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30 years of vagus nerve stimulation trials in epilepsy: Do we need neuromodulation-specific trial designs?

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ABSTRACT

Neuromodulation therapies represent an important treatment arm for patients with drug-resistant epilepsy (DRE) who are not candidates for resective surgery. Vagus nerve stimulation (VNS) – the neurostimulation modality in focus in this review – was the first available neuromodulatory therapy for DRE and was followed by anterior thalamic deep brain stimulation (ANT-DBS) and responsive neurostimulation (RNS). Although no comparative trials of these treatments have been performed, published data and clinical experience suggest comparable effectiveness. In VNS, DBS and RNS seizure reduction is delayed and increases over time raising the question of anti-epileptogenic mechanisms of neuromodulation. Considering the long-term effectiveness assumed for neuromodulatory treatments and the chronic nature of drug-resistant epilepsy, study designs allowing for long-term comparative observations would be of great value, but are hindered by the inherent nature of a long-term [surgical] control group and the bias associated with open-label trials. New trial designs using objective endpoints are needed, and may be aided by novel biomarkers of risk and disease severity for specific epilepsy populations.

1. Introduction

The inability to adequately treat all patients with drug resistant epilepsy provides a continuous impetus to investigate novel forms of treatment. Administration of electrically or magnetically induced current directly to, or in the vicinity of nervous tissue aims to modulate neuronal activity. Various neurostimulation strategies have been developed to target epileptic networks such as bottom-up interference through manipulation of cranial nerve-brainstem pathways, like in vagus nerve stimulation, or top-down control over cortico-subcortical networks like in transcranial magnetic stimulation. Therapies based on acute seizure interruption using closed-loop approaches as well as more neuromodulation-based approaches are being used in clinical practice. Furthermore, direct targeting of seizure onset regions or epileptic network hubs are under development, as well as multiple non-invasive technologies. With an increasing number of neuromodulatory therapies on the horizon and the expansion of their use in clinical practice, trials aimed at evaluating their efficacy and effectiveness must be optimized based on greater understanding of clinical effects and underlying mechanisms.

The first patient to undergo neuromodulatory therapy for epilepsy received adjunctive vagus nerve stimulation (VNS) in 1988 for drug-resistant seizures due to encephalitis and became seizure-free with the combination of VNS and carbamazepine (Penry and Dean, 1990). Thirty years later, there are three invasive neuromodulatory treatments approved for drug-resistant epilepsy and numerous non-invasive stimulation devices lacking proof of efficacy in randomized-controlled trials (RCTs) (Boon et al., 2018).

Many challenges remain to be resolved to fully explore the potential of neurostimulation in epilepsy and related disorders. One of the main drawbacks is our limited knowledge of the mechanism of action of many of the neurostimulation approaches and how applied current affects neural tissue and its target organs. Directly related to this, there is almost complete ignorance on dose response curves and individual responder identification of the various investigated neurostimulation therapies. Despite these basic limitations, RCTs and long-term follow-up efficacy and safety data is available for vagus nerve stimulation (VNS), anterior nucleus thalamic deep brain stimulation (ANT DBS) and responsive cortical stimulation (RNS).

2. Vagus nerve stimulation

Cervical stimulation of the vagus nerve is a neurostimulation therapy that was extensively investigated both pre-clinically and in

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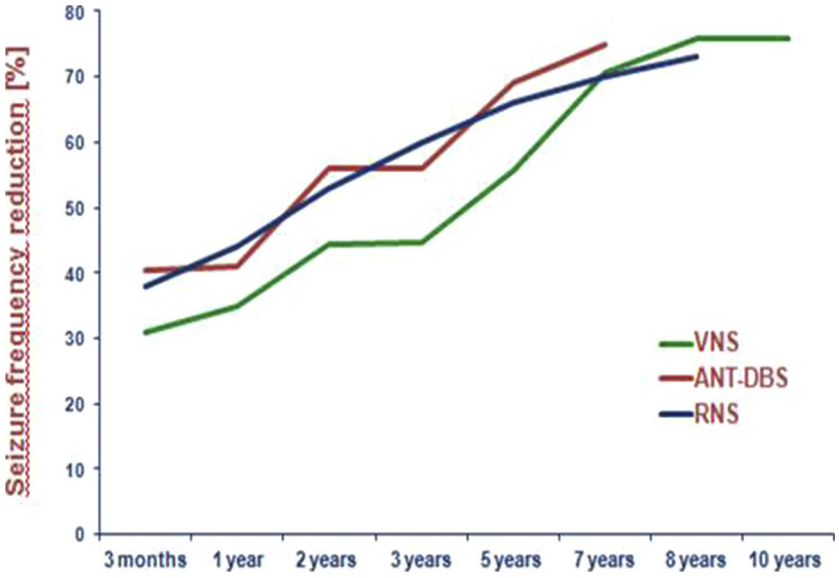

Fig. 1. Overview of clinical efficacy of the invasive neurostimulation modalities based on the original trials and extension follow-up studies. Overall time-courses of seizure reduction of the three neuromodulation modalities are similar; more so for ANT-DBS and RNS which are both approved for focal epilepsies in adults-only as opposed to VNS which is approved for focal and generalized epilepsies in adults and pediatric patients (of all ages in Europe and over the age of 4 in the US). Adapted from Carrette et al Seizure 2016; Morell et al American Epilepsy Society 2016;Sandok et al American Epilepsy Society.

RCTs, and in long-term open label trials. Before the first human implant of the VNS Therapy™ system in 1988, various animal seizure models had demonstrated its potential to interrupt seizure activity (Woodbury and Woodbury, 1990; Zabara, 1992; Zanchetti et al., 1952).

Despite a growing body of clinical experience a significant number of patients remain unresponsive to the therapy, mechanisms of action have yet to be fully elucidated and the optimal stimulation parameters for specific patient profiles have yet to be identified. Experiments in GAERS (Dedeurwaerdere et al., 2005), the motor cortex stimulation model, amygdala and hippocampal kindling models (Dedeurwaerdere et al., 2006; Wyckhuys et al., 2007) have been used in translational approaches, advancing our knowledge from mechanistic work in animal models to patients.

One of the main brainstem relay nuclei of the vagus nerve is the locus coeruleus (LC), the major source of noradrenaline within the brain, through profuse branching throughout the entire cortex (Krahl et al., 1998). In response to cervical electrical activation of the vagus nerve, microdialysis experiments have demonstrated significant increases in hippocampal noradrenaline (Raedt et al., 2011). In addition to this, it was demonstrated that the degree of noradrenaline increase correlates to the seizure suppressing effects in the pilocarpine rat model, demonstrating that this vagal-LC-hippocampal noradrenergic pathway may represent a key mechanism of VNS (Raedt et al., 2011). In humans, the cognitive evoked potential P300 (or P3) is known to be mediated by changes in noradrenergic activity (Murphy et al., 2011; Nieuwenhuis et al., 2005). It has therefore been investigated whether VNS-induced changes of P300 in epilepsy patients, are able to identify responders to the therapy. It was found that responders to VNS, indeed demonstrate a larger P300 amplitude in response to switching on VNS (De Taeye et al., 2014; Neuhaus et al., 2007). With the current technological advances, and the development of non-invasive VNS devices, combined tVNS-P300 measures may help in identifying responders prior to VNS implantation.

3. Deep brain and cortical stimulation

As for VNS, similar challenges exist for the other currently available neurostimulation therapies. Preclinical studies have been performed to investigate the efficacy and induced intracranial activity of deep brain stimulation (DBS).(Wyckhuys et al Neuroimage 2010) The efficacy of various hippocampal DBS parameters was investigated and demonstrated that high frequency stimulation (130 Hz) successfully suppresses seizure characteristics in electrically kindled rats (Wyckhuys et al Epilepsia 2007). A follow-up study demonstrated superior efficacy of high frequency stimuation compared to low frequency at 5 Hz. (Wyckhuys et al Epi Res 2010). A novel type of high frequency DBS ie. continuous stimuli with Poisson distributed intervals (Poisson distributed stimulation, PDS) in the kainic acid (KA) rat model with spontaneous seizures was even more efficacious. (Buffel et al Int J Neural Syst 2014).

MicroSPECT of the rat brain was applied to evaluate rCBF changes induced by various hippocampal DBS protocols with subtraction analyses of stimulation on/off periods. (Wyckhuys et al Neuroimage 2010). DBS induced significant decreases in relative rCBF, both in the ipsi- (the side of DBS) and contralateral hippocampus which was most extensive when bipolar PDS was applied. (Wyckhuys et al Neuroimage 2010).

4. RCTs for neurostimulation

VNS, anterior-thalamic deep brain stimulation (ANT-DBS) and responsive neurostimulation (RNS) have been evaluated in RCTs (Fisher et al., 2010; Heck et al., 2014), the first of which was the E03 trial initiated in 1990 to study the effect of adjunctive VNS in adults with partial drug resistant epilepsy (The Vagus Nerve Stimulation Study Group 1995). In this study, patients were randomized to 12 weeks of either “low stimulation” or “high stimulation” paradigms after 12 weeks of pre-operative baseline. Due to the lack of precedent and insight into the “electricodynamics” and “electricokinetics” of VNS and neuromodulation in general, the E03 trial design was derived from antiepileptic drug (AED) trials applying the same pharmacological rationale to neuromodulation. Patients receiving “high stimulation” displayed significantly greater seizure reduction at 12 weeks than the control group ultimately leading to regulatory approval of VNS for drug-resistant epilepsy but the study did raise important questions related to trial design in neuromodulation that have yet to be fully resolved to date.

The first significant difference between drugs and devices may lie in dose-response. Open-label trials of VNS (but also DBS and RNS) suggest that effects of VNS continuously increase over many years (Elliott et al., 2011; Orosz et al., 2014) (see Fig. 1) raising the question of a cumulative therapeutic effect, which in turn also has implications for even very low levels of stimulation. Latency to onset of effect, or to loss of effect upon therapy withdrawal have yet to be systematically assessed for specific stimulation paradigms. Taken together, one may hypothesize that 12-week observation periods may not suffice to optimally assess therapeutic efficacy of VNS. However, it is ethically challenging to

extend sham-control periods to several months or years.

Furthermore, based on the continuous seizure-frequency and seizure severity reduction observed in VNS trials, one may question whether therapeutic effects of VNS like those of AEDs are based on "anti-seizure" mechanisms or whether VNS has disease-modifying properties and is thereby anti-epileptogenic.

The contribution of neuro-inflammation to disease progression in epilepsy may have been underestimated in the past, with more recent studies suggesting a strong inflammatory component to ictogenesis in certain epileptic pathologies such as temporal lobe epilepsy due to hippocampal sclerosis, post-traumatic epilepsy or cortical dysplasia (Gales and Prayson, 2017; Iyer et al., 2010). The role of the vagus nerve as the key mediator of inflammatory signaling between the CNS and the periphery is being increasingly discussed and investigated from various perspectives. It is hypothesized that the vagus nerve has anti-inflammatory properties both through its afferent (cytokine receptors of vagal afferents activating the hypothalamic-pituitary adrenal axis) and efferent fibers (the anti-TNFα effect of the cholinergic anti-inflammatory pathway) placing it at the interface of the brain-gut axis (Bonaz et al., 2017a, b). On this basis, VNS has been recently piloted in inflammatory disorders such as Crohns Disease (CD) and rheumatoid arthritis (RA): five out of seven CD patients were in clinical, biological and endoscopic remission at 6 months of VNS (Bonaz et al., 2017a, b) and in RA patients, VNS significantly reduced RA disease severity and inhibiting peripheral blood production of TNF, IL-1β, and IL-6 (Koopman et al., 2016). Taking these initial observations into consideration it is of great interest to investigate whether VNS may have effects on neuroinflammation and thereby on disease progression in certain epilepsy etiologies. A case- control analysis of the VNS outcomes registry (Englot et al., 2012) found that patients (n = 317) with post-traumatic epilepsy (PTE) were 1.32 times more likely to respond to VNS than non-PTE patients (n = 1763; OR 1.32, 95% CI 1.07–1.61p < 0.0001) raising the question whether VNS may also be acting via neuroimmunomodulation in PTE, an etiology with a suggested strong inflammatory driver of ictogenesis.

Assessing efficacy of disease modifying therapies in RCTs will be challenging as a large number of patients would need to be followed for a very long period of time. However, PTE is seen by many authors as one of the few opportunities to realistically assess anti-epileptogenesis. A large-body of evidence documents the time-course of risk of developing PTE after varying degrees of traumatic brain injury (Mahler et al., 2015), allowing for identification of a high risk population and high-risk period. In this population, patients could be randomized to a drug (or intervention) and placebo (or sham) in order to compare latency to first seizure, incidence of PTE and seizure frequency between the groups (Mahler et al., 2015). This may be an opportunity to investigate anti-inflammatory effects of VNS, however it does not solve the ethical challenge of maintaining a control group for extended periods of time, which is considered to be of greater significance when it comes to a surgical intervention.

To overcome this VNS-specific challenge of long-term sham control groups, one study explored the option of open-label randomization resulting in patients with drug-resistant epilepsy receiving either best medical practice (BMP) or BMP with adjunctive VNS (Ryvlin et al., 2014a, b). Originally the study aimed to enroll n = 362 patients and assess quality-of-life (using the QOLIE-89 questionnaire) and seizure-frequency over 2-years, however the study only managed to recruit n = 112 patients before being terminated early due to low enrollment rates. The study did show significantly superior quality-of-life in patients receiving adjunctive VNS and illustrated the so-called "honeymoon" effect (a transient reduction in seizure-frequency upon initiation of a new [pharmacologic] treatment regimen) in the BMP group in contrast to a continuous long-term seizure reduction in the BMP + VNS group (Ryvlin et al., 2014b), but also highlighted problems that may arise from attempting to assess a surgical intervention in an open-label randomized trial. The authors of the study explain that low enrollment was primarily due to the fact candidates had strong views (either positive or negative) about VNS, therefore were reluctant to be randomized. One may assume that randomization to a surgical intervention is different to a placebo arm of a drug trial, and thus, patients were hesitant to enroll. Surgical interventions create larger expectations of an effect rather than a pharmacological intervention, which increases the placebo effect in the surgical group. However, it may be argued that this effect is unlikely to persist over a long period of time.

Possible alternatives to assess real world effectiveness of VNS in epilepsy could be prospective non-randomized controlled studies in large populations with long follow-up periods to account for natural fluctuations in disease severity. An example for such an approach is the D-23 trial of VNS for treatment resistant depression (TRD): 795 patients could choose between treatment-as-usual (TAU) or TAU + VNS (Aaronson et al., 2017) and were followed-up for more than 5 years. The trial not only demonstrated significantly less depressive symptoms in the TAU + VNS group throughout the 5 year observation period, but also offered insight into real-world phenomena associated with adjunctive VNS therapy: patients in the VNS + TAU group had more severe depression at baseline as well as more suicide attempts and psychiatric hospitalizations in the 5 years prior to the study suggesting that VNS is either accepted by or offered to more severely ill patients in real-world treatment scenarios. To date, there is no trial comparing long-term real-world outcomes of patients with drug-resistant epilepsy treated with different therapies. Such a study may be of great value due to the fact that drug-resistant epilepsy is a chronic and often life-long disease requiring management strategies that are effective and tolerable on the long-term.

Further lessons have been learned from trials of VNS in TRD. In 2012, outcomes from a large-scale randomized double-blinded trial aimed at assessing the most optimal stimulation settings for VNS in TRD were published (Aaronson et al., 2013). Patients were randomized to either "low dose stimulation" (0.25 mA, pulse width: 130μsec)," medium dose stimulation" (0.5–1.0 mA, pulse width: 250μsec) or "high dose stimulation" (1.25–1.5 mA, pulse width: 250μsec) and followed for 22 weeks in an acute observation phase without the option for dose adjustments, and then for another 38 weeks with optional dose adjustments. Although the total charge delivered by the VNS device per day significantly correlated with the reduction of depressive symptoms, the study did not show significant differences between the dose groups. After unblinding, it was found that 27% of patients in the "high dose stimulation" group did not receive "high dose stimulation", 12% of the patients in the "medium dose stimulation group" did not receive "medium dose stimulation" and "14% of the patients in the "low dose stimulation group" did not receive "low dose stimulation" primarily due to tolerability issues. In clinical practice, tolerability of VNS shows high inter-individual variability and is thought to be dependent on surgical implantation technique, placement location of the electrode on the vagus nerve and most importantly vagal anatomy. The majority of side-effects of VNS are related to stimulating the largyngeal nerve fibres (Al Omari et al., 2017; Ardesch et al., 2010). Therefore, the location of laryngeal fibres within the vagus nerve (e.g. towards the center vs the periphery) as well as the placement of electrode which only covers 270 ° of the nerve may be a key determinant of tolerability, complicating efforts to find the most-optimal therapeutic stimulation paradigm for all. Due to the inherent nature of direct brain stimulation, tolerability of acute stimulation may be less of an issue for intra-cranial stimulation paradigms allowing for such investigations of stimulation optimization. However, large-scale randomized controlled dose-finding studies have yet to be performed for DBS or RNS.

In the past four years, two responsive neuromodulation therapies have been approved aimed at stopping a developing seizure: responsive vagus nerve stimulation (rVNS) which uses specific signs of ictal cardiac dysfunction to trigger stimulation, and responsive neurostimulation (RNS) which uses ictal ECoG activity to trigger stimulation aimed a stopping a developing seizure. Whether responsive systems are superior

to open-loop systems has yet to be demonstrated in RCTs, however, their availability creates new opportunities to study acute seizure cessation. In a uniquely designed series of trials including 51 patients, the ability of rVNS to acutely impact EEG seizure activity was investigated during video-monitoring (Boon et al., 2015; Fisher et al., 2016). Seizures that were detected and stimulated by the rVNS device were found to be shorter due to less spatial propagation of ictal EEG activity and associated with less cardiac dysfunction (Ravan, 2017; Ravan et al., 2017). It remains to be shown in long-term studies whether the addition of acute seizure cessation by rVNS reduces seizure severity to a degree that it translates into improved overall seizure control and improved mortality and morbidity.

5. Conclusion

This review is focused on the history and challenges in trial designs for VNS, however challenges in trials of ANT-DBS and RNS can be viewed in a similar context. Despite the extensive need for novel antiepileptic therapies, the advancement of neurostimulation therapies has been relatively slow due to scepticism towards these novel approaches within the epilepsy field, limited knowledge of mechanisms of action, invasiveness, initial costs of the devices and uncertainty of the optimal clinical scenarios for use. Technological advances and increased interests into device development from industrial players are rapidly changing the neurostimulation landscape and will hopefully contribute to more extensive investigation in this field.

RCTs with three to four month blinded periods modeled after AED trials have been successfully performed for all three approved neuromodulation modalities for epilepsy. This trial design, however, may not be optimal for understanding the true efficacy of these potentially neuromodulatory treatments. Considering the long-term effectiveness assumed for neuromodulatory treatments and the chronic nature of drug-resistant epilepsy, study designs allowing for long-term comparative observations would be of great value, but are hindered by the inherent nature of a long-term [surgical] control group and the bias associated with open-label trials. Thus, new trial designs using objective endpoints are needed, and may be aided by novel biomarkers of risk and disease severity for specific epilepsy populations. A true challenge will be to investigate synergistic combinations of neurostimulation, immunomodulation, anti-seizure drugs and novel approaches such as stem cell technology.

Disclosures

Maxine Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators and holds stock options. Kristl Vonck has received personal compensation for consulting for LivaNova and has received research support (including for clinical trials) through her institution from Cerbomed, LivaNova, Medtronic, Neurosigma and UCB.

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