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Original Article

Very-High-Dose Prednisolone Before ACTH for Treatment of Infantile Spasms: Evaluation of a Standardized Protocol

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ABSTRACT

Background: There is ongoing debate regarding the comparative effectiveness of adrenocorticotropic hormone and prednisolone in the treatment of infantile spasms. With a large cohort and extended follow-up, we set out to evaluate a protocol in which adrenocorticotropic hormone is reserved for prednisolone nonresponders.

Methods: The following standardized hormonal therapy protocol was adopted. Patients initially receive prednisolone (8 mg/kg/day [maximum 60 mg/day], divided in three daily doses for 14 days). Prednisolone responders taper it over 14 days, whereas prednisolone nonresponders immediately transition to natural adrenocorticotropic hormone (150 U/m^2/day, divided in two daily doses for 14 days). We evaluated short-term response, defined as video-electroenecphaloagraphy-confirmed resolution of both epileptic spasms and hypsarrhythmia on day 14, without relapse for 28 additional days. We then evaluated long-term relapse and calculated the rates of sustained response at six, 12, and 18 months.

Results: We identified 102 children with infantile spasms who were treated with prednisolone. Prior exposure to hormonal therapy and vigabatrin was observed among 12% and 35% of patients, respectively. Sixty (59%) patients responded to prednisolone, and 13 (33%) prednisolone nonresponders then responded to adrenocorticotropic hormone. Cumulative response to prednisolone and adrenocorticotropic hormone (if needed) was higher among treatment-naive patients (84%) than among patients with prior exposure to first-line treatment (51%), with $P < 0.001$. Relapse was relatively common among all subgroups.

Conclusion: Short-term response to prednisolone was favorable and higher among treatment-naive patients. These data suggest that prednisolone is a reasonable approach to initial therapy and that adrenocorticotropic hormone exhibits substantial efficacy after prednisolone failure.

Introduction

Infantile spasms represent an often devastating form of epileptic encephalopathy that typically presents in the first year of life with epileptic spasms, hypsarrhythmia (including variations thereof), and neurodevelopmental arrest.[1] A lack of prompt and successful treatment is associated with adverse long-term developmental outcomes.[2] There is relatively broad consensus that appropriate first-line therapies for infantile spasms include vigabatrin and an array of hormonal therapies.[3] The hormonal therapies include adrenocorticotropic hormone (ACTH)—either natural (the full 39-amino acid peptide) or synthetic (the 24-amino acid N-terminal fragment)—as well as a variety of oral corticosteroids including prednisolone and prednisone (the prodrug of prednisolone). However, in contrasting ACTH and prednisolone, there are

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conflicting data, highly varied practices, and considerable debate as to the best agent and dosage.[4-8] In the United States, this controversy is especially contentious given an enormous disparity in cost. The cost of a typical course of ACTH exceeds US $100,000, whereas prednisolone costs less than US $100. Our center opted for a standard protocol in which hormonal therapy is initiated with high-dose prednisolone, with nonresponders immediately transitioning to ACTH. As an update to our prior report on this protocol, this study was conducted to evaluate response in a larger cohort with extended follow-up.

Methods

Standard protocol approvals

The participation of human subjects and the analyses presented here were approved by the institutional review board at the University of California, Los Angeles (UCLA).

Study design

This was a retrospective cohort study. Using a database that includes all patients who underwent video-electroencephalography (EEG) at the UCLA Mattel Children's Hospital, we identified patients with video-EEG-confirmed epileptic spasms who were treated with the UCLA hormonal therapy protocol (see below). There were no other inclusion or exclusion criteria.

Hormonal therapy protocol

Beginning in April 2009 and ending in May 2017, our center implemented a standardized hormonal therapy protocol for the treatment of epileptic spasms, as described previously.[9] Briefly, upon confirmation of epileptic spasms—with or without hypsarrhythmia—children are prescribed oral prednisolone (8 mg/kg/day; maximum 60 mg/day, divided in three equal doses). After two weeks, patients with clinical response (parent-reported resolution of epileptic spasms) return for inpatient overnight video-EEG to establish electroclinical response (freedom from both epileptic spasms and hypsarrhythmia). Complete responders taper off prednisolone over two additional weeks, whereas nonresponders immediately transition to intramuscular natural ACTH (H.P. Acthar Gel, Mallinckrodt Pharmaceuticals), with a dosage of 150 U/m^2/day, divided in two equal doses, and without tapering prednisolone. Upon clinical response to ACTH, overnight video-EEG is similarly conducted to determine electroclinical response. Regardless of the response, ACTH is tapered off over 14 days.

Hypotheses

Based on our prior study,[9] we anticipated approximately 60% to 70% response to prednisolone and 30% to 50% response to ACTH after prednisolone failure. We further hypothesized that response would be higher among patients without prior exposure to first-line therapy (i.e., prednisolone, ACTH, or vigabatrin), as well as patients with *cryptogenic* etiology (i.e., unknown etiology and normal development before onset of infantile spasms), older age of onset of infantile spasms, and shorter latency from onset of infantile spasms to protocol entry. Similarly, based on contemporary experience in the (United States) National Infantile Spasms Consortium, we expected that response would not be associated with the presence of hypsarrhythmia at protocol entry.[10]

Data acquisition

All data were abstracted from the electronic medical record. For each patient, we recorded the dates of birth, onset of epileptic spasms, prednisolone initiation, ACTH initiation (if applicable), relapse (if applicable), and most recent follow-up. We catalogued all therapies administered before prednisolone (if any). For each video-EEG, we recorded the presence or absence of epileptic spasms and hypsarrhythmia using EEG reports as opposed to *post hoc* review of video and EEG tracings.

Efficacy outcome measures

Short-term response was defined as present when the follow criteria were met: (1) freedom from both epileptic spasms and hypsarrhythmia on day 14 (relative to the initiation of prednisolone or ACTH) based on overnight video-EEG, (2) no recurrence of epileptic spasms over the next 28 days, (3) initiation of hormonal therapy taper, and (4) notation in the medical record that the patient responded to therapy. Long-term response was defined as freedom from epileptic spasms and hypsarrhythmia on day 14, without relapse over the next six, 12, or 18 months.

Adverse events

With regard to potential adverse events during hormonal therapy, we focused on hypertension, infection, hyperglycemia, and hypokalemia. Hypertension was defined as present in those cases in which hypertension was explicitly mentioned in progress notes (regardless of more specific documentation) or in those cases in which there was specific documentation of at least two separate blood pressure measurements defined as high (i.e., either systolic or diastolic blood pressure above an age- and sex-specific ninety-fifth percentile reference value[11]). Given that upper respiratory tract infections are common in this patient population, we sought only to identify “clinically significant” infection, which we defined as an infection noted in medical record that prompted hospitalization or prolongation of hospitalization. Hyperglycemia was defined as present when specifically mentioned in the medical record, upon discovery of two separate fasting blood glucose measurements exceeding 100 mg/dL, or upon presence of glucose (“1+” or greater) on at least two random urine screenings.[12] Hypokalemia was defined as present if explicitly mentioned in the medical record, or with documentation of two separate serum potassium measurements less than 2.5 mEq/L.[13]

Statistical methods

Continuous summary data were presented as median and interquartile range (IQR) based on nonparametric distributions. Comparisons of continuous and dichotomous variables were accomplished with the Wilcoxon rank-sum test and the Fisher exact test, respectively. Comparisons of percentages across ordered groups (successive time points) were performed using the nonparametric test for trend (Stata function “nptrend”). Survival analyses were carried out with the Kaplan-Meier procedure and Cox proportional hazards regression. Exploratory analyses to identify factors associated with response were carried out with sequential univariate and multivariate logistic regression, without adjustment for multiple comparisons. All comparisons were two-sided, and only $P < 0.05$ were considered statistically significant. Statistical calculations were facilitated with STATA software (Statacorp, version 14, College Station, Texas, USA).

Results

Subjects

Baseline clinical and demographic characteristics of the study population are presented in Table 1. Among a total of 409 patients who were evaluated at UCLA, we identified 102 children with video-EEG-confirmed epileptic spasms who were treated with high-dose prednisolone. The remaining 307 patients were not treated with prednisolone—and thus excluded from this analysis—because (1) they were already receiving hormonal therapy (prescribed at another center), (2) they had already failed an adequate trial (in the view of the treating physician) of prednisolone or ACTH (prescribed at another center), or (3) the treating physician opted for nonhormonal therapy (i.e., vigabatrin in the setting of tuberous sclerosis complex). In general, patients with prior exposure to hormonal therapy at other institutions were prescribed hormonal therapy (according to our protocol) if there was history of prompt response or if the prior dose or duration of hormonal therapy was deemed too low or too short. In contrast, it was far more common that patients presented to UCLA during the study period having already failed an "adequate" trial of hormonal therapy, on the basis of nonresponse or relapse immediately upon taper. In these latter cases, patients were typically treated with nonhormonal therapy.

Of note, the cohort in this analysis includes the 27 patients described in our previous study.[9] As there were no significant differences with respect to demographics and response rates between the 27 patients in our prior report and the subsequent 75 patients, we combined these subgroups in all analyses that follow.

With regard to etiology, 10 patients were classified as *cryptogenic,* and the most common specific etiologies were hypoxic ischemic encephalopathy (n = 9), Down syndrome (n = 6), and tuberous sclerosis complex (n = 5). Of note, median latency from the onset of epileptic spasms to prednisolone treatment was 2.3 months (IQR 0.5, 6.2), and prior treatment with hormonal therapy (prednisolone or ACTH prescribed at other centers) and vigabatrin was observed among 12 and 36 patients, respectively.

TABLE 1.
Baseline Characteristics of the Study Population

Total patients, n	102
Female, n (%)	41 (40)
Age of onset of IS, mo, median (IQR)	7.1 (4.9-12.1)
Age of onset of IS, corrected for prematurity, mo, median (IQR)	7.6 (4.9-12.7)
Latency from diagnosis to protocol entry, mo, median (IQR)	2.3 (0.5-6.2)
Hypsarrhythmia present at protocol entry, n (%)	43 (42%)
Prior vigabatrin therapy, n (%)	36 (35)
Prior hormonal therapy, n (%)	12 (12)
Development	
Normal development before onset of IS, n (%)	24 (24)
Etiology	
Unknown, n (%)	30 (29)
Cryptogenic[*], n (%)	10 (10)
Known[†], n (%)	72 (71)
Structural, n (%)	51 (50)
Genetic, n (%)	33 (32)
Metabolic, n (%)	2 (2)
Total duration of follow-up, mo, median (IQR)	22.6 (10.9-39.9)

Abbreviations:
IQR = Interquartile range
IS = Infantile spasms
[*] *Cryptogenic* indicates unknown etiology and normal development before onset of epileptic spasms.
[†] The sum of specific etiologic classifications (i.e., structural, genetic, metabolic) exceeded the sum of patients with known etiology because some patients exhibited dual classification.

Short-term efficacy

Sixty (59%) patients responded to prednisolone. Two patients exhibited a protocol violation and did not commence ACTH immediately following prednisolone failure. In one case, the rationale for lack of transition to ACTH was not documented in the medical record. In the second case, the patient was lost to follow-up upon prednisolone failure. Among the remaining 40 prednisolone nonresponders, 13 (33%) subsequently responded to ACTH. In sum, the cumulative response rate to prednisolone and ACTH (if needed) was 73 of 102 (72%).

Factors associated with short-term response

We used logistic regression to evaluate factors that may be associated with response (Table 2).

With sequential univariate regression, the only statistically significant factor associated with response to prednisolone was lack of prior first-line therapies (odds ratio [OR] 3.3, $P = 0.005$), although there was a trend such that identified genetic etiology was associated with lower likelihood of response (OR 0.44, $P = 0.06$). In evaluating factors potentially associated with cumulative short-term response to prednisolone and ACTH, significant factors included lack of prior first-line therapy (OR 5.0, $P = 0.001$), genetic etiology (OR 0.44, $P = 0.033$), and age of onset of infantile spasms (OR 2.9, $P = 0.025$), such that age of onset greater than the median was associated with a higher likelihood of response. In a multivariate model (Table 2, model 1) that included all three candidate factors, the only factor independently associated with response was lack of prior first-line therapy. Of note, the presence of hypsarrhythmia on baseline EEG was not associated with response in any model.

Among the 63 patients who were not previously treated with hormonal therapy or vigabatrin—and thus naive to first-line treatments for infantile spasms—44 (70%) responded to prednisolone. Among the 19 (30%) patients without response to prednisolone, nine (47%) then responded to ACTH. Accordingly, in this treatment-naive subgroup, the cumulative short-term response to prednisolone and ACTH was 53 of 63 (84%). In contrast, among 39 children with prior exposure to hormonal therapy or vigabatrin, 16 (41%) responded to prednisolone and 23 (59%) did not respond. Among these 23 nonresponders, only 21 transitioned to ACTH (two protocol violations as described above) and four (19%) of 21 then responded to ACTH. As illustrated in Fig 1, the treatment-naive subgroup exhibited superior response to prednisolone ($P = 0.007$) and superior cumulative response to prednisolone followed by ACTH ($P < 0.001$).

Of note, latency to protocol entry among the treatment-naive subgroup (median 0.9 months; IQR [0.2, 3.0]) was shorter than the subgroup with prior first-line treatment exposure (median 5 months; IQR [2.8, 14.1]), with $P < 0.001$. However, latency to protocol entry was not significantly associated with response to prednisolone or ACTH in the overall cohort and it did not confound the observed association of response with prior first-line treatment (Table 2, model 2).

In evaluating the association of response with prior first-line therapies, we then considered prior hormonal treatment and prior vigabatrin treatment separately. In considering the 90 patients without prior hormonal therapy exposure, among whom median latency from onset of epileptic spasms to prednisolone treatment was 0.9 months (IQR 0.2, 3.0), response to prednisolone was higher among the vigabatrin-naive patients (70%) than vigabatrin-exposed patients (37%), with $P = 0.005$. Similarly, cumulative response to prednisolone and ACTH was 84% among

TABLE 2.
Factors Associated With Short-Term Response to Hormonal Therapy

Sequential Univariate Logistic Regression	Response to PRED Only		Cumulative Response to PRED and ACTH (After PRED Failure)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
No prior VGB or hormonal therapy	3.33 (1.44, 7.67)	**0.005**	5.04 (2.00, 12.7)	**0.001**
Etiology				
Cryptogenic[*] etiology	1.06 (0.28, 4.00)	0.94	1.66 (0.33, 8.34)	0.54
Structural	1.92 (0.86, 4.28)	0.11	1.98 (0.82, 4.78)	0.13
Genetic	0.44 (0.19, 1.04)	0.06	0.38 (0.15, 0.92)	**0.033**
Developmental delay before IS	0.65 (0.25, 1.69)	0.37	0.80 (0.28, 2.26)	0.67
Age of IS onset[†,‡]	1.80 (0.81, 4.00)	0.15	2.85 (1.14, 7.09)	**0.025**
Latency from IS onset to protocol entry[‡]	0.61 (0.28, 1.36)	0.23	0.62 (0.26, 1.47)	0.27
Hypsarrhythmia on baseline EEG	0.95 (0.43, 2.12)	0.91	0.71 (0.30, 1.68)	0.43
Multivariate Logistic Regression (Model 1)	Adj. OR (95% CI)	*P* value	Adj. OR (95% CI)	*P* value
No prior VGB or hormonal therapy	3.15 (1.34, 7.43)	**0.009**	4.72 (1.80, 12.4)	**0.002**
Genetic etiology	0.47 (0.19, 1.14)	0.094	0.40 (0.15, 1.06)	0.065
Age of IS onset[‡]	1.42 (0.61, 3.33)	0.42	2.23 (0.84, 5.97)	0.11
Multivariate Logistic Regression (Model 2)	Adj. OR (95% CI)	*P* value	Adj. OR (95% CI)	*P* value
No prior VGB or hormonal therapy	3.45 (1.33, 8.92)	**0.011**	6.12 (2.05, 18.3)	**0.001**
Latency from IS onset to protocol entry[‡]	1.07 (0.42, 2.74)	0.88	1.47 (0.49, 4.41)	0.49

Abbreviations:
ACTH = Adrenocorticotropic hormone
Adj. OR = Adjusted odds ratio
EEG = Electroencephalography
IS = Infantile spasms
OR = Odds ratio
PRED = Prednisolone
VGB = Vigabatrin
95% CI = 95% Confidence interval
P-values < 0.05 are highlighted in boldface.
[*] Cryptogenic refers to unknown etiology and normal development before onset of infantile spasms.
[†] Age of onset was not corrected for prematurity.
[‡] These continuous variables were coded as dichotomous (above or below median) given skewed distribution. The reported odds ratios estimate "risk of response" associated with age or latency greater than the median.

vigabatrin-naive patients and 48% among those with prior VGB treatment, with $P = 0.001$.

Long-term efficacy and relapse

The median duration of follow-up for the cohort was 22.6 months (IQR 10.9, 39.9). As illustrated in Fig 2A, there were 88, 71, and 60 patients with at least six, 12, and 18 months of follow-up, respectively. Compared with 59% response to prednisolone (only) on day 14, the rates of sustained response without relapse were 48%, 48%, and 40%, among patients at six, 12, and 18 months follow-up, respectively. The rate of sustained response diminished over time, with P (for trend) = 0.023. Similarly, when compared with initial cumulative response to prednisolone and ACTH (72%), the rates of sustained response were 57%, 55%, and 48%, at six, 12, and 18 months, respectively. Again, we observed diminishing rates of sustained response across successive time points, with P (for trend) = 0.003. As was the case for short-term response, the factor exhibiting the strongest association with sustained response to prednisolone and ACTH (if needed) was lack of prior exposure to hormonal therapy and vigabatrin (Fig 2B).

Among the 73 children who responded to any hormonal therapy, there were 23 (32%) relapses, occurring at a median of 4.3 months (IQR 1.7, 9.0) following response. In an exploratory survival analysis to evaluate whether time to relapse was distinct among patients who responded to prednisolone alone versus ACTH following prednisolone failure, there was a trend such that relapse was more likely among ACTH responders (hazard ratio = 2.14, 95% confidence interval [0.88, 5.22], $P = 0.09$). No other factors associated with time to relapse were identified, and in particular, exposure to first-line therapies before protocol entry did not predict time to relapse (Fig 3).

Safety and tolerability

Side effects of hormonal therapy were common in this cohort. Hypertension was identified in 30 patients, but only three patients received antihypertensive treatment. In the vast majority of cases, clinicians determined that antihypertensive therapy was unnecessary. There were no cases in which hypertension led to end-organ damage or early discontinuation of therapy, and hypertension was not more common among patients who received prednisolone and ACTH when compared with those who received prednisolone only. With regard to infection, we identified four cases in which known or suspected infection prompted hospitalization or prolongation of hospitalization. Two patients developed pneumonia (both prompting intubation and antibiotic therapy and one complicated by sepsis), one patient with urinary tract infection without urosepsis, and one patient with an infected sublingual cyst. All four patients recovered without sequelae. Hyperglycemia was identified in only one patient, who exhibited preexisting hyperglycemia in the setting of DEND (developmental delay, encephalopathy, neonatal diabetes) syndrome. There were no cases of hypokalemia.

Discussion

This study is noteworthy because we report a favorable rate of video-EEG-confirmed response to prednisolone and extend the results of our prior study[9] to a much larger cohort with long-term follow-up. Foremost, response to prednisolone among the

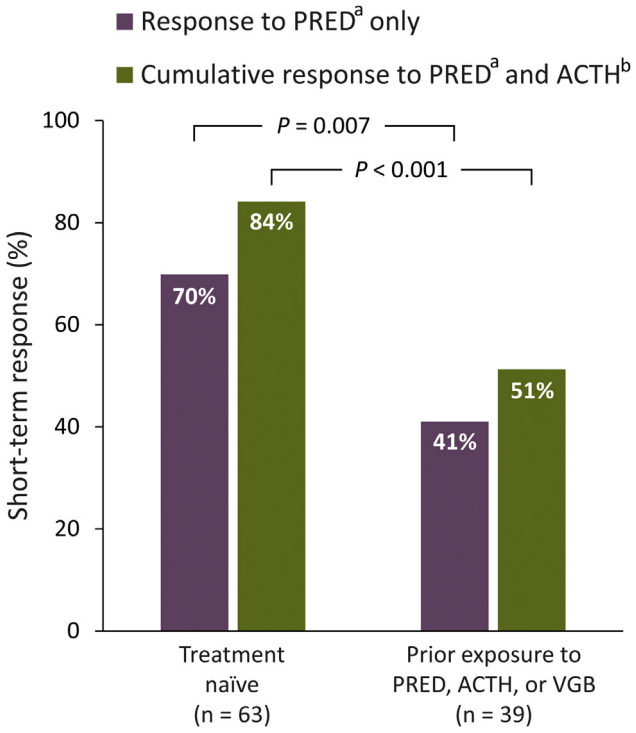

FIGURE 1. Short-term response to hormonal therapy stratified by prior treatments. This comparison included all patients. Short-term response was defined as absence of epileptic spasms and hypsarrhythmia on day 14 video-EEG, without relapse over the next 28 days. ACTH, adrenocorticotropic hormone; PRED, prednisolone; VGB, vigabatrin. [a]Prednisolone treatment: 8 mg/kg/day (maximum 60 mg/day), divided in three daily doses, for 14 days. [b]Natural ACTH was administered only to prednisolone nonresponders: 150 U/m^2/day, divided in two daily doses, for 14 days. The color version of this figure is available in the online edition.

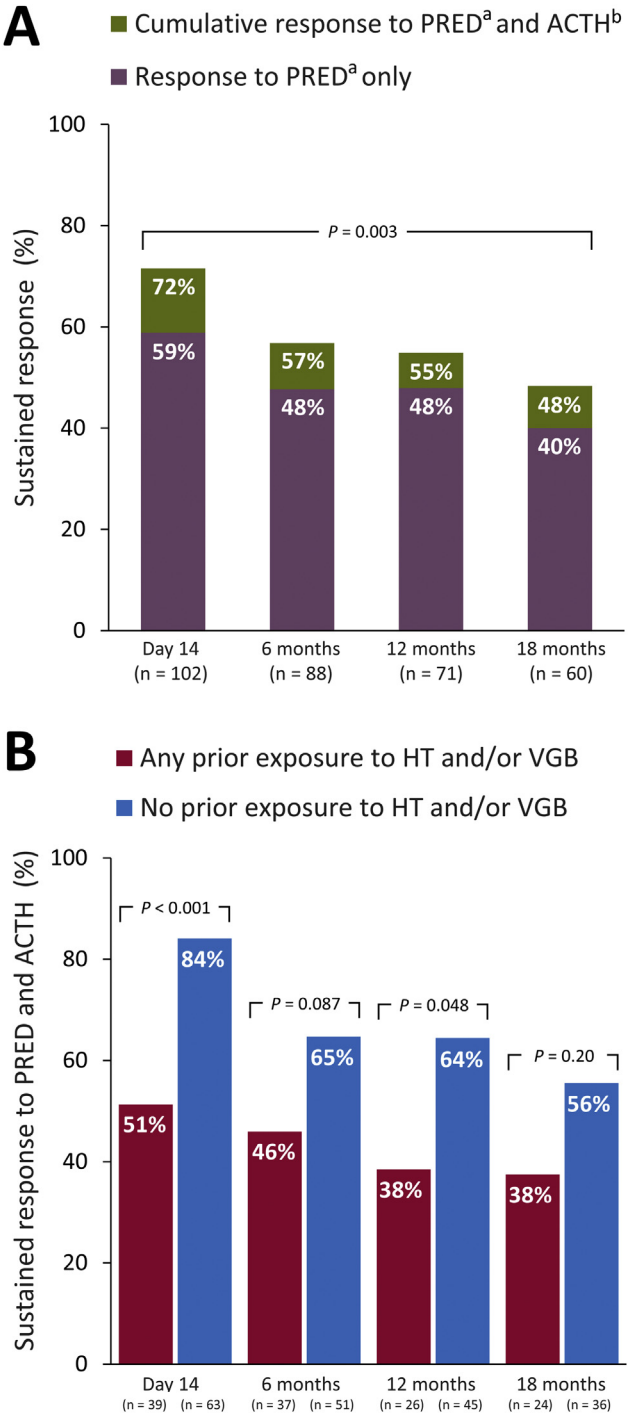

FIGURE 2. Long-term response to hormonal therapy. (A) Considering response to prednisolone only (purple) or prednisolone followed by ACTH (green), sustained response without relapse diminishes over time. *P* value obtained using a nonparametric test for trend. (B) Sustained response to prednisolone and/or ACTH over time, stratified by prior exposure to prednisolone, ACTH, or vigabatrin. [a]Prednisolone treatment: 8 mg/kg/day (max 60 mg/day), divided in three daily doses, for 14 days. [b]Natural ACTH was administered only to prednisolone nonresponders: 150 U/m^2, divided in two daily doses, for 14 days. ACTH, adrenocorticotropic hormone; HT, hormonal therapy; PRED, prednisolone; VGB, vigabatrin. The color version of this figure is available in the online edition.

treatment-naive subgroup (70%) compares favorably with several contemporary reports describing the use of high-dose prednisolone and ACTH as first-line treatments.[14-19] It is possible that the relatively high response rate reflects the exceptionally high dose of prednisolone used. Similarly, cumulative response to prednisolone and ACTH (when needed) among our treatment-naive subgroup (84%) is very close to the highest reported response rates to high-dose (150 U/m^2/day, divided twice daily) natural ACTH (~90%).[20,21] Still, our cumulative response required 28 days of hormonal therapy rather than just 14 days. Although this represents a relatively small delay in response, it might nevertheless impact long-term developmental outcomes.[22] Importantly, response to prednisolone in this cohort was much higher than the 29% to 33% response observed in older studies, which employed lower-dose regimens (2 mg/kg/day) of prednisone,[21,23] and supports the general view that high dosage is critical in the use of any hormonal therapy for treatment of infantile spasms. However, despite these external comparisons, it is critical to note that our study is not a randomized controlled trial and does not permit a direct within-study comparison of the efficacy and tolerability of prednisolone and ACTH.

This study does not resolve ongoing debate as to the comparative efficacy of prednisolone and ACTH. Although a majority of patients exhibited complete response to prednisolone, it is notable that one-third of prednisolone nonresponders subsequently responded to ACTH. This may indicate superior efficacy of ACTH relative to prednisolone (and perhaps a distinct mechanism of action), superior efficacy with a longer course of any hormonal therapy, or both. The possibility that ACTH may act via interactions with central melanocortin receptors is intriguing and represents a promising avenue for the development of effective therapies that do not confer the risks of endogenous or exogenous corticosteroids.[24] On the other hand, the apparent short-term yield of ACTH after prednisolone failure may be undercut by a high relapse rate.

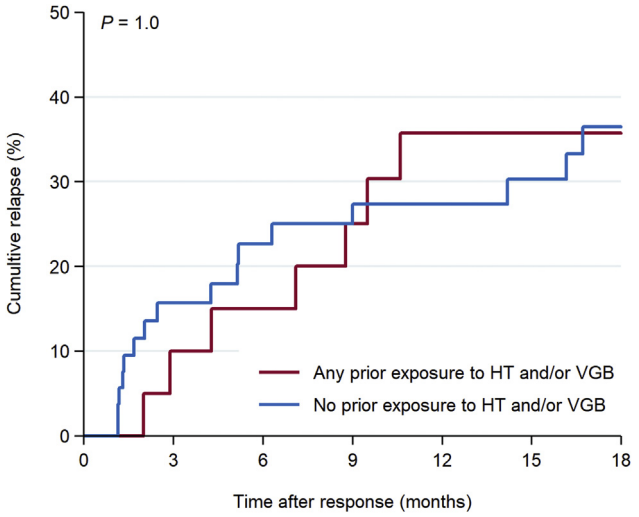

FIGURE 3. Cumulative relapse as a function of prior treatment. This is a Kaplan-Meier plot of time to relapse, including all patients who responded to any hormonal therapy regimen (n = 73). Of note, the *P* value was derived from univariate Cox proportional hazards regression. HT, hormonal therapy; VGB, vigabatrin. The color version of this figure is available in the online edition.

Among those who eventually responded to ACTH after prednisolone failure, we observed a trend such that the cumulative rate of relapse was approximately double that of prednisolone-only responders. We suspect that those patients who fail prednisolone but ultimately respond to ACTH represent a refractory subpopulation with higher disease burden and higher risk of relapse. Furthermore, it is important to note that no study has evaluated the efficacy of high-dose prednisolone immediately following high-dose ACTH failure. If the substantial ACTH response observed in this study is due to prolonged exposure to any hormonal therapy—rather than a distinct mechanism of action—we would expect patients who fail high-dose ACTH to exhibit substantial response with crossover to high-dose prednisolone. Along these lines, it is notable that whereas response to lower-dose prednisone (2 mg/kg/day) was substantial after failure of low-dose ACTH (30 U/day) in the report of Hrachovy and colleages,[23] response to the same dose of prednisone was very modest after failure of high-dose ACTH (150 U/m^2/day) in the study of Baram and colleagues.[21]

Short-term response to prednisolone (and ACTH) in this study was favorable, especially among treatment-naive patients, whereas long-term sustained response rates are disappointingly low (Fig 2). In considering all responders, the cumulative relapse rate exceeds 36% at 18 months follow-up (Fig 3). This high relapse rate is similar to prior reports[25,26] and highlights the unmet need for effective therapies that can be continued long-term in the effort to prevent relapse. Of note, whereas exposure to first-line therapies before protocol entry was strongly associated with lack of short-term response, remote first-line therapies did not impact time to relapse (Fig 3).

The strength of our conclusions is limited by our study design, with lack of randomization and other experimental controls, as well as our dependence on electroclinical outcomes, which are both unblinded and which exhibit unfavorable inter-rater reliability.[27] To the extent that we evaluated long-term outcomes, we must emphasize the limitations of our follow-up data. As this study was retrospective and did not involve a dedicated effort to follow patients, there may have been differential loss to follow-up such that patients with the best outcomes discontinued neurology care entirely, and perhaps some patients with poor short-term outcomes transitioned care to other centers in hopes of pursuing substantially different treatments. Although we mandated and uniformly prescribed prednisolone before ACTH, there is nevertheless the potential for selection bias. The patients included in this analysis represent only a fraction of all patients with infantile spasms evaluated during the study period, with the majority of patients excluded because of ongoing hormonal therapy at first UCLA encounter, prior failure of an adequate course of hormonal therapy, or preference for nonhormonal therapy—namely, vigabatrin. As a referral center with highly refractory cases, our patient population is not representative of all children with infantile spasms. Especially with respect to those patients with prior hormonal therapy exposure, it is not clear that our high short-term response rates, as well as our high relapse rates, can be generalized to the broader infantile spasms population. Equally important, like most studies of epileptic spasms, we have not presented rigorous data on the most important long-term outcomes—namely, intellectual function in later childhood and beyond, as well as the development of autism. Furthermore, although our sample size was relatively large when compared with other recent studies that have evaluated the efficacy of high-dose prednisolone, the cohort was still relatively small from a statistical standpoint. We were not sufficiently powered to detect risk factors that confer a relatively small impact on response rate or relapse risk (i.e., OR or hazard ratio < 2). As such, our attempt to identify associations with short- and long-term outcomes should be viewed as exploratory, and it is therefore not altogether surprising that outcomes in this study were unaffected by lead time to treatment, etiologic classification, and premorbid developmental status.

Since May, 2017, our center has continued to employ prednisolone before ACTH, but we have modified the standard protocol for initial treatment of epileptic spasms by incorporating combination therapy with vigabatrin.[28] In brief, we now commence therapy upon diagnosis with prednisolone (8 mg/kg/day, maximum 60 mg/day) and vigabatrin (100 mg/kg/day). In the absence of complete response on day 14, we substitute ACTH (150 U/m^2/day) for prednisolone, and in the absence of complete response on day 28, we titrate vigabatrin (150 mg/kg/day) and taper ACTH over 14 days. This protocol change was inspired by the superior short-term electroclinical outcomes that accompanied combination therapy (prednisolone or synthetic ACTH, in combination with vigabatrin) when compared with hormonal therapy alone, as observed in the International Collaborative Infantile Spasms Study (ICISS).[15] We have so far continued to employ this approach despite the first ICISS follow-up analysis in which developmental outcome at age 18 months was not clearly distinct among recipients of combination therapy or hormonal therapy alone.[29] Subsequent ICISS analysis of developmental outcome at 42 months, as well as the results of an ongoing and potentially confirmatory study (ClinicalTrials.gov NCT03347526), which contrasts vigabatrin alone, synthetic ACTH alone, and combination therapy, are highly anticipated. Inasmuch as this study lends support to the use of prednisolone as first-line therapy (especially in those circumstances in which access to ACTH is challenging), it more importantly highlights enduring uncertainty as to the comparative effectiveness of prednisolone and ACTH and underscores the need for novel therapies that confer greater safety and long-term efficacy.

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