The weight-based dosage (mg/kg/d) of each subinterval was calculated based on the dosage (mg/day), d_i, and weight (kg), w_i, at the beginning of each subinterval, using the last observation carry forward approach. We then calculated weighted-average weight-based dosage across the entire exposure interval, D_w, with the contribution of each subinterval weighted by the duration of the subinterval, as follows:

$$D_w = \left(\sum_{i=1}^{n} \frac{d_i}{w_i} t_i \right) / \left(\sum_{i=1}^{n} t_i \right)$$

For each patient, peak weight-based dosage was defined as the largest weight-based dose(d_i/w_i) in any subinterval.

2.5 Statistical Methods

Continuous summary data were presented as median and interquartile range based on nonparametric distributions. Comparisons of percentages and medians were accomplished with the Fisher exact test and Wilcoxon rank-sum test, respectively. Time to IS relapse was evaluated using the Kaplan-Meier method and Cox proportional hazards regression, with censorship at 12 months post-response. All comparisons were two-sided and *P*-values less than 0.05 were considered statistically significant. Given the interdependence of the three primary (planned) analyses (evaluation of the association between time to relapse and [1] VGB treatment duration, [2] weighted-average dosage, and peak dosage) we did not adjust for multiple comparisons. Statistical calculations were facilitated with Stata software (Statacorp, version 14, College Station, Texas, USA).

3. Results

3.1 Subjects

Clinical and demographic characteristics of the study population are summarized in Table 1 and illustrated in Figure 1. Among 172 total patients enrolled in the parent studies, we identified 81 (47%) patients with IS, of whom 50 (62%) responded to VGB, with median follow-up of 16.6 months (IQR 10.3 – 22.9). These 50 patients comprise the nested cohort for the analyses in this study. Importantly, six of 50 (12%) children received a course of hormonal therapy (prednisolone or ACTH) which overlapped with VGB treatment. Among these cases, it is unclear if hormonal therapy was added after VGB initiation because of a lack of early complete response, lack of immediate availability of ACTH, or other reasons. We did not have access to all clinical notes of referring providers with explicit rationale for the sequence and timing of therapy. In these cases, it is thus unclear whether response was attributable to VGB, hormonal therapy, or both. Among the 31 patients who were not identified as VGB responders, six patients had not yet returned for study follow-up after first identification of IS. In short, although we have identified patients receiving VGB at the time of initial IS resolution, we cannot reliably estimate the initial response rate to VGB alone. Of note, there were no instances in which response defined on a clinical basis (seizure diary) was contradicted by study protocol video-EEG. However, as we did not have complete access to clinical EEGs performed by treating physicians, it is possible that some patients we have classified as responders were incorrectly classified (i.e. hypsarrhythmia or subtle spasms persisted), or that complete response occurred later than we have estimated (i.e. clinical response preceded video-EEG confirmed “complete” response). Twenty-five (50%) of patients became completely seizure-free upon IS resolution. Among the remaining 25 (50%) patients with continued focal seizures, seizure frequency was generally low (median 0.7, IQR 0.3 – 2.7 seizures/month), though six (12%) continued to suffer more than one seizure per week, on average. With regard to genetic characterization of TSC, Page 9 of 23 genetic data were available for 28 patients, among whom there were 25 children with *TSC2* mutations, one child with a *TSC1* mutation, and two children with no identified mutations.

3.2 VGB exposure

Among the 50 VGB responders, the median duration of VGB therapy was 9.2 months (5.7 – 16.3), median peak weight-based dosage was 118.9mg/kg/d (88.2 – 162.6), median

weighted-average weight-based dose was 91.6 mg/kg/d (49.3 – 120.5), and the median cumulative dose was 781.8 grams (422.8 – 1043.0). We were surprised to encounter a high proportion of responders (resolution of epileptic spasms) who continued to exhibit focal seizures. In an exploratory, post-hoc analysis, we found that in comparison to patients who became completely seizure-free (n = 25), the remaining children with ongoing focal seizures after IS resolution (n = 25) exhibited higher median weighted-average dose (112.3 vs 72.7 mg/kg/d, $P = 0.02$), higher median peak dose (159.1 vs 101.3 mg/kg/d, $P < 0.001$), and longer (albeit statistically indistinct) median duration of treatment (12.0 vs 8.4 months, $P = 0.18$) (Figure 2). VGB exposure did not vary as a function of age of onset of IS, duration of IS prior to response, age at response, simultaneous treatment with hormonal therapy, or any other clinical/demographic variable.

3.3 Time to IS Relapse

Twelve (24%) patients suffered relapse of IS during follow-up, which occurred after a median of 7.8 months (3.1 – 9.6). Relapse occurred after VGB discontinuation in four patients, and during VGB therapy in eight patients. Although the presence or absence of VGB treatment after relapse (evaluated as a time-dependent covariate) did not affect time to relapse (HR 0.31, 95%CI 0.01 – 28.4, $P = 0.61$), weighted-average and peak dosage were associated with marked reduction in relapse risk. Each 50 mg/kg/d increment in weighted-average dosage was associated with 61% reduction in risk (HR 0.39, 95%CI 0.17 – 0.90, $P = 0.026$), and similarly, each 50 mg/kg/d increment in peak dosage was associated with a 45% reduction in risk (HR 0.55, 95%CI 0.30 – 0.99, $P = 0.048$). To illustrate these associations, we compared patients with weighted-average dosage above or below 100 mg/kg/d (Figure 3A) as well as patients with peak dosage above or below 150 mg/kg/d (Figure 3B). Furthermore, in considering both peak and weighted-average dosage simultaneously, there were no relapses among patients with both peak dosage > 150 mg/kg/d and weighted-average dosage > 100 mg/kg/d (Figure 4).

To evaluate whether simultaneous hormonal therapy modified the aforementioned associations between VGB dosage and time to relapse, we conducted an exploratory analysis in which we evaluated time to relapse as a function of weighted-average VGB dosage, with simultaneous hormonal therapy (present/absent) as a covariate. After adjustment for simultaneous hormonal therapy, each 50 mg/kg/d increment in weighted-average VGB dosage was again associated with a 61% reduction in risk (adjusted HR 0.39, 95%CI 0.17 – 0.90, $P = 0.027$). Similarly, among the subset of 44 patients without simultaneous hormonal therapy, we found that each 50 mg/kg/d increment in weighted average VGB dosage was associated with a 59% reduction in risk (HR 0.41, 95%CI 0.17 – 1.00,$P = 0.050$). Although the subgroup with simultaneous hormonal therapy (n = 6) was too small to permit meaningful statistical analysis, we observed a similar trend: Of four patients with weighted-average VGB dose < 100 mg/kg/d, there were two relapses, and neither patient with weighted-average VGB dose > 100 mg/kg/d exhibited a relapse.

Upon observing that half of the responders exhibited persistence of other seizures types (focal seizures), we hypothesized (post-hoc) that the risk of IS relapse might be linked to the presence of other seizures after resolution of IS. However, in an exploratory analysis, we

observed the opposite trend such that the presence of other seizures seemed to favor lower risk (HR 0.30, 95%CI 0.08 – 1.12, $P = 0.074$). Nevertheless, as indicated above, the presence of other seizures was correlated with—and may have prompted—higher peak and weighted-average VGB dosages. As such, it is not clear from our data whether the persistence of other seizure types is associated with IS relapse. No other clinical or demographic variables were associated with time to IS relapse in a univariate fashion, and none significantly modified the association of VGB dosage and time to relapse.

4. Discussion

Given the high cumulative incidence of IS relapse(Hayashi et al.,2016; Rajaraman et al., 2016) and the presumptive impact on development, this study is noteworthy in that we have linked high-dose VGB therapy to lower risk of relapse. It is especially significant in the context of a prior report demonstrating that that use of topiramate and zonisamide exhibit little utility in secondary prevention.(Rajaraman et al., 2016) However, we must be cautious in the interpretation of these data and several important limitations must be acknowledged.

First, this study was not a randomized controlled trial. Although this was a prospective observational study, the duration and dosage of VGB was determined at the discretion of treating providers, and neither patients (parents) nor investigators were blinded to treatment parameters. In particular, the anticipated duration and dosage of VGB treatment upon response and prior to any relapse is seldom documented in progress notes and was not ascertained as part of the research protocol. It is not clear if these VGB treatment parameters simply vary across providers in an idiosyncratic fashion, or perhaps they vary as a function of patient-specific attributes. Second, identification of response and relapse was based on parent report and not adequately verified with blinded long-duration video-EEG review to exclude the possibility of ongoing hypsarrhythmia or continued subtle spasms. Further investigation is clearly warranted and an ideal study would be a larger-scale, randomized, double-blind, placebo-controlled study in which both initial response to VGB as well as identification of relapse are confirmed by blinded video-EEG review.

Along with high dosage, we had hypothesized that longer duration VGB treatment would be associated with lower rates of relapse in the first year. Although we did not detect this association, we were limited in observing this potential effect because short-duration treatment (i.e. less than 6 months) was less common than anticipated in this cohort. With longer follow-up, a subsequent analysis may demonstrate that VGB treatment duration—regardless of dose—may be associated with lower risk of relapse in the second year following initial response.

In an exploratory post-hoc analysis, we speculated that the presence of other seizure types after IS resolution would be linked to higher rates of IS relapse, with the assumption that patients with multiple seizure types, and more frequent seizures, harbor more “severe” epilepsy overall or exhibit greater potential for de novo epileptogenesis. Curiously, we found the opposite trend, such that the burden of other seizure-types was linked to both lower risk of IS-specific relapse and higher VGB dosage. However, we do not suspect that a high burden of other seizures is protective against relapse; rather, we hypothesize that other forms

of ongoing epilepsy prompted treating physicians to employ higher-dose and longer-duration VGB regimens, which may have then led to lower rates of IS relapse. Conversely, some patients classified as VGB responders may instead represent patients with an evolution in epilepsy classification (e.g. transition to Lennox-Gastaut syndrome), which coincidentally occurred at the time of initial VGB treatment. In short, given that we did not randomize treatment allocation (i.e. VGB treatment dosage/duration), and our observation that the burden of non-IS seizures was highly associated with VGB exposure, we cannot disentangle these competing risk factors.

Although these data suggest that high-dose VGB treatment may reduce the risk of IS relapse, we have not established that high-dose VGB is associated with improvement in meaningful long-term outcomes such as enduring seizure-freedom, developmental/behavioral outcomes, or quality of life. In a subsequent analysis, with longer follow-up and dedicated neurobehavioral evaluation, we shall search for a link between VGB treatment, IS relapse, and these long-term endpoints.

To the extent that high-dose VGB protocols may be incorporated into clinical practice or clinical trials, the potential benefit in secondary prevention of IS must be weighed against the risks of VGB toxicity. Although the risk of clinically apparent visual field loss appears to be low among VGB-treated infants with IS (Schwarz et al., 2016), several studies have linked longer duration VGB therapy to retinotoxicity (Riikonen et al., 2015; Westall et al., 2014), and risk of MRI abnormalities is dose-dependent, especially with doses greater than 175 mg/kg/day (Hussain et al., 2017). Accordingly, any high-dose VGB protocol should include vigilant monitoring for the emergence of MRI abnormalities. Given that risk of IS relapse was especially low with peak VGB dose of at least 150 mg/kg/day and weighted-average VGB dosage of at least 100 mg/kg/day, this appears to be a favorable target dosage to maximize benefit with respect to relapse prevention and minimize risk with respect to MRI abnormalities. However, this suggested peak dose conflicts with regulatory guidance from the Food and Drug Administration and others, which specify a maximum dose of 150 mg/kg/d (Sabril (vigabatrin) package insert, 2009). It is also noteworthy that VGB dosage in this study was quite high, with nearly one-third of responders exposed to peak VGB dosage exceeding 150 mg/kg/d. Although we could not reliably discern the rationale for prescribed dosage in this study, we observed that some practitioners aggressively—and successfully—titrated VGB well beyond the recommended maximum dosage. Importantly, this study did not provide an adequate means to assess the potential impact of VGB-associated MRI toxicity on the prescribed duration or dosage of VGB. As these reversible MRI abnormalities are transient, they are likely to have often escaped detection by study protocol MRIs. Moreover, there is scant guidance in the literature as to whether or not VGB should be tapered or discontinued upon discovery of MRI changes.

Although the results of this study are encouraging, further rigorous study is warranted. In particular, the evaluation of long-term neurodevelopmental and epilepsy outcomes is essential to establish any meaningful clinical benefit that may accompany high-dose VGB treatment after IS resolution. More generally, it is not clear that the potential benefit of high-dose VGB extends to patients without TSC. As such, further study of an etiologically diverse cohort would be of value to better guide VGB treatment for all patients with IS.

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Dr. Wu serves on the professional advisory board for the Tuberous Sclerosis Alliance; has received honoraria from and serves on the scientific advisory board and the speakers' bureau for Novartis Pharmaceuticals Inc. and Lundbeck; and has received research support from the Tuberous Sclerosis Alliance, Novartis harmaceuticals Inc., Today and Tomorrow Children's Fund, Department of Defense/ ongressionally Directed Medical Research Program, and the NIH (P20NS080199, U01NS082320, R01NS082649, U54NS092090, and R01 NS092595).

5. References

Appleton RE, Peters AC, Mumford JP, Shaw DE, 1999 Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. Epilepsia 40, 1627–1633. [PubMed: 10565592]

Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ, 1996 High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics 97, 375–379. [PubMed: 8604274]

Chiron C, Dumas C, Jambaqué I, Mumford J,Dulac O,1997Randomized trial comparing vigabatrin and hydrocortisone in infantile spasms due to tuberous sclerosis. Epilepsy Research 26, 389– 395. [PubMed: 9095401]

Dracopoulos A, Widjaja E, Raybaud C, Westall CA, Snead OC, 2010 Vigabatrin-associated reversible MRI signal changes in patients with infantile spasms. Epilepsia 51, 1297–1304. [PubMed: 20384718]

Eke T, Talbot JF, Lawden MC, 1997 Severe persistent visual field constriction associated with vigabatrin. BMJ 314, 180–181. [PubMed: 9022432]

Elterman RD, Shields WD, Bittman RM, Torri SA, Sagar SM, Collins SD, 2010 Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. J.Child Neurol 25, 1340–1347. [PubMed: 20404353]

Elterman RD, Shields WD, Mansfield KA, Nakagawa J, US Infantile Spasms Vigabatrin Study Group, 2001 Randomized trial of vigabatrin in patients with infantile spasms. Neurology 57, 1416– 1421. [PubMed: 11673582]

Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, Lagae L, Moshé SL, Peltola J, Roulet Perez E, Scheffer IE, Zuberi SM, 2017 Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 58, 522–530. [PubMed: 28276060]

Hayashi Y, Yoshinaga H, Akiyama T, Endoh F, Ohtsuka Y, Kobayashi K, 2016 Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome. Brain and Development 38, 32–39. [PubMed: 26547521]

Hernández Vega Y, Kaliakatsos M, U-King-Im J, Lascelles K, Lim M, 2014 Reversible vigabatrin-induced life-threatening encephalopathy. JAMA Neurol 71, 108–109. [PubMed: 24247994]

Hrachovy RA, Frost JD, Kellaway P, 1984 Hypsarrhythmia: variations on the theme. Epilepsia 25, 317–325. [PubMed: 6539199]

Hussain SA, Lay J, Cheng E, Weng J, Sankar R, Baca CB, 2017 Recognition of infantile spasms is often delayed: The ASSIST study. J. Pediatr 190, 215–221. [PubMed: 29144248]

Hussain SA, Shinnar S, Kwong G, Lerner JT, Matsumoto JH, Wu JY, Shields WD, Sankar R, 2014 Treatment of infantile spasms with very high dose prednisolone before high dose adrenocorticotropic hormone. Epilepsia 55, 103–107. [PubMed: 24446954]

Hussain Shaun A., Tsao J, Li M, Schwarz MD, Zhou R, Wu JY, Salamon N, Sankar R, 2017 Risk of vigabatrin-associated brain abnormalities on MRI in the treatment of infantile spasms is dose-dependent. Epilepsia 58, 674–682. [PubMed: 28230253]

Knupp KG, Coryell J, Nickels KC, Ryan N, Leister E, Loddenkemper T, Grinspan Z, Hartman AL, Kossoff EH, Gaillard WD, Mytinger JR, Joshi S, Shellhaas RA, Sullivan J, Dlugos D, Hamikawa L, Berg AT, Millichap J, Nordli DR, Wirrell E, the Pediatric Epilepsy Research Consortium, 2016 Response to treatment in a prospective national infantile spasms cohort. Ann Neurol 79, 475–84. [PubMed: 26704170]

Lux AL, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, O'Callaghan FJK, Verity CM, Osborne JP, 2004 The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. Lancet 364, 1773–1778. [PubMed: 15541450]

O'Callaghan FJK, Edwards SW, Alber FD, Hancock E, Johnson AL, Kennedy CR, Likeman M, Lux AL, Mackay M, Mallick AA, Newton RW, Nolan M, Pressler R, Rating D, Schmitt B, Verity CM, Osborne JP, 2017 Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. The Lancet Neurology 16, 33–42. [PubMed: 27838190]

O'Callaghan FJK, Lux AL, Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Newton RW, Verity CM, Osborne JP, 2011 The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia 52, 1359–1364. [PubMed: 21668442]

Pearl PL, Vezina LG, Saneto RP, McCarter R, Molloy-Wells E, Heffron A, Trzcinski S, McClintock WM, Conry JA, Elling NJ, Goodkin HP, de Menezes MS, Ferri R, Gilles E, Kadom N, Gaillard WD, 2009 Cerebral MRI abnormalities associated with vigabatrin therapy. Epilepsia 50, 184–194. [PubMed: 18783433]

Pellock JM, Hrachovy R, Shinnar S, Baram TZ, Bettis D, Dlugos DJ, Gaillard WD, Gibson PA, Holmes GL, Nordl DR, O'Dell C, Shields WD, Trevathan E, Wheless JW, 2010 Infantile spasms: a U.S. consensus report. Epilepsia 51, 2175–2189. [PubMed: 20608959]

Rajaraman RR, Lay J, Alayari A, Anderson K, Sankar R, Hussain SA, 2016 Prevention of infantile spasms relapse: zonisamide and topiramate provide no benefit. Epilepsia 57, 1280–7. [PubMed: 27312124]

Riikonen R, Rener-Primec Z, Carmant L, Dorofeeva M, Hollody K, Szabo I, Krajnc BS, Wohlrab G, Sorri I, 2015 Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study. Dev Med Child Neurol 57, 60–67. 10.1111/dmcn.12573 [PubMed: 25145415]

Riikonen RS, 2010 Favourable prognostic factors with infantile spasms. Eur J Paediatr Neurol 14, 13–18. [PubMed: 19362867]

Sabril (vigabatrin) package insert, 2009.

Schwarz MD, Li M, Tsao J, Zhou R, Wu YW, Sankar R, Wu JY, Hussain SA, 2016 A lack of clinically apparent vision loss among patients treated with vigabatrin with infantile spasms: The UCLA experience. Epilepsy & Behavior 57, Part A, 29–33. 10.1016/j.yebeh.2016.01.012 [PubMed: 26921595]

Shields WD, 2006 Infantile Spasms: Little Seizures, BIG Consequences. Epilepsy Currents 6, 63–69. [PubMed: 16761063]

Vanhatalo S, Nousiainen I, Eriksson K, Rantala H, Vainionpää L, Mustonen K, Aärimaa T, Alen R, Aine M-R, Byring R, Hirvasniemi A, Nuutila A, Walden T, Ritanen-Mohammed U-M, Karttunen-Lewandowski P, Pohjola L-M, Kaksonen S, Jurvelin P, Granström M-L, 2002 Visual field constriction in 91 Finnish children treated with vigabatrin. Epilepsia 43, 748–756. [PubMed: 12102679]

Westall CA, Wright T, Cortese F, Kumarappah A, Snead OC, Buncic JR, 2014 Vigabatrin retinal toxicity in children with infantile spasms: An observational cohort study. Neurology 83, 2262–2268. [PubMed: 25381295]

Wheless JW, Carmant L, Bebin M, Conry JA, Chiron C, Elterman RD, Frost M, Paolicchi JM, Donald Shields W, Thiele EA, Zupanc ML, Collins SD, 2009 Magnetic resonance imaging abnormalities associated with vigabatrin in patients with epilepsy. Epilepsia 50, 195–205. [PubMed: 19054414]

Highlights

- Higher vigabatrin dosage after resolution of infantile spasms is associated with lower risk of relapse.
- The potential benefit of high-dose vigabatrin must be weighed against the risk of toxicity, especially vigabatrin-associated MRI phenomena.
- Further study is needed to determine if high vigabatrin dosage is associated with long-term outcomes.

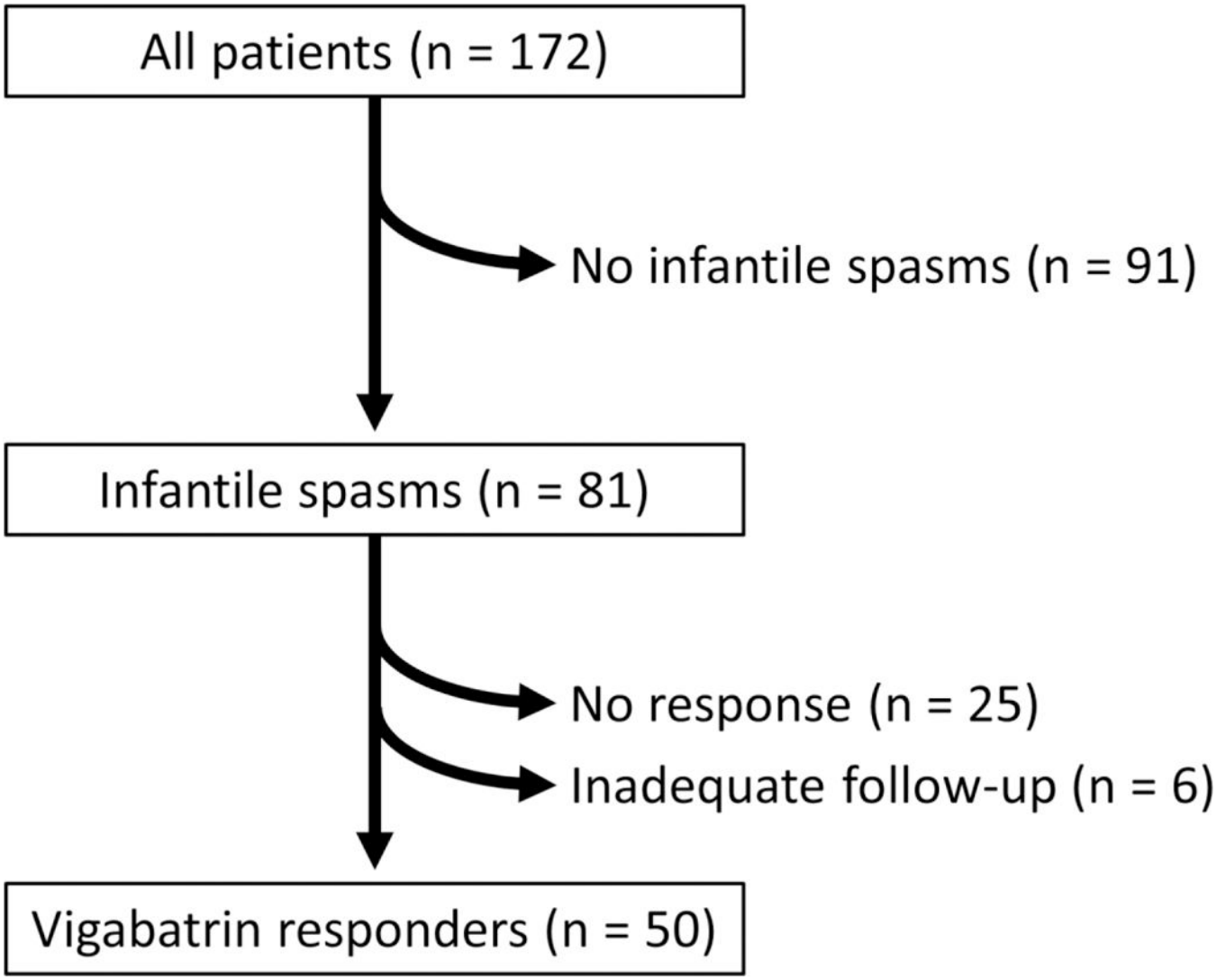

Figure 1: Formation of the nested study cohort

The analyses in the study are based on the 50 patients with infantile spasms who responded to VGB.

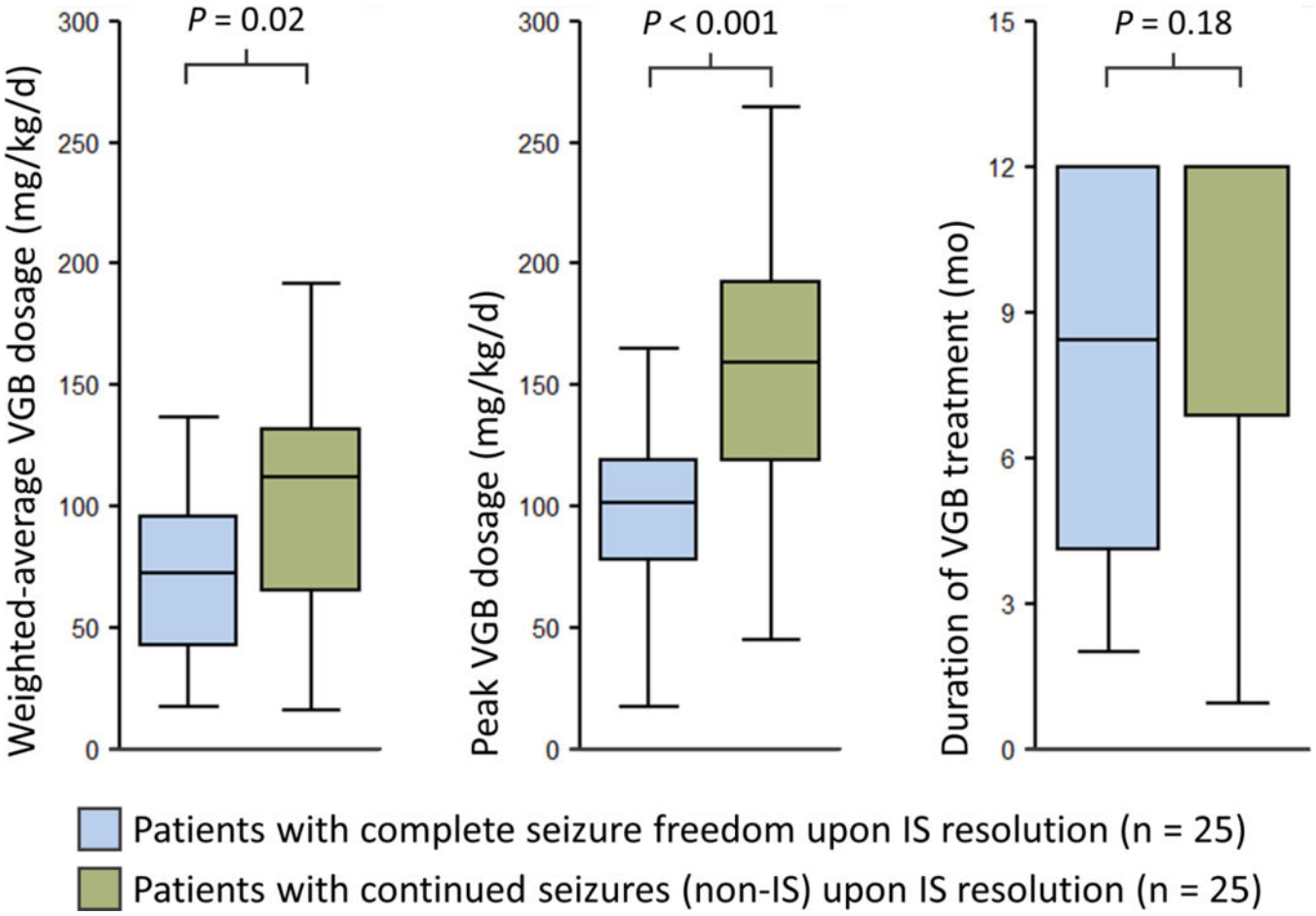

Figure 2: VGB exposure after IS resolution as a function of non-IS seizure burden

In the period following resolution of IS, VGB exposure was higher among patients with other (non-IS) continued seizures.

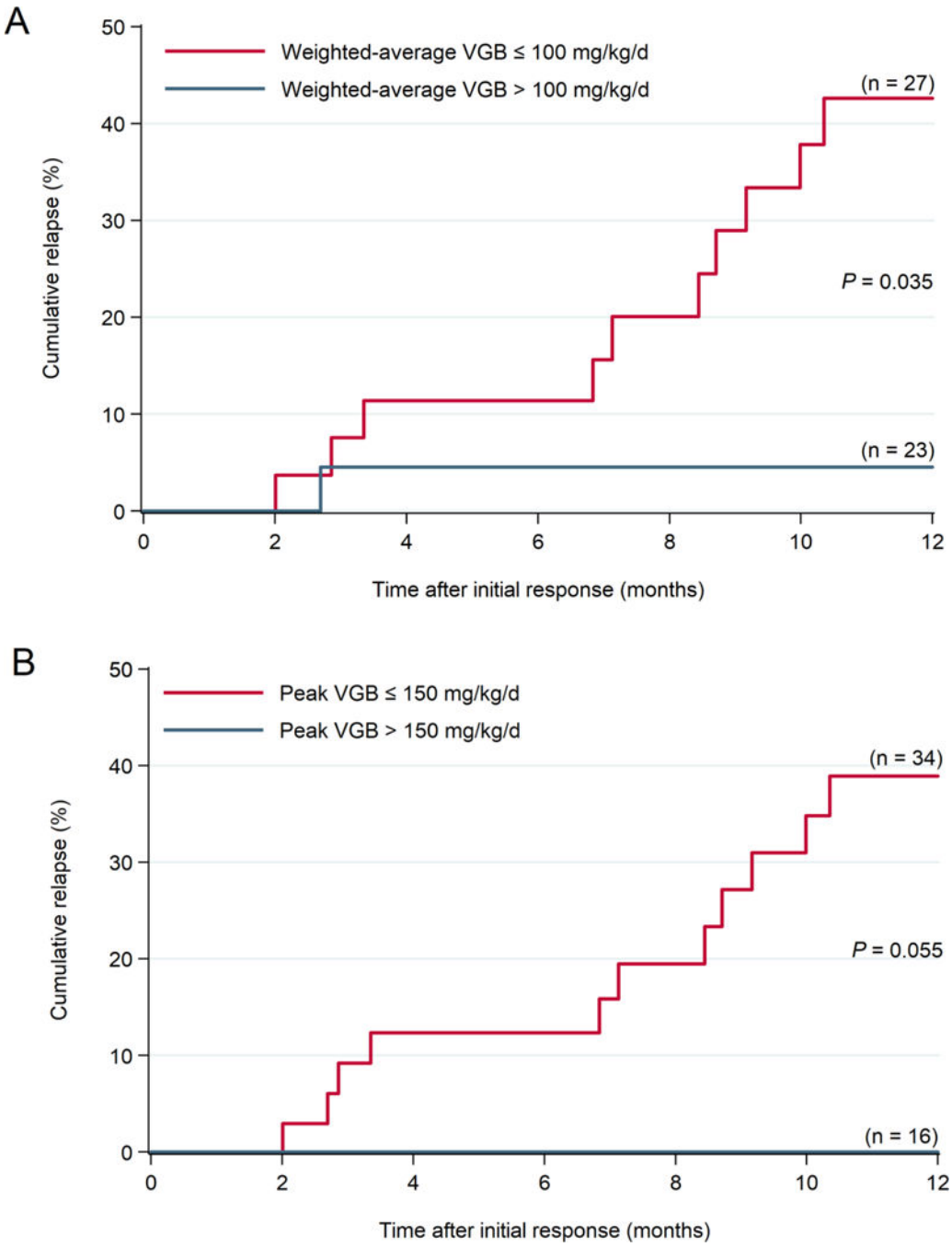

Figure 3: Time to IS relapse as a function of weighted-average VGB dosage

Kaplan-Meier plot of cumulative relapse as a function of weighted-average VGB dosage (Panel A) and peak VGB dosage (Panel B). *P*-value determined by Cox proportional hazards regression with single dichotomous risk-factor.

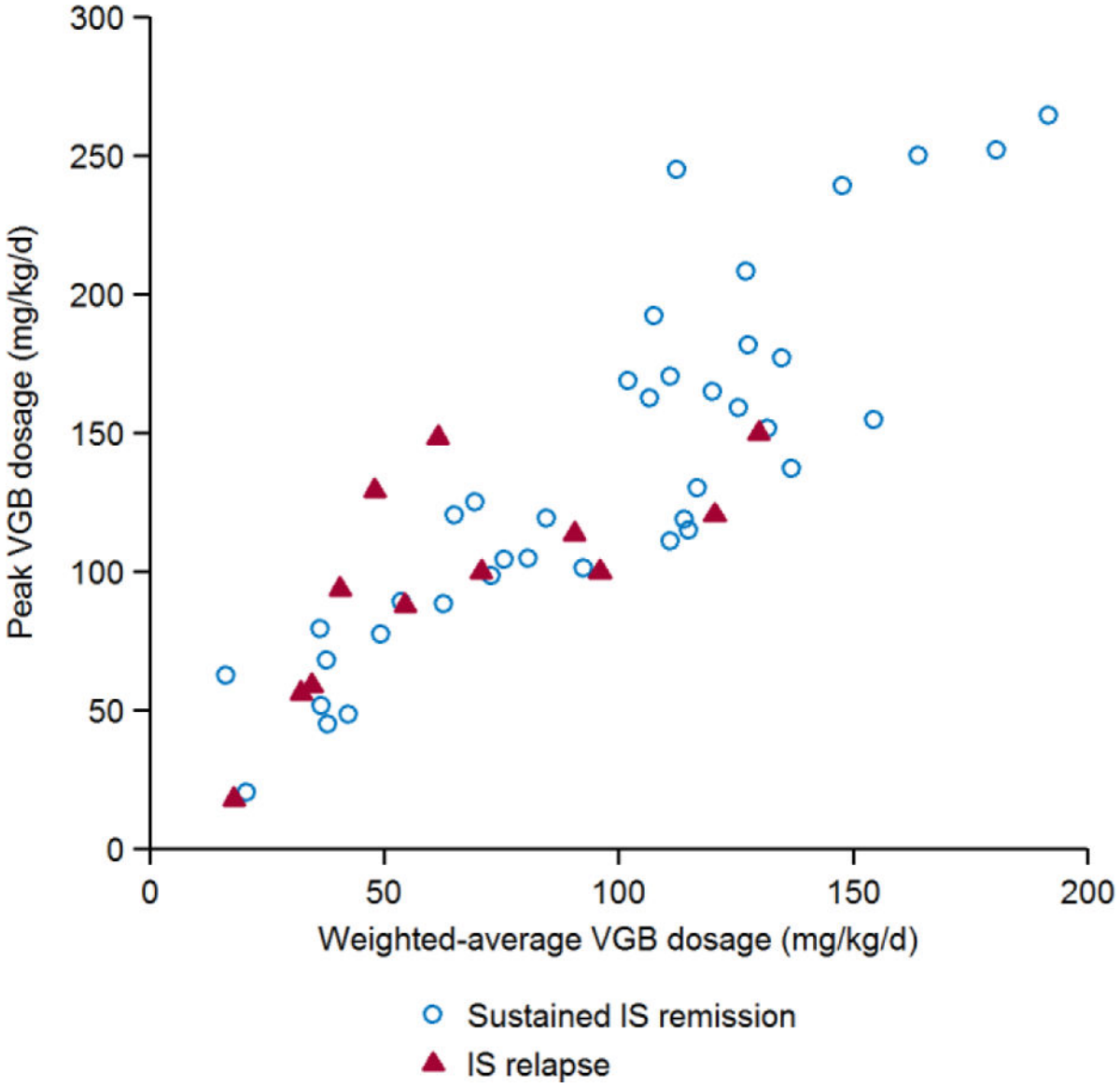

Figure 4: IS relapse as a function of weighted average and peak VGB dosage

IS relapse was least common among patients with high peak and weighted-average VGB dosage in the period following resolution of IS.

Table 1.

Characteristics of the study population (n = 50)

Demographics	
Female, n (%)	23 (46%)
Age at infantile spasms onset, mo[a]	5.4 (4.1 – 7.0)
Genetics	
Known *TSC1* mutation, n (%)	1 (2%)
Known *TSC2* mutation, n (%)	25 (50%)
Neither *TSC1* nor *TSC2*, n (%)	2 (4%)
Unknown/unavailable, n (%)	22 (44%)
Epilepsy Burden	
Duration of spasms prior to response, days[a]	11 (3 − 41)
Presence of other (focal) seizures after IS resolution, n (%)	25 (50%)
Frequency of other (focal) seizures after IS resolution (sz/mo)[a]	0 (0 − 0.7)
VGB treatment parameters	
Duration of therapy, mo[a]	9.2 (5.7 − 16.3)
Peak weight-based dosage, mg/kg/d[a]	119 (88 − 163)
Weighted-average weight-based dosage, mg/kg/d[a]	92 (49 − 121)
Cumulative VGB dosage, g[a]	782 (422 − 1043)
Simultaneous hormonal therapy, n (%)	6 (12%)

[a]Median (interquartile range)