Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy

Christopher M. DeGiorgio, Jason Soss, Ian A. Cook, et al.

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Christopher M. DeGiorgio, MD
Jason Soss, MD
Ian A. Cook, MD
Daniela Markovic, MS
Jeffrey Gornbein, DrPH
Diana Murray
Sandra Oviedo, BS
Steven Gordon
Guadalupe Corralle-Leyva
Colin P. Kealey, MD
Christi N. Heck, MD, MMM

Correspondence to Dr. DeGiorgio: cmd@mednet.ucla.edu

ABSTRACT

Objective: To explore the safety and efficacy of external trigeminal nerve stimulation (eTNS) in patients with drug-resistant epilepsy (DRE) using a double-blind randomized controlled trial design, and to test the suitability of treatment and control parameters in preparation for a phase III multicenter clinical trial.

Methods: This is a double-blind randomized active-control trial in DRE. Fifty subjects with 2 or more partial onset seizures per month (complex partial or tonic-clonic) entered a 6-week baseline period, and then were evaluated at 6, 12, and 18 weeks during the acute treatment period. Subjects were randomized to treatment (eTNS 120 Hz) or control (eTNS 2 Hz) parameters.

Results: At entry, subjects were highly drug-resistant, averaging 8.7 seizures per month (treatment group) and 4.8 seizures per month (active controls). On average, subjects failed 3.35 antiepileptic drugs prior to enrollment, with an average duration of epilepsy of 21.5 years (treatment group) and 23.7 years (active control group), respectively. eTNS was well-tolerated. Side effects included anxiety (4%), headache (4%), and skin irritation (14%). The responder rate, defined as >50% reduction in seizure frequency, was 30.2% for the treatment group vs 21.1% for the active control group for the 18-week treatment period (not significant, $p = 0.31$, generalized estimating equation [GEE] model). The treatment group experienced a significant within-group improvement in responder rate over the 18-week treatment period (from 17.8% at 6 weeks to 40.5% at 18 weeks, $p = 0.01$, GEE). Subjects in the treatment group were more likely to respond than patients randomized to control (odds ratio 1.73, confidence interval 0.59–0.51). eTNS was associated with reductions in seizure frequency as measured by the response ratio ($p = 0.04$, analysis of variance [ANOVA]), and improvements in mood on the Beck Depression Inventory ($p = 0.02$, ANOVA).

Conclusions: This study provides preliminary evidence that eTNS is safe and may be effective in subjects with DRE. Side effects were primarily limited to anxiety, headache, and skin irritation. These results will serve as a basis to inform and power a larger multicenter phase III clinical trial.

Classification of evidence: This phase II study provides Class II evidence that trigeminal nerve stimulation may be safe and effective in reducing seizures in people with DRE. ***Neurology***® **2013;80:786–791**

GLOSSARY

AED = antiepileptic drug; **ANOVA** = analysis of variance; **BDI** = Beck Depression Inventory; **DRE** = drug-resistant epilepsy; **eTNS** = external trigeminal nerve stimulation; **GEE** = generalized estimating equation; **GTC** = generalized tonic-clonic seizure; **HR** = heart rate; **IRB** = institutional review board; **OR** = odds ratio; **TNS** = trigeminal nerve stimulation; **VNS** = vagus nerve stimulation.

Drug-resistant epilepsy (DRE) affects 30% of all people with epilepsy, and may lead to disability and death.[1–4] Trigeminal nerve stimulation (TNS) is a novel investigational neuromodulation therapy for patients with DRE.[5] TNS can be delivered noninvasively, bilaterally, and at high frequencies, with positive effects on mood.[5–7] The anatomy and biology of the trigeminal nerve support potential mechanisms by which TNS may impact epilepsy and mood disorders, and animal data demonstrate that stimulation of the trigeminal nerve and its related structures

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From the Departments of Neurology (C.M.D., J.S., D.M., S.G.), Psychiatry and Biobehavioral Sciences (I.A.C.), and Biomathematics-SPCC (D.M., J.G.), David Geffen School of Medicine at UCLA; Department of Neurology (S.O., G.C.-L., C.N.H.), Keck-USC School of Medicine; and NeuroSigma, Inc. (C.P.K.), Los Angeles, CA.

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inhibits seizures.[8–17] In a rat pentylenetetrazole model, TNS resulted in reductions in the number of seizures (range −36% to 58%) depending on stimulus intensity.[11,12] The magnitude of the seizure-reduction effect increased as the amplitude and frequency of stimulation increased, and bilateral stimulation was more effective than unilateral stimulation.[11,12] Further, studies of local field potentials in rat primary sensory cortex indicate that TNS causes direct inhibition of pyramidal neurons.[12] Taken as a whole, these data provide a basis to explore TNS for drug-resistant localization-related epilepsy.[11,12]

In 2009, an acute and long-term pilot feasibility study of external TNS (eTNS) for epilepsy was reported.[5] Based on the results from this study, a randomized double-blind active control study of eTNS was performed to test the hypothesis that eTNS is safe and effective in subjects with DRE, and to plan and inform a phase III randomized controlled trial.

METHODS

This study employed a double-blind randomized parallel-group design to compare treatment with eTNS vs active control eTNS as adjunctive therapy. This study was designed to provide Class II evidence for eTNS in drug-resistant partial seizures. The primary outcomes were change in seizure frequency, responder rate, and time to the fourth seizure.

Institutional review board (IRB) approval was obtained at 2 clinical sites: Olive-View/UCLA Medical Center and Keck-USC Medical Center. Fifty subjects with drug-resistant partial-onset seizures were enrolled. Inclusion criteria were age 18–70 years; intractable drug-resistant partial seizures, with 2 or more complex partial or generalized tonic-clonic seizures (GTC) per month for the last 2 consecutive months; adequate trials of at least 2 antiepileptic drugs (AEDs) prior to enrollment; concurrent use of at least 1 AED; and no changes to AED dose for at least 30 days before study enrollment. Exclusion criteria included history of nonepileptic seizures; other serious or progressive medical or psychiatric illnesses; history of facial pain or trigeminal neuralgia; concurrent vagus nerve stimulation (VNS, or neurostimulation); and pregnancy. EEG and MRI were required to support the clinical diagnosis of partial-onset complex partial and GTC seizures. Subjects who met these entry criteria underwent informed consent and were enrolled in the study. After obtaining signed informed consent on an IRB-approved consent form, subjects were instructed on how to classify and tabulate seizures in a seizure diary. Vital signs, a history and physical examination, and Beck Depression Inventory (BDI) score were obtained. Subjects then entered a 6-week baseline period, from which the baseline seizure frequency was calculated.

Trigeminal nerve stimulation. An external pulse generator was utilized to deliver eTNS at treatment (high intensity) or active control (low intensity) parameter settings. Treatment device settings were frequency = 120 Hz and pulse duration <250 μs. Active control settings were frequency 2 Hz, duty cycle 2 seconds on and 90 seconds off, and pulse duration 50 μs. Settings for the treatment group were based upon those observed to be efficacious in the earlier, open-label pilot study and informed by data derived from animal experiments, where frequencies >100 Hz were efficacious in a pentylenetetrazole model of epilepsy. Active control parameters were informed by settings used in trials of VNS for DRE, which used an active-control design and a frequency of 1 Hz, with the restriction that our pulse generator had a maximum off time of 90 seconds.[18] A novel bipolar transcutaneous gel-based electrode was also utilized, specifically designed to contact the right and left branches of the ophthalmic and supratrochlear nerves to provide bilateral stimulation. Subjects were trained to use the device by an unblinded individual who managed device programming. Instruction included education on correct electrode placement, and a review of the precautions and warnings included in the informed consent process. After completing the 6-week baseline, subjects initiated eTNS and applied the device for a minimum of 12 hours per day. Subjects were evaluated at 6, 12, and 18 weeks. At each visit, vital signs were obtained, any side effects or adverse events assessed, and focused physical and neurologic examinations performed.

Randomization and blinding. This study used a double-blind, controlled design, with randomization performed by the UCLA Biomathematical Consulting Center, using blocks of 4 subjects across the 2 sites. Unblinded study coordinators were instructed to contact a central coordinator to obtain the randomization status for each subject. Study physicians were blinded to the randomization status. A series of precautions were implemented to ensure the integrity of the blinding process: 1) device programming was performed by an unblinded coordinator in a private room, away from the study physicians and staff; 2) during the double-blind study period, subjects received stimulation at only one set of parameters (treatment or control) so that all subjects had an experience of being stimulated without being able to determine which set of parameters were being used (no comparison for reference); 3) subjects were told that the sensory experience may vary from person to person, and that prior subjects have used words like "tingling," "vibration," "buzzing," and "tickling" to describe their experiences; 4) throughout the study all subjects were instructed to describe the stimulation sensation only to the unblinded coordinator and never to the blinded study physicians or staff; and 5) assessments of seizure control and of side effects were performed by blinded physicians and staff. Each device was covered with an opaque adhesive label, so that patients or physicians could not view the device settings. The integrity of this label was confirmed at each follow-up visit.

Data collection and statistical methods. Patients were instructed on how to classify seizures and how to maintain a seizure calendar at study entry. Seizure frequency was calculated based on the total number of verifiable complex partial or tonic-clonic seizures with alteration of consciousness since the last visit, and then expressed as the total number of complex partial or generalized tonic/tonic-clonic seizures per day for each 6-week baseline or treatment period. Only seizures with alteration or loss of awareness (complex partial or GTC seizures, localization-related epilepsy) were included for measurements of seizure frequency. Data on mood were collected at baseline and the visits at weeks 6, 12, and 18, using the BDI.

In planning this trial, 3 primary outcomes were explored: change in seizure frequency, responder rate, and time to the fourth seizure. An a priori sample size calculation for percentage change in seizure frequency was performed based on the mean/median change in seizure frequency from the pilot feasibility study of TNS in epilepsy.[5] In the preliminary data from that

Table 1 Summary of baseline data for the treatment and active control groups

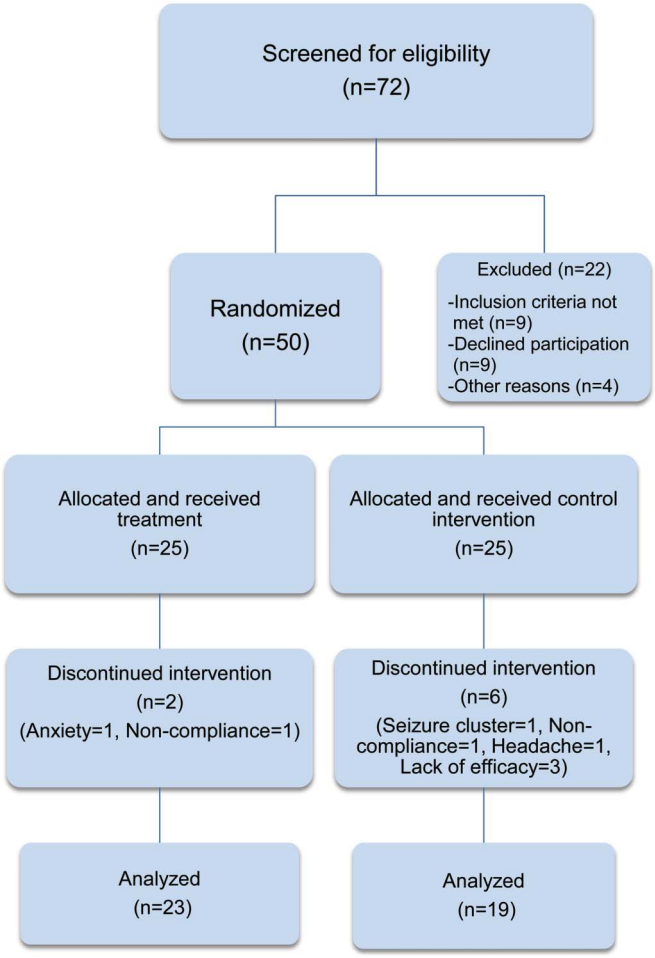
	Treatment	Active control
No.	25	25
Age, y, mean (range)	33.1 (20–58)	34.2 (19–52)
M/F	9/16	14/11
Seizure frequency, median (SD)	8.7 (56.2)	4.8 (20.8)
Duration of epilepsy, y (SD)	21.5 (9.7)	23.7 (12.1)
Beck Depression Inventory, mean (SD)[a]	16.7 (9.6)	12.0 (10)
UCLA, %	56	52
USC, %	44	48

[a] Differences were not significant, $p = 0.07$, Wilcoxon rank sum test.

study, the median percent reduction from baseline was 45% (SD 37%). A conservative estimate of mean/median percent reduction in the control group was 15% with a smaller SD.[18] Based on these estimates, a sample size of 25 per group was projected to provide 80% power for significance. Due to the 3 primary outcomes, a Bonferroni correction was utilized, with a significance level of $p = 0.0167$ ($p = 0.05/3$).

Baseline measures were compared between groups using the Wilcoxon rank sum test for continuous variables or the χ^2 test for categorical variables. Responder rates were calculated at each visit and across the entire 18-week treatment period. A responder was defined as someone exhibiting a 50% or greater reduction in seizures from baseline. Responder rates were compared within group and between groups using the generalized estimating equation (GEE) logistic model. To normalize outcome, the response ratio statistic was utilized. The response ratio is defined as $[T - B] \div [T + B] \times 100\%$, where T is the seizure frequency with treatment and B is the baseline, pretreatment seizure frequency. The response ratio was compared within group and between groups using repeated-measures analysis of variance (ANOVA). Median seizure rate change from baseline was assessed in each group using the Wilcoxon signed rank test and compared between groups using the Wilcoxon rank sum test for data that do not follow a Gaussian distribution. Missing data were imputed using last observation carried forward method for intent-to-treat analyses. All analyses were performed using SAS (version 9.2, SAS Institute Inc., Cary, NC).

Figure 1 Consort flow diagram



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Standard protocol approvals, registrations, and patient consents. The study was registered with clinicaltrials.gov, identifier NCT01159431. The study protocols and consents were approved by the Olive-View/UCLA IRB and the Keck-USC IRB.

RESULTS Fifty subjects with drug-resistant partial-onset epilepsy (complex partial and GTC seizures) were enrolled at the 2 sites (table 1). Twenty-five subjects were randomized to each of the 2 intervention groups. Forty-nine subjects completed at least one treatment visit. Of the 25 subjects randomized to treatment, 2/25 (8%) dropped out, and 6/25 (24%) dropped out in the active control group during the 18-week treatment period. Overall, a total of 42 subjects completed the study (figure 1).

Subjects were highly drug-resistant, having failed 3.35 AEDs prior to enrollment, with an average duration of epilepsy of 22.6 years. Table 1 summarizes the characteristics of the 2 treatment groups. Table e-1 on the *Neurology*® Web site at www.neurology.org summarizes individual subject data for age, seizure frequency, etiology, localization, use of video-EEG, lateralization, and current and prior AEDs.

TNS was well tolerated. When present, treatment-related adverse events were mild. Anxiety (4%), headache (4%), and skin irritation (14%) were the most common side effects. No serious device-related adverse events or deaths occurred at any time during the 18-week acute trial period. Overall, there was no significant effect of eTNS on heart rate (HR) or systolic or diastolic blood pressure within or between groups over the entire treatment period (not significant, repeated-measures ANOVA). At 6 weeks, there was a significant increase in HR in the treatment group, but the increase in HR was not significant across the entire treatment period (week 6 mean difference in HR 5.09 bpm SE 2.17, $p = 0.02$, repeated-measures ANOVA).

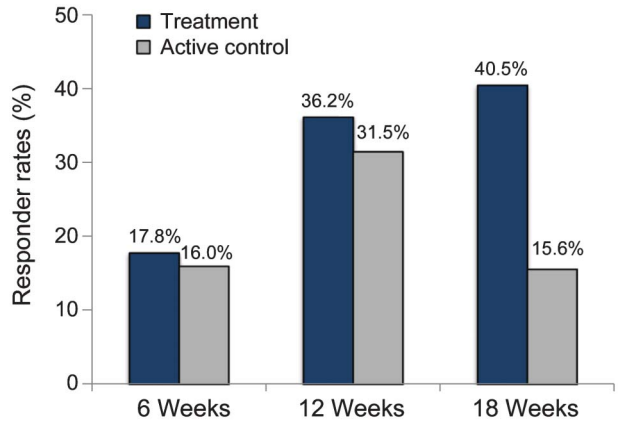
Efficacy is summarized in table 2. For the entire treatment period, the median change in seizures was −1.4 (−16.1%) for the control group, and −0.5 (−10.5%)

Table 2 Summary of the primary and secondary outcomes for the treatment and active control groups

	Treatment	Active controls	Significance
Primary outcomes			
Median reduction in seizures, seizures per month (%)	−1.4 (−16.1)	−0.5 (10.5)	Within group, $p = 0.10$; between groups, $p = 0.51$
50% Responder rate at 18 weeks for treatment group, %	40.5	15.6	Within group, $p = 0.0136$; between groups, $p = 0.078$
50% Responder rate, entire treatment period, %	30.2	21.1	Between groups, $p = 0.31$; odds ratio of responding to active treatment 1.73, confidence interval 0.59–5.1
Time to the fourth seizure, d, median (SD)			
Baseline	12.5 (18)	23 (19)	Wilcoxon signed rank, $p = 0.75$
Treatment	15.0 (28)	18 (31)	
Secondary outcomes			
Seizure frequency, response ratio (SE)	−13.9 (6.7)	−9.0 (6.8)	Within group, $p < 0.04$; between groups, p = NS, analysis of variance
Beck Depression Inventory (SD)	−8.13 (1.35)	−3.95 (1.22)	Within and between groups, $p < 0.02$, odds ratio of remission 5.5, $p = 0.002$

for the active control group (not significant, repeated-measures ANOVA). For the active treatment group, the median monthly seizure frequency was significant at 12 weeks, −2.2 seizures/month (−25.3%) for the treatment group, +0.1 seizure/month (+1.2%) for active controls ($p = 0.01$ within group, $p = 0.06$ between groups). Due to variability in seizure frequency in both groups, the response ratio was utilized. For the entire treatment period, the mean response ratio for the treatment group was reduced −13.9 SE 6.7 vs −9.0 SE 6.8 for the control group ($p = 0.04$ within group, $p = 0.06$ between groups, ANOVA).

Figure 2 Responder rates by visit across the 18-week treatment period



Fifty-percent responder rates at 6, 12, and 18 weeks during the double-blind acute treatment period. Darker columns are the responder rates for the treatment group, lighter columns are the responder rates for the active control group. The responder rate for the treatment group increased at 18 weeks (from 17.8% at 6 weeks to 40.5% at 18 weeks, $p = 0.0136$, general estimating equation [GEE] logistic model). The between-groups responder rate at the end of the 18-week treatment period approached but did not achieve significance (40.5% for the treatment group vs 15.6% for the active control group, $p = 0.078$, GEE).

The responder rate (defined as a ≥50% reduction in seizures) for the entire treatment period was 30.2% for the active treatment group, vs 21.1% for the control group ($p = 0.31$, GEE logistical model). Subjects were more likely to respond to active treatment than control (odds ratio [OR] 1.73, confidence interval 0.59–5.1). The responder rate increased over the 18-week treatment period for the active treatment group. The responder rate for the active treatment group was 17.8% at 6 weeks, 36.2% at 12 weeks, and 40.5% at 18 weeks ($p = 0.01$, GEE logistic model). For the control group, the responder rate was 16% at 6 weeks, 31.5% at 12 weeks, and 15.6% at 18 weeks (figure 2).

Time to the fourth seizure was the third primary outcome explored in this study. For the treatment group, the median time to the fourth seizure increased from 12.5 days SD 18 during the baseline period, to 15 days SD 28 during the treatment period (net increase 2.5 days or 20%). For the active control group, the time to the fourth seizure decreased from 23 days SD 19 to 18 days SD 31 (net decrease 5 days or 21.7%). These differences were not significant (Wilcoxon rank sum, $p = 0.73$) (table 2).

Mood was evaluated at baseline and at 6, 12, and 18 weeks during the acute treatment period using the BDI. At study entry, the mean BDI for the active group at baseline was 16.7 SD 9.6 vs 12.0 SD 10.0 for the control group ($p = 0.07$), where BDI <10 is considered to reflect the absence of clinically significant depressive symptoms. Mood scores improved significantly for both groups as early as 6 weeks, but mood was significantly more improved in the treatment group compared with the control group. The overall mean change in BDI for the entire 18-week treatment period was −8.13 (1.35) for the treatment group vs −3.95 (1.22) for the control group (between-

groups comparison, ANOVA, $p = 0.02$) (figure e-1 and table 2). The OR of achieving remission in depressive symptoms relative to baseline (defined as a BDI < 10) was significant for the treatment group at each visit (OR 4.8–5.7, $p = 0.002$–0.005 at 6, 12, and 18 weeks). For the entire 18-week treatment period, the OR of remission was 5.5 in the treatment group ($p = 0.0006$). For the control subjects, the OR for achieving remission was not significant at any time point. Improvement in mood was independent of the antiepileptic response to TNS, and was not significantly correlated with improvement in seizure frequency ($r = 0.28$, Spearman correlation, $p = 0.10$ at 18 weeks).

DISCUSSION The primary findings of this study are that eTNS was well-tolerated, and was associated with a responder rate of 40.5% for the treatment group at 18 weeks ($p = 0.0136$, GEE). Though the within-group responder rate increased over the 18-week treatment period, the between-groups comparisons and other primary outcomes did not achieve significance.

Secondary measures, specifically mood (as measured by the BDI), and response ratio improved for the entire treatment period (figure e-1 and table 2). The improvement in mood was independent of changes in seizure frequency. Since depression is a major comorbidity in persons with seizure disorders, and a major component of health-related quality of life in epilepsy, the ability of eTNS to positively impact mood in this population is an important discovery.[19,20]

Though this study demonstrated within-group differences sufficient to justify a larger multicenter study, between-groups differences were difficult to demonstrate with the exception of mood. This was likely a function of the relatively small sample size (when compared with a large pivotal study), the numerically different seizure frequencies between treatment groups, the number of seizures required for inclusion (≥ 2), and the active control settings. Since the purpose of a phase II trial is to help plan and inform the design of phase III multicenter study, we will incorporate the following protocol changes in the new trial: much larger sample size ($n > 200$) and higher seizure frequency for inclusion (4 or more seizures/month). These changes will help to constrain variability, and prevent spurious responses in patients with baseline seizure frequencies. Furthermore, it will be helpful to change the active control parameters to reduce the possibility of a placebo response. The device employed in this trial allowed a maximum "off" time of only 90 seconds for the active control settings, which is significantly shorter than what had been used in VNS studies (180 minutes), and may have resulted in some of the 50% responders in the active control subjects at the 12-week visit.[18,21] We anticipate "off" times of 5–10 minutes would help reduce the possibility of a placebo or active control response.

We report the results of the first randomized active controlled trial of eTNS in drug-resistant partial seizures. eTNS was safe and well-tolerated, and resulted in within-group improvement in responder rate. Mood was also significantly improved. The results from this trial justify a phase III multicenter trial of eTNS for drug-resistant partial seizures.

AUTHOR CONTRIBUTIONS

Christopher DeGiorgio: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Jason Soss: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Ian Cook: drafting/revising the manuscript, analysis or interpretation of data. Daniela Markovic: analysis or interpretation of data, statistical analysis. Jeffrey Gornbein: analysis or interpretation of data, statistical analysis. Diana Murray: analysis or interpretation of data, acquisition of data. Sandra Oviedo: analysis or interpretation of data, acquisition of data, study supervision. Guadalupe Corrale-Leyva: analysis or interpretation of data, acquisition of data, study supervision. Colin Kealey: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Christi Heck: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

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DISCLOSURE

C.M. DeGiorgio is the inventor on patents related to TNS, has an equity interest in NeuroSigma, and is Vice President of NeuroSigma, which is not a sponsor of the study, but licensee on patents related to TNS. Dr. DeGiorgio received grant support from the Epilepsy Therapy Project, Epilepsy Foundation, and Boston Scientific for the execution of the study. J. Soss reports no disclosures. I.A. Cook is a consultant to NeuroSigma and inventor of patents licensed to NeuroSigma. D. Markovic, S. Gordon, J. Gornbein, D. Murray, S. Oviedo, G. Corralle-Leyva, and C.P. Kealey report no disclosures. C.N. Heck reports grant support from Neuropace. Go to Neurology.org for full disclosures.

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load of varicella-zoster virus (VZV) is higher in patients with MS at relapse phase than those in remission. The status of the disease course in all patients with MS should be determined before sampling.

Four out of the 15 patients with MS with relapse were on interferon (IFN)-β treatment. It has been shown that the administration of IFN-β can lead to the reduction of JCV genome[3] and may result in a false-negative due to decreasing the JCV titer and T-cell response. Thus, patients taking IFN-β should be excluded from this study.

In addition, we would not have included clinically isolated syndrome (CIS) in this study cohort. Approximately 80% of patients with CIS develop MS, while the rest do not.[4] Patients with CIS should not be considered for evaluation of JCV-specific T-cell response under corticosteroid therapy.

Author Response: Renaud A. Du Pasquier, Mathieu Canales, Myriam Schluep, Lausanne, Switzerland: We thank Mr. Zahednasab for his interest in our article. As we explained in the Methods, we enrolled only patients with MS who had a relapse severe enough to warrant 3 days of IV corticosteroids followed by tapering oral prednisone. The mean delay between the onset of symptoms and steroid treatment was 11.6 days (range 0–54 days). Concerning VZV and MS, the paper of Sotelo et al. has been challenged.[5] In addition, VZV is not JCV so it is difficult to draw any conclusions from this comparison.

Regarding IFN-β, as we mentioned: "If a patient exhibited no T-cell response against a given virus before and after CS, then this patient was not taken into account in our analyses for the given virus and the given assay." This was the case in 2 of 4 patients on IFN-β, who are not part of the JCV-specific cellular immune response part of our article and thus not included into the analysis of corticosteroids effects. Finally, in the patients with CIS, diseases other than MS were carefully ruled out. Currently, 4 of 8 of these patients with CIS have converted to definite MS, confirming that their inclusion was appropriate.

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CORRECTIONS

Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy

In the article "Randomized controlled trial of trigeminal nerve stimulation for drug-resistant epilepsy" (*Neurology*® 2013;80:786–791) by DeGiorgio et al., two corrections are needed. The first is in the abstract, where the confidence interval should read "Subjects in the treatment group were more likely to respond than patients randomized to control (odds ratio 1.73, confidence interval 0.59–5.1)." The second correction is in the level of evidence statement. Although there was improvement within the active treatment group alone, there was no significant difference in effect between the treatment and control groups. The study was insufficiently powered to exclude an important difference. Therefore, the level of evidence statement should read "Because of a lack of statistical precision, this Class II study provides insufficient evidence to determine the efficacy of trigeminal nerve stimulation in patients with DRE." The editors regret the error and the misstatement.

Write*e*Click: Do acute phase markers explain body temperature and brain temperature after ischemic stroke?

In the Write*e*Click Author Response "Do acute phase markers explain body temperature and brain temperature after ischemic stroke?" by J.M. Wardlaw et al. (*Neurology*® 2013;80:778), there is an error in one of the author affiliations. It should read Bartosz Karaszewski, Gdansk. The authors regret the error.

Author disclosures are available upon request (journal@neurology.org).