Original article

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Outcome of vagus nerve stimulation for drug-resistant epilepsy: the first three years of a prospective Japanese registry

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ABSTRACT – *Aims.* Vagus nerve stimulation (VNS) is an established option of adjunctive treatment for patients with drug-resistant epilepsy, however, evidence for long-term efficacy is still limited. Studies on clinical outcomes of VNS in Asia are also limited. We report the overall outcome of a national, prospective registry that included all patients implanted in Japan.
Methods. The registry included patients of all ages with all seizure types who underwent VNS implantation for drug-resistant epilepsy in the first three years after approval of VNS in 2010. The registry excluded patients who were expected to benefit from resective surgery. Efficacy analysis was assessed based on the change in frequency of all seizure types and the rate of responders. Changes in cognitive, behavioural and social status, quality of life (QOL), antiepileptic drug (AED) use, and overall AED burden were analysed as other efficacy indices.

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Results. A total of 385 patients were initially registered. Efficacy analyses included data from 362 patients. Age range at the time of VNS implantation was 12 months to 72 years; 21.5% of patients were under 12 years of age and 49.7% had prior epilepsy surgery. Follow-up rate was >90%, even at 36 months. Seizure control improved over time with median seizure reduction of 25.0%, 40.9%, 53.3%, 60.0%, and 66.2%, and responder rates of 38.9%, 46.8%, 55.8%, 57.7%, and 58.8% at three, six, 12, 24, and 36 months of VNS therapy, respectively. There were no substantial changes in other indices throughout the three years of the study, except for self/family-accessed QOL which improved over time. No new safety issues were identified.
Conclusions. Although this was not a controlled comparative study, this prospective national registry of Japanese patients with drug-resistant epilepsy, with >90% follow-up rate, indicates long-term efficacy of VNS therapy which increased over time, over a period of up to three years. The limits of such trials, in terms of AED modifications and during follow-up and difficulties in seizure counting are also discussed.

Key words: epilepsy, epilepsy surgery, vagus nerve stimulation, outcome, drug-resistant epilepsy

Vagus nerve stimulation (VNS) therapy (VNS Therapy®; LivaNova) is an approved adjunctive therapy for drug-resistant epilepsy (DRE). Efficacy has been verified by several randomized controlled trials (RCTs) (Ben-Menachem *et al*., 1994; The Vagus Nerve Stimulation Study Group, 1995; Handforth *et al*., 1998; DeGiorgio *et al*., 2005; Klinkenberg *et al*., 2012; Ryvlin *et al*., 2014), prospective observational studies (Amar *et al*., 1999; DeGiorgio *et al*., 2000; Vonck *et al*., 2004; Garcia-Navarrete *et al*., 2013), registry studies (Labar, 2002; Renfroe and Wheless, 2002; Amar *et al*., 2004; Labar, 2004; Englot *et al*., 2012; Patel *et al*., 2013), and numerous retrospective cohort studies (Ben-Menachem *et al*., 1999; Frost *et al*., 2001; Helmers *et al*., 2001; Scherrmann *et al*., 2001; Kawai *et al*., 2002; Murphy *et al*., 2003; Uthman *et al*., 2004; Alexopoulos *et al*., 2006; Benifla *et al*., 2006; De Herdt *et al*., 2007; You *et al*., 2007; Elliott *et al*., 2011a, 2011b, 2011c; Wheeler *et al*., 2011; Cukiert *et al*., 2013; Menascu *et al*., 2013; Arya *et al*., 2014; Orosz *et al*., 2014; Yu *et al*., 2014; Camp *et al*., 2015). However, the study duration of the RCTs was six months or less except in one study. The number of large-scale cohort studies with >100 patients and with >one year treatment is also limited. Considering the ethical difficulty in conducting a RCT on long-term efficacy of VNS therapy, a large registry study with a high level of enrolment and follow-up rates is worthwhile. Studies on clinical outcomes of VNS therapy in Asia are also extremely limited.

VNS therapy was approved in Japan as an adjunctive treatment for reduction of seizure frequency in patients with DRE in 2010. As part of the terms and conditions for approval in Japan, the health authorities required all patients, or a minimum of 300 patients, who underwent implantation of VNS from approval in 2010 to the end of 2012 to be registered in a patient registry in which treatment indication, the qualifications of surgeons and physicians, and patient follow-up was strictly controlled. Here, we report on three-year outcomes from this nationwide up-to-date registry of patients receiving VNS therapy for DRE. The use of this registry represents an ideal opportunity to evaluate the long-term efficacy of VNS therapy for patients with DRE.

Materials and methods

Registry design

This post-marketing surveillance registry that included all patients implanted in Japan was designed as a multicentre, open-label, long-term, and prospective observational study of the clinical efficacy and safety of VNS Therapy® for adult and paediatric patients with DRE in Japan. The registry included 52 sites in Japan, representing academic, national, municipal, and private hospitals. Patients included in this report underwent VNS device implantation surgery between July 2010 and December 2012. The study was registered in the University Hospital Medical Information Network (UMIN) Clinical Trials Registry in Japan (UMIN ID: UMIN000014728).

Importantly, only patients who met the approved indication for VNS therapy were allowed to undergo the treatment and be included in the registry. VNS Therapy® is approved in Japan as an adjunctive treatment for patients with DRE, with the exception of those for whom satisfactory outcome is expected after resective epilepsy surgery. There were no limitations regarding patients' age and type of seizure. Only epilepsy specialists were allowed to use VNS therapy

in compliance with its indication for use, after they obtained sufficient understanding of its efficacy, safety, and procedures. The treating physician was required to be an epilepsy specialist qualified by the Japan Epilepsy Society and the implanting surgeon an active epilepsy surgeon qualified by the Japan Epilepsy Society and Japan Neurosurgical Society.

While the registry did not document pre-operative evaluation, leaving the selection of examinations to each hospital, imaging studies (including MRI) and electrophysiological studies (including long-term video-EEG) were used in principal to exclude patients for whom satisfactory outcome was expected after resective epilepsy surgery.

The registry and following analytical studies were approved by the ethics committee at each centre and hospital, and were conducted in accordance with internationally recognized ethical standards and local requirements. The centres and hospitals that participated in the study are listed at the end of this report. Patients or their guardians provided written informed consent prior to collection of patient data, as directed by the local ethics committee.

Study treatment

VNS device implantation was performed under general anaesthesia by qualified epilepsy surgeons following a standardized procedure (Kawai, 2008). The devices used were VNS-G103 (Demipulse Model 103) or VNS-G105 (Aspire HC Model 105) as a generator, and VNS-L302S (Model 302-20), VNS-L302L (Model 302-30), VNS-L303S (Model 303-20), or VNS-L304S (Model 304-20) as a lead (LivaNova PLC, Houston, TX; Nihon Kohden Co. Ltd. as the Japanese distributor). The treating physicians and the epilepsy specialists who were trained and qualified to prescribe VNS therapy adjusted medications and VNS parameters, as clinically indicated.

Study data

Data were recorded using study-specific Case Report Forms (CRFs). Data collected prior to VNS implantation included patient age at seizure onset, the type and frequency of seizures, classification and aetiology of epilepsy, MRI findings, EEG findings, electrocardiogram findings, cognitive/developmental status, behavioural/psychiatric status, social status (employment or schooling), self-assessed and/or family-assessed quality of life (QOL), and treatment history, including antiepileptic drugs (AEDs) and prior epilepsy surgeries. The frequency of seizures was determined based on the mean number of seizures during the three months prior to implantation. Data collected at implantation, the start of stimulation, and after three, six, 12, 24, and 36 months of treatment included frequency of each type of seizure, cognitive/developmental status, behavioural/psychiatric status and social status, self-assessed and/or family-assessed QOL, types of AEDs and their dose, presence or absence of adverse effects, mechanical failure, and VNS stimulation parameters.

The types of seizure in the CRF were listed according to the 2010 ILAE proposal (Berg *et al*., 2010). Since it is often difficult to differentiate between primary and secondary generalized tonic-clonic seizures, these were categorized together as tonic-clonic seizure under unknown classification. The frequency of seizures was reported as the number of seizures occurring daily, weekly, monthly, or yearly. Daily to monthly seizures were recorded as the mean for the previous three months. Yearly seizures were recorded for the previous year.

Epilepsy in the CRF was classified according to the 1989 ILAE proposal (Epilepsy, 1989), and re-categorized using aetiology information in the 2010 ILAE proposal (Berg *et al*., 2010). Cognitive/developmental status was divided into six categories using pre-treatment intelligence quotient (IQ) and developmental quotient (DQ). The study protocol did not require specific tests for evaluation of IQ and DQ. Behavioural/psychiatric status was evaluated as the presence or absence of any disorders including attention-deficit hyperactivity disorder, autism, depression, hallucinatory-paranoid state, aggression, or others. Social status (employment or schooling) was divided into three categories: as full employment or schooling, employment or schooling with social support, and incapable of employment or schooling. Change in QOL was assessed by comparing with the pre-implantation QOL and expressed in four categories (much improved, improved, unchanged, or deteriorated). Treatment history included duration and number of AEDs used, presence or absence of surgical treatment, and other treatment modalities including ketogenic diet, adrenocorticotropic hormone therapy (ACTH), and treatment with immunoglobulin, liposteroid therapy, or vitamin B6. The type of epilepsy surgery was recorded when performed. Information on VNS stimulation parameters at each time point included output current (mA), pulse width (msec), frequency (Hz), ON time (sec), and OFF time (min). Total charge delivered per day was calculated according to the formula by Orosz *et al*. (2014).

Study objectives and endpoints

The primary objective of efficacy analysis was to assess the change in frequency of all seizure types and the rate of responders. The change in seizure frequency was expressed as the percent of change from the baseline frequency. Seizure reduction was expressed as an

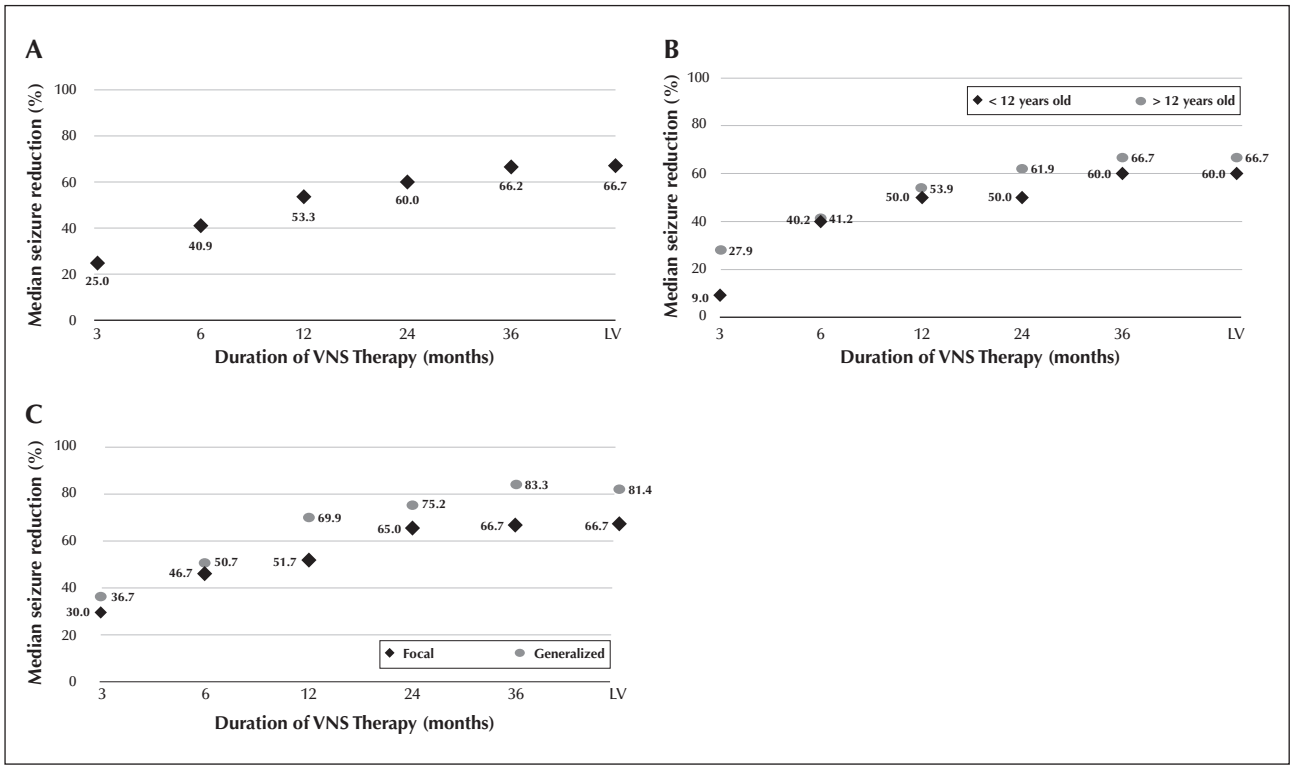

Figure 1. Changes in median seizure frequency from baseline in all patients (A), in patients younger than 12 years or 12 years or older (B), and in patients with focal or generalized seizures (C). Median seizure frequency gradually decreased over time with more than 50% decrease at 12 months and later. For mean and standard deviation of seizure frequency relative to baseline, see *table S1*. For patients younger than 12 years (but older than three months), the decrease in seizure frequency relative to the baseline was statistically significant throughout the study period ($p<0.001$). LV: last visit.

absolute value of change in seizure frequency. Efficacy values were calculated at three months, six months, 12 months, 24 months, and 36 months. The values at the last visit refer to all last visits; for a small number of patients, the last visit occurred before 36 months.

The predominant seizure type was not documented during baseline evaluation. Using the total number of seizures instead of the number of predominant seizures as an index for seizure control may carry a risk of overestimating efficacy, particularly when a less disabling seizure type is the predominant seizure type for a given patient. To deal with this issue, we evaluated the frequency of seizures excluding simple partial seizures.

We classified the response to VNS therapy according to seizure reduction as: seizure free, >90% reduction, 50-90% reduction, <50% reduction, and no change, since this classification can be re-categorized as either the modified Engel's classification or McHugh classification (McHugh *et al*., 2007). Other indices for efficacy analysis were changes in cognitive/developmental status, behavioural/psychiatric status, social status, self/family-assessed QOL, AED use, and overall AED burden. AED burden was defined as the total value of dosage rate to standard dose for all AEDs used, as follows (Elliott *et al*., 2011b):

$$\text{Overall AED burden} = \sum \text{Dosage}_a \ / \text{Standard dosage}_a$$

The standard dose was established by the World Health Organization as the "assumed average maintenance dose per day for a drug used for its main indication in adults" (WHOCfDS, 2013). Since the standard dose for each age in children is not available, we evaluated AED burden only in patients older than 18 years.

Statistical analysis

The change in seizure frequency is expressed as the percent of change from baseline frequency, and presented as mean, standard deviation, median, and range (*supplementary table S1, S2*). The decrease in seizure frequency, expressed as median, is presented in *figure 1*.

Results

Patient population

The registry included 385 patients, all of whom were included in the safety analysis population. However, 23 of these patients were excluded from the efficacy analysis: 15 patients underwent the VNS implantation surgery in order to exchange the existing implanted generator that was implanted during either another trial or in a foreign country; five patients started receiving VNS therapy but dropped out before completing three months of follow-up; implantation surgery was aborted in two patients during the procedure as the patients experienced arrhythmia during the lead test; and one patient underwent VNS device implantation but the stimulation was not started as the patient did not experience any seizures after registration. The remaining 362 patients had at least one post-implant evaluation after three months and were included in the efficacy analysis population (*supplementary figure S1*).

Demographic features and baseline characteristics of the 362 patients included in the efficacy analyses are presented in *table 1*. Males made up 59.4% of the patients enrolled. The median age at VNS implantation was 23 years (range: 1 to 73 years); 215 patients were (59.4%) ≥19 years , 69 patients (19.1%) were between 12 and 19 years, and 78 patients (21.5%) were <12 years. All patients had a diagnosis of DRE with a median seizure frequency of 10.3 per week. The median duration of epilepsy prior to VNS implantation was 13 years. The patients had received a median of five AEDs (range: 1-17; mean: 5.7; standard deviation: 3.2) prior to implantation. In addition, 180 (49.7%) had prior cranial surgery for epilepsy and the average number of AEDs at registration was 3.4; underscoring the severity of their disease.

Changes in seizure frequency and responder rate

The median decrease in seizures after three, six, 12, 24, 36 months of VNS therapy, and at the last visit were 25.0%, 41.0%, 53.3%, 60.0%, 66.2%, and 66.7%, respectively (*figure 1A, supplementary table S1*).

The median decrease in all seizures after three, six, 12, 24, 36 months of VNS therapy, and at the last visit was 9.0%, 40.2%, 50.0%, 50.0%, 60.0%, and 60.0% in the patients younger than 12 years old at implantation (*figure 1B*), respectively. The median decrease in focal seizures after three, six, 12, 24, 36 months, and at the last visit was 30.0%, 46.7%, 51.7%, 65.0%, 66.7%, and 66.7%, respectively. The median decrease in generalized seizures was 36.7%, 50.7%, 69.9%, 75.2%, 83.3%, and 81.4%, respectively (*figure 1C*).

Table 1. Demographic and clinical data (*n*=362).

Variable	Number (%) or descriptive statistics
Sex	
Female	147 (40.6%)
Male	215 (59.4%)
Age at seizure onset (years)	
Mean±SD	9.1±11.6
Median (Min-Max)	5 (0-64)
Duration of epilepsy prior to VNS (years)	
Mean±SD	15.6±11.1
Median (Min-Max)	13.0 (0-61)
Age at VNS implantation (years)	
≥19	215 (59.4%)
12 to <19	69 (19.1%)
<12	78 (21.5%)
Mean±SD	24.8±14.7
Median (Min-Max)	23.0 (1.0-73.0)
Median seizure frequency (per week)	
Mean±SD	106.0±762.7
Median (Min-Max)	10.3 (0.0-14000.0)
Number of AEDs at registration	
Mean±SD	3.4±1.1
Median (Min-Max)	3 (0-7)
Number of AEDs prior to VNS implantation	
Mean±SD	5.7±3.2
Median (Min-Max)	5 (1-17)
Duration of AED treatment (years)	
Mean±SD	14.7±10.6
Median (Min-Max)	12 (1-48)
Prior cranial surgery	180 (49.7%)
Resection	97 (26.8%)
Corpus callosotomy	82 (22.7%)
Type of seizure	
Focal	
Simple partial seizures	88 (24.3%)
Complex partial seizures	182 (50.3%)
Generalized	
Tonic-clonic seizures	170 (47.0%)
Absence seizures	19 (5.2%)
Tonic seizures	65 (18.0%)
Myoclonic seizures	27 (7.5%)
Atonic seizures	34 (9.4%)
Spasms	41 (11.3%)

Table 1. (*Continued*) Demographic and clinical data (*n*=362).

Variable	Number (%) or descriptive statistics
Classification of epilepsy	
Structural-metabolic	238 (65.7%)
Unknown	103 (28.7%)
Genetic	20 (5.5%)

VNS: vagus nerve stimulation; AED: antiepileptic drug; SD: standard deviation.

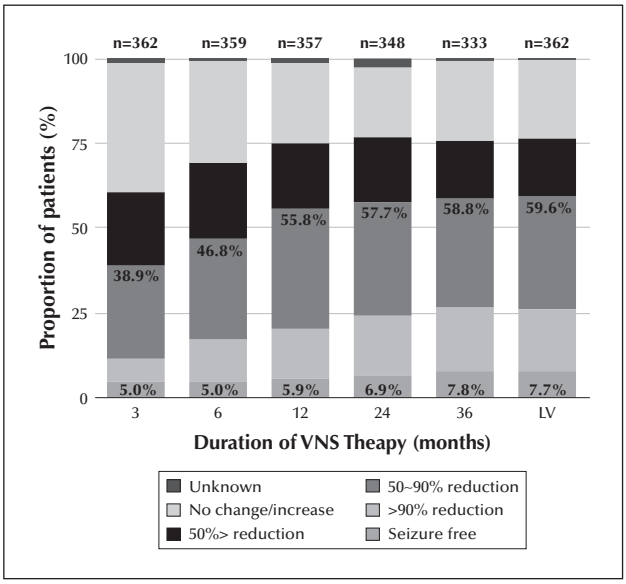

Figure 2. The proportion of patients with different seizure frequencies according to duration of VNS therapy. The upper and lower percentages of each bar represent patients who achieved >50% seizure reduction from baseline and seizure freedom, respectively. LV: last visit.

The proportion of responders also increased over time (*figure 2*). Seizure-free rates at 12, 24, and 36 months were 5.9%, 6.9%, and 7.8%, respectively, and the rate of >50% reduction in seizure frequency was 55.8%, 57.7%, and 58.8%, respectively. When simple partial seizures were excluded, the reduction in seizure frequency was the same or greater than that for all types of seizures (*supplementary table S2*).

When a change in seizure frequency and the responder rate were compared between patients with and without prior craniotomy, there were no significant differences throughout the study period, although there was a tendency for increased efficacy in patients without prior craniotomy (*supplementary table S3*). The comparison was made between corpus callosotomy and resection as prior craniotomy; there was no difference throughout the study period.

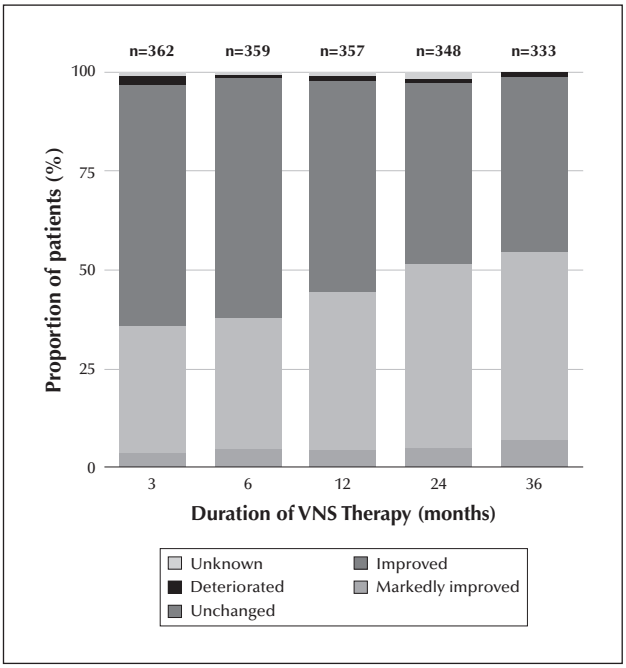

Figure 3. The proportion of patients with different QOL changes from baseline according to duration of VNS therapy. Change in QOL was assessed by comparing with QOL at pre-implantation and expressed in four categories (much improved, improved, unchanged, or deteriorated).

Changes in cognitive/developmental, behavioural, and social status, and self-assessed and/or family-assessed QOL

There were no substantial changes in cognitive disability (developmental/intellectual disability), behavioural/mental disorders, or social status throughout the three years of VNS therapy (*data not shown*). Self/family-assessed QOLs after three, six, 12, 24, and 36 months of VNS therapy showed improvement in QOL (based on a classification of "improved" or "markedly improved") in 35.9%, 37.9%, 44.3%, 51.1%, and 54.7% of patients, respectively (*figure 3*).

Changes in AED use, overall AED burden, and VNS therapy stimulation parameters

Over the course of three years, there were no significant changes in either the number of AEDs used in all patients or the overall AED burden in adults. The median number of AEDs was three throughout the period and the median AED burden was 2.40, 2.35, 2.39,

2.51, and 2.49 at three, six, 12, 24, and 36 months of VNS therapy, respectively (*supplementary table S4*).

Regarding the changes in stimulation parameters, there was a greater proportion of patients with higher output current over time (*figure 4A*). The proportions of patients with the starting ON time (30 seconds) or starting OFF time (5 minutes) decreased over time (*figure 4B, 4C*). Signal frequency and pulse width were not changed significantly in 90.4% and 86.2% of patients, respectively, with the same values from the start being used over the three years (30 Hz for signal frequency and 500 μsec for pulse width). Consequently, the proportion of patients with higher total charge delivered per day increased markedly over time (*figure 4D*). For instance, the proportion of patients with >200 mC/day increased from 3.6% at three months to 74.5% at 36 months.

Safety

The safety population included all registered patients. Safety was monitored by assessing the incidence of all adverse events from the date of VNS implantation surgery. Overall, long-term treatment with VNS therapy was well-tolerated and did not produce any unanticipated adverse device effects (*table 2 and supplementary table S5 for detailed information*). Most adverse events were similar to those seen in previous trials of VNS therapy (Handforth *et al*., 1998; Morris and Mueller, 1999). The VNS system was removed in 13 patients among 385 patients of the safety analysis population (*supplementary figure S1*). The cause of removal was infection in six, high lead impedance in six, and the need for MRI in one.

The most commonly reported adverse events starting at implantation surgery and up to 36 months of treatment with VNS therapy were a change in voice or hoarseness (*n*=58; 15.1%) and coughing (*n*=50; 13.0%). These events occurred most frequently upon stimulation and at the start of stimulation, and less frequently during a later phase of the treatment.

No other adverse events were reported in ≥5% of the population. Fourteen subjects died during participation in the study. The cause of death included SUDEP in six patients and rectal cancer, lung cancer, primary brain tumour, pneumonia, subarachnoid haemorrhage, drowning during bathing, and suffocation due to a secondary generalized seizure each in one patient.

Discussion

We report the results of an efficacy and safety analysis of three-year treatment of VNS therapy for drug-resistant epilepsy patients using a registry of 385 patients in Japan; a first nationwide multicentre registry of VNS patients. With a significant follow-up rate of over 90% at three years, we demonstrate that the efficacy of VNS therapy increased over time, up to three years. The reduction in seizure frequency and improvement of QOL in the population were at a similar level to precedent reports with a shorter treatment timeframe (McGlone *et al*., 2008; Garcia-Navarrete *et al*., 2013; Ryvlin *et al*., 2014). Interestingly, the decrease in seizure frequency and responder rates at 12 and 24 months was very similar to that reported in the largest long-term data set from a single institute (Elliott *et al*., 2011a).

The majority of registry studies reported to date are derived from the VNS Therapy Patient Outcome Registry which is maintained by the manufacturer of the device, with a registration rate of approximately 40% (Labar, 2002; Amar *et al*., 2004; Patel *et al*., 2013). Participation by physicians was voluntary and each physician did not necessarily register all of his/her patients, causing possible bias of registered patients. The other weakness of the Patient Outcome Registry was a low follow-up rate, 15% at 24 months, in the long-term treatment group (Amar *et al*., 2004). Because of these limitations, general conclusions about the expected degree of long-term VNS treatment efficacy in all treated patients in previous studies has been limited, and comparisons were made only between subgroups within the registry. Our data based on a nationwide patient registry, with a follow-up rate of over 90% at 36 months, is in strong agreement with previous studies. The selection bias at registration and due to reporting, which was criticized in previous registry studies on VNS, was minimal in this study.

Since the Japanese government did not set up any limitation regarding patient age and type of seizure, the use of VNS was under strict control of the associated academic societies and Nihon Koden Co., Ltd. (the distributor of VNS therapy devices in Japan). To avoid over-utilization, the final decision was made by board-certified epilepsy surgeons to exclude patients for whom resective surgery was expected to be successful. Therefore, the patients registered in this study do not reflect the whole population of DRE. DRE and refractory non-curable epilepsy differ based on the fact that a subpopulation of DRE may enjoy seizure freedom after resective surgery (Tellez-Zenteno *et al*., 2010). Our results have clarified the significance of VNS therapy as an adjunctive treatment for the major subpopulation of patients with DRE who are not suitable for resective surgery and live with truly refractory epilepsy.

The rate of patients who had prior craniotomy surgery for epilepsy was 47.8% in the present study population. This rate is much higher than that of previous registry studies (Amar *et al*., 2004). Although we are unable to

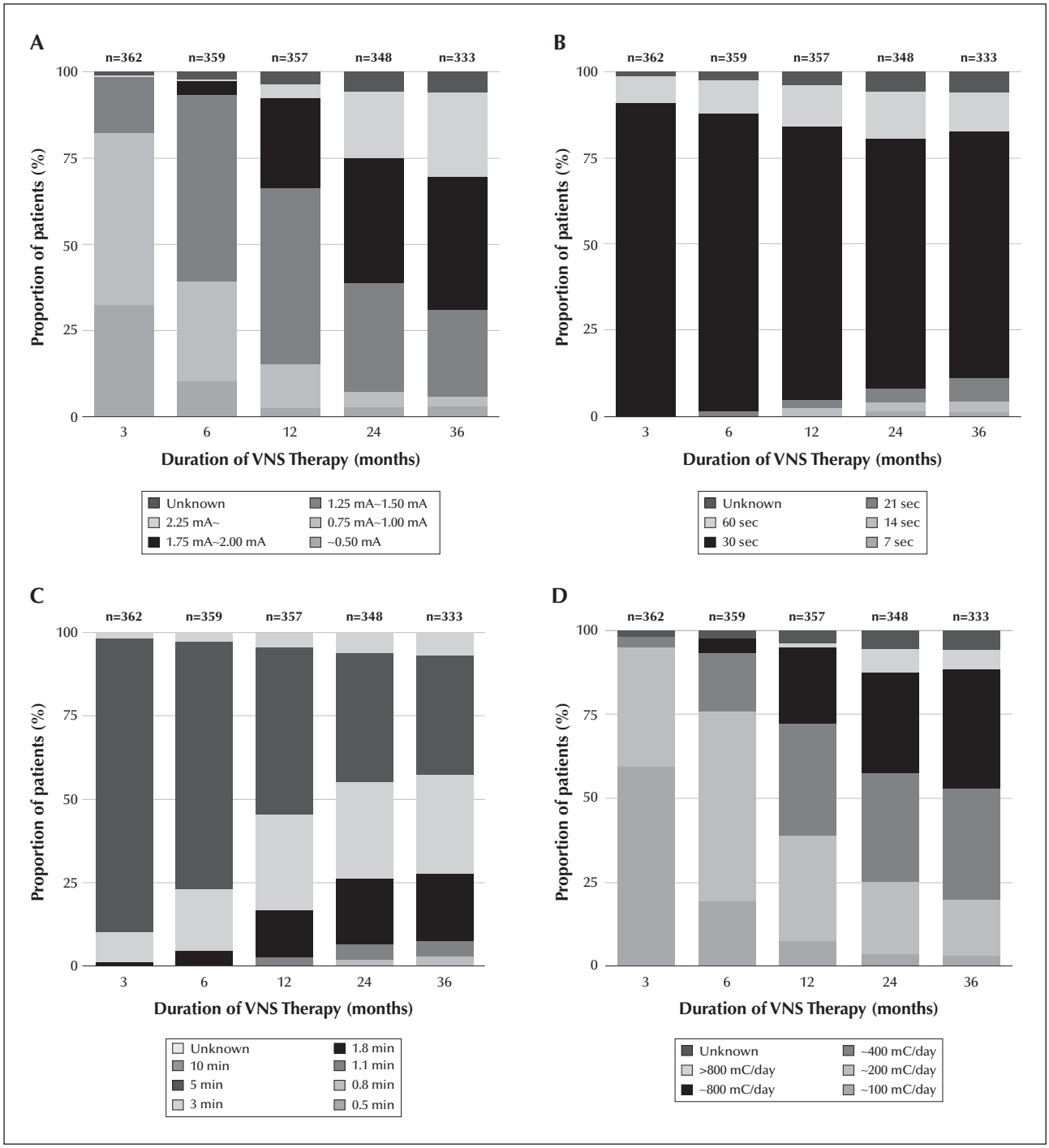

Figure 4. Changes in the proportions of patients with various ranges of output current (A), ON time (B), OFF time (C), and total charge delivered per day (D). Dosing of VNS parameters was not controlled and left to the discretion of each physician.

identify the precise reason for the high rate of patients who had previous craniotomy for epilepsy surgery, we speculate that the following unique situations in Japan may have contributed. Firstly, the government requires that candidates for VNS therapy are selected by epilepsy surgeons, who follow most of the post-surgical patients themselves. There is a possibility that epilepsy surgeons may have preferentially proposed VNS therapy to patients with residual seizures after previous craniotomy. In particular, corpus callosotomy had been the only choice for patients with severe refractory generalized epilepsy before VNS therapy

Table 2. Summary of adverse events at each evaluation.

	At implantation	At stimulation start	3 months	6 months	12 months	24 months	36 months
Laryngeal symptoms including hoarseness and coughing	36 (9.7%)	41 (11.2%)	28 (7.7%)	20 (5.6%)	9 (2.5%)	16 (4.6%)	15 (4.5%)
Local dysesthesia	4 (1.1%)	6 (1.6%)	0	4 (1.1%)	2 (0.6%)	1 (0.3%)	1 (0.3%)
Cardiac complications including asystole and bradycardia	7 (1.9%)	0	0	0	1 (0.3%)	0	0
Respiratory complications	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Local infection	0	1 (0.3%)	2 (0.6%)	0	2 (0.6%)	0	1 (0.3%)
High lead impedence	0	1 (0.3%)	1 (0.3%)	2 (0.6%)	3 (0.8%)	3 (0.8%)	10 (3.0%)
Others	2 (0.5%)	0	4 (1.1%)	2 (0.6%)	3 (0.8%)	6 (1.7%)	2 (0.6%)

was approved for use in 2010 in Japan. Since corpus callosotomy is not a curative treatment for generalized seizures other than drop attacks, VNS therapy may have been proposed preferentially for patients with residual seizures after corpus callosotomy. Secondly, VNS therapy was the first device to be implanted for epilepsy treatment in Japan and many patients expressed hesitation to have a device implanted in their body when it was first proposed. It is possible that patients with prior craniotomy demonstrated less hesitation. Nevertheless, in spite of the difference in the proportion of patients with and without prior craniotomy and in the reference pattern between the present Japanese study and the previous US registry, efficacy indices were very similar between the two populations (Amar *et al*., 2004).

In this study, dosing of AEDs and adjusting parameters during VNS therapy were not controlled and left to the discretion of each physician. Output current and the total charge per day were significantly increased over time. Although the number and burden of AEDs did not change significantly, a small decrease was observed at six and 12 months, and a small increase at 24 and 36 months (*supplementary table S3*). These trends are consistent with previous non-controlled studies (Elliott *et al*., 2011b, Orosz *et al*., 2014). In practical settings, it has been shown that both titration of AEDs and VNS may affect long-term efficacy. In our study, the increase in AED burden at 24 and 36 months was less than 3%, while the decrease in seizure frequency was 60.0% and 66.2%, respectively. We may attribute this seizure reduction more to VNS dosing and/or time on VNS therapy.

VNS therapy is strikingly under-utilized in Asian countries, while it has become a widely accepted treatment in the United States and Europe, representing a significant portion of surgical procedures for DRE (Neligan *et al*., 2013). Only a few reports of small series with VNS have been reported from Asian countries (Kawai *et al*., 2002; Kang *et al*., 2006; You *et al*., 2007; Bao *et al*., 2011). The Asian population constitutes approximately 60% of the world, but less than 5% of VNS implantations have been performed in Asian countries (data on file at Cyberonics, Inc.). Based on the outcome of the present study, VNS has a long-term clinical benefit for the DRE population and should also be encouraged in Asian countries.

Supplementary data.

Supplementary figure and tables are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) What is the approximate percent decrease in median seizure frequency resulting from VNS therapy for drug-resistant epilepsy?

(2) What is the approximate >50% responder rate resulting from VNS therapy for drug-resistant epilepsy?

(3) What is the common adverse effect of VNS therapy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".