RACCOLTA ITALIANA TERAPIE AVANZATE (RITA) - DEVICE-AIDED THERAPIES FOR PARKINSON'S DISEASE: ITALIAN MULTICENTER STUDY ON OUTCOMES AND PREDICTORS

STUDY PROTOCOL

Premise

Device-aided therapies (D-TH) have allowed to improve quality of life of people with Parkinson's disease (PD). They include surgical (Deep Brain Stimulation -DBS- or ablative procedures like focused ultrasound -MRgFUS-) and infusion (apomorphine infusion -Apo-inf-, levodopa subcutaneous infusion – LD-inf-, and Levodopa/Carbidopa Gastrointestinal Infusion -LCGI-) therapeutic options.
DBS for PD is an adjunct therapy to the pharmacological treatment based on chronic, high-frequency stimulation of deep brain nuclei via neurosurgically implanted electrodes and a neurostimulator system [Krack, 2019]. MRgFUS is an incisionless, accurate, ablative therapy recently introduced for the treatment of movement disorders. It has the ability to deliver precise, thermal lesions to deep brain structures, exerting the beneficial effect of ablative procedures without invasive procedures by Magnetic Resonance-guided focused ultrasound [Walters, 2019]. Apo-inf consists in the administration of a potent dopamine-agonist, apomorphine, by means of a small infusion pump, a fine-caliber tube, and a needle that delivers the apomorphine subcutaneously during the day [Fabbri, 2018]. LCGI is a gel containing l-dopa and the decarboxylase inhibitor carbidopa at concentrations of 20 and 5 mg/mL, respectively. The infusion pump is carried in a small bag around the neck or the waist and the gel is infused continuously through the abdominal wall by means of a percutaneous endoscopic gastrostomy, inserted under local anesthesia, up to the upper jejunal part of the small intestine [Fabbri, 2018]. LD-inf consists of a liquid formulation of levodopa/carbidopa continuously administered via a subcutaneous pump that provides plasma levodopa levels with less variability than standard oral levodopa [Giladi, 2017].
Although randomized controlled trials have demonstrated the efficacy of these treatments on PD motor and non-motor symptoms as well on the quality of life, the selection of patients for each one of these advanced interventions might be challenging. Few predictors of better response have been demonstrated for DBS of the subthalamic nucleus (DBS), such as younger age and absence of prominent axial symptoms. Yet, the selection of borderline cases is mainly based on experts' experience, and the selection for a specific D-TH is not yet an evidence-based process.

Aim of the study

Using data from a large cohort of PD patients candidates for D-TH, namely DBS, LCGI, Apo-INF, LD-INF and MRgFUS, we set the following aims.
Primary Aims:
1) to identify demographic and clinical factors influencing the selection for a specific D-TH or BMT;
2) for each D-TH, to identify predictors of short-term efficacy categorizing each group in poor responders and good responders as per quality of life (PDQ8 summary index score) improvement.
Secondary Aims:
1) to compare clinical and demographic features for each D-TH, and among different D-THs;
2) to analyze withdrawal rates, causes of withdrawal, type and number of adverse events for each D-TH, and among different D-THs;
3) to analyze psychiatric symptoms and complications for each D-TH, and among different D-THs;

4) only for DBS patients, to compare clinical and quality of life outcomes between those treated with standard ring mode stimulation and those treated with complex stimulation programming.

Research description

Patients will be invited to participate in the study after having been informed in detail (also with the help of a written information form attached) of the objectives of the project, as well as the ways in which it is intended to pursue these objectives. The person in charge of the center to which the patient belongs will inform them. The person who freely accepts will authorize inclusion in the project by signing the informed consent form of which he/she will receive a signed copy. It will also be clearly explained in the information sheet attached to the informed consent that any participant will have the opportunity to withdraw its participation in the project study at any time, without giving any reason and without affecting the doctor-patient relationship with the specialists involved in the project.
The collection of sensitive data of a clinical nature will be carried out in full compliance with the principles expressed in the Declaration of Helsinki (latest version) to avoid any discomfort to participants, both physical and psychological.
No payment will be offered for participation in the study. There will be no cost to the patient or to the NHS for participation in this study.

Study design

Observational, prospective, multicenter, nonprofit of 5-year duration. The target sample of patients is 1600 for all centers.

Protocol

Patients will be included in the study after having given their informed consent (attachment 1)

Screening phase

Patients will be judged eligible for the study according to the following criteria:

Inclusion criteria:
- Diagnosis of Parkinson's disease according to the criteria of Postuma et al.
- Patient evaluated for possible D-TH: DBS, Duodopa, Apo-INF, LD-INF, MRgFUS

Exclusion criteria:
- Inability to understand and express informed consent

Enrollment phase

A prospective collection of demographic and clinical data from PD patients candidates to D-TH and judged to be eligible for the study. We plan the evaluation at 2 different time points: T0, at the evaluation time for D-TH, and T1, 12-18 months after starting the D-TH or deciding to continue the best medical treatment (BMT). All treatments will be used according to clinical practice. We will collect:

- Comprehensive collection of demographic data and history of PD
- Combined Comorbidity score (Gagne, 2011)

- Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part-I, -II, -IV
- MDS-UPDRS part III in OFF and ON medication at T0 and UPDRS part III in daily ON at T1 (except for DBS patients who will be evaluated in OFF and ON medication also at T1)
- Ad-hoc questionnaire for motor symptoms
- Schwab and England, OFF and ON medication
- Neuropsychiatric symptoms, as per an ad-hoc questionnaire, QUIP-RS, psychosis, and MOCA, diagnosis of MCI (single and multiple domain) according to Livain et al criteria, diagnosis of dementia according to DSM-V
- Non-motor symptoms, as per an ad-hoc checklist, blood pressure measurement both supine and after 1 and 3 minutes from orthostatism, WOQ-19, RBD1Q and PDSS-2, NoMoFa
- Quality of life, as per the PDQ8
- Ongoing therapies, both dopaminergic and non dopaminergic therapies
- Instrumental tests requested
- Type of D-TH chosen
- Causes of D-TH exclusion
- Dosage/settings of the D-TH
- D-TH adverse events, as per an ad hoc questionnaire
- Causes of D-TH withdrawal
- Caregiver burden, as per the Zarit Burden Scale

Preliminary planning of data analysis

A descriptive analysis of the clinical-instrumental data collected during the observational study will be preliminarily performed, with verification of the frequency distribution of the variables of interest. Then, possible statistical inferences on clinical-instrumental scalar variables will be made using tests for unpaired data and/or analysis of variance in order to assess differences between two or more identified groups, as well as using tests for paired data and/or tests for repeated measures in order to assess differences between different temporal assessments in the same group or in multiple groups. Finally, possible correlations between the collected clinical-instrumental variables will be tested, including by means of regression models created ad hoc.

Data collection and confidentiality of information collected

The study will be conducted in compliance with current privacy regulations and in accordance with the ethical principles of the Declaration of Helsinki. All patients enrolled in the study will sign an informed consent. The data obtained will be collected into databases on electronic format. Data will be collected anonymously by assigning to each selected patient an identification code. Clinical facilities, sources of the data collection registry, are in charge of case detection, enrollment, coding and registration and are functionally linked with the coordinating center. Sensitive data will be annotated, anonymized through a coding procedure, and sent to the coordinating center.

Location of the database

Patient records from the coordinating center will be kept at the individual center of competence, in accordance with the technical and organizational measures adopted by each facility. The clinical-demographic information contained in the records will be entered into a database located on a Cloud platform set up for the LIMPE Foundation by an experienced and trusted IT service provider, acting as the External Data Processor. The database and the related ad hoc web portal will both be managed by the LIMPE Foundation for Parkinkson onlus; access to the IT platform will be possible only and exclusively with the credentials assigned to the data entry employee, and to the center manager (either the coordinating center or one of the peripheral centers). The peripheral center will have access only to the records related to the patients pertaining to that center. The coordinating center, on the other hand, will retain access to the entire database. It should also be noted that the network from which

data will be entered is protected by firewalls, that the Internet connection is encrypted with a digital certificate (SSL technology), and that periodic backups of the database will be made. The database is located on a server, protected by means of a password that is changed periodically, and access is by means of credentials, held only by the center manager, and the data entry employee. The coded clinical information will be used for the production of periodic reports by the RADAC scientific committee.

Ownership of the archives related to RADAC

Ownership of the computer archives created in the course of the RADAC and at the outcome of the RADAC, will belong exclusively to the LIMPE Foundation for Parkinson's Disease Onlus, which will take care to facilitate access to them to all those (researchers, non-profit organizations, national and foreign scientific institutes, etc...) who, for research reasons, will manifest in due form the need to be able to consult the data collected and the materials collected over time.