Parkinsonism and Related Disorders xxx (2016) 1–5

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Short communication

Advanced therapies in Parkinson's disease: Long-term retrospective study

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ARTICLE INFO

Article history:
Received 21 March 2016
Received in revised form
20 April 2016
Accepted 15 May 2016

Keywords:
Parkinson's disease
Electrical stimulation
Movement disorders
Neuropharmacology
Neurosurgery

ABSTRACT

Background: Levodopa/carbidopa intestinal gel infusion (LCIG) and subthalamic nucleus deep brain stimulation (STN-DBS) are approved therapies for advanced Parkinson's disease (PD) whose long-term comparability remains unclear.
Methods: We reviewed the 5-year data on activities of daily living (ADL) and motor complications (OFF time, dyskinesia duration, and dyskinesia severity), as measured by the Unified Parkinson Disease Rating Scale (UPDRS) section-II and section-IV (items 39, 32, and 33, respectively) in 60 PD patients exposed to STN-DBS (n = 20), LCIG (n = 20), and oral medical therapy (OMT) (n = 20) at similar baseline disability and cognitive state.
Results: STN-DBS and LCIG showed a similar magnitude of deterioration in ADL (+6.1 vs. +5.7 UPDRS-II; $p = 0.709$), but lesser than with OMT (+13.7 UPDRS-II; $p = 0.005$). OFF time also improved to the same extent in STN-DBS and LCIG (−62% vs. −54.5%; $p = 0.830$), while worsened with OMT (+78.6%; $p < 0.001$). STN-DBS and LCIG yielded greater improvement on dyskinesia compared to OMT (dyskinesia duration: −66.1% vs. −9.0% vs. +24.2% [$p = 0.001$]; dyskinesia severity: −68.8% vs. −18.0% vs. +16.2% [$p = 0.002$]), with relative superiority of STN-DBS over LCIG ($p = 0.004$ for duration; $p = 0.014$ for severity). The annualized rate of complication was lower in STN-DBS vs. LCIG (0.13 vs. 0.68; $p < 0.001$) but not different between STN-DBS and OMT (0.13 vs. 0.10; $p = 0.795$).
Conclusions: STN-DBS and LCIG showed comparable efficacy in ADL and OFF time, superior to OMT. STN-DBS yielded greater improvement in dyskinesia and lower long-term rate of complications than LCIG.

1. Introduction

Continuous intraduodenal levodopa/carbidopa intestinal gel (LCIG) infusion and subthalamic nucleus deep brain stimulation (STN-DBS) are effective therapeutic options for patients with advanced Parkinson's disease (PD) [1,2]. These treatments can reduce the severity of motor complications [3,4] and improve the activities of daily living (ADL) through distinct mechanisms: LCIG stabilizes L-dopa plasma level fluctuations [1] whereas STN-DBS modulates pathologic basal ganglia oscillatory patterns [2].

While STN-DBS is associated with rare but serious adverse events, such as brain hemorrhage and/or central nervous system infections [2,5], LCIG is associated with more frequent but usually less severe complications, including obstruction or dislocation of the percutaneous enteral gastrostomy (PEG) tube and/or infusion pump malfunction [1,4,6]. However, no head-to-head comparative study exists between these therapeutic options in advanced PD, and their relative efficacy, safety profile, and complications rate can only be inferred from the results of heterogeneous clinical studies.

We aimed to review the 5-year efficacy and safety of patients treated with STN-DBS (n = 20) or LCIG (n = 20) in two specialized Movement Disorders Centers, as compared with a disability-matched control group of patients who opted to continue OMT after becoming eligible for STN-DBS (n = 20).

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http://dx.doi.org/10.1016/j.parkreldis.2016.05.015
1353-8020/

2. Methods

2.1. Patient selection and surgical procedures

Five-year data from patients at similar baseline disability, treated with STN-DBS (n = 20), LCIG (n = 20), or OMT (n = 20) in two Movement Disorders Centers (University of Turin and University of Cincinnati) were retrospectively evaluated. All patients fulfilled the CAPSIT-PD [7] clinical and neuropsychological criteria at their baseline clinical evaluation for both STN-DBS and LCIG. The LCIG cohort comprised patients not treated with STN-DBS for their unwillingness to undergo neurosurgery and/or claustrophobia (1 case excluded from STN-DBS due to an implanted cardiac pacemaker) and, at the University of Cincinnati, willing to initiate open-label LCIG treatment as part of the initial US-based safety/tolerability phase of Duopa® development. After PEG tube placement [6,8], patients were converted from oral dopaminergic therapies to an intestinal infusion of levodopa (20 mg/mL) and carbidopa (5 mg/mL) in carboxymethylcellulose gel (LCIG, AbbVie Inc., North Chicago, Illinois, U.S.A.) titrated to reach adequate control of motor symptoms.

In order to facilitate comparability, the STN-DBS cohort included 20 patients, consecutively selected among those with age and baseline Unified Parkinson's Disease Rating Scale (UPDRS) sections I–IV comprised within the interquartile range (IQR) of the LCIG cohort. The OMT control cohort included 20 consecutive patients fulfilling the same IQR criteria listed above, who opted to continue medical treatment after an initial clinical selection for STN-DBS.

2.2. Clinical and neuropsychological assessments

Clinical assessments were performed in the OFF state (after at least 12 h since the last levodopa dose) and during the best ON state (a period of perceived maximal efficacy of dopaminergic medications) at baseline and after a minimum follow-up of 3 years. Primary endpoints included activities of daily living (ADL; UPDRS-II), evaluation of OFF time (reemergence of parkinsonian features between dose cycles, measured by the UPDRS-IV item 39), dyskinesia duration (item 32), and dyskinesia severity (item 33). Secondary endpoints included motor severity (UPDRS-III) in the ON and OFF state, side effects, complications, changes in levodopa equivalent daily dose (LEDD) and total electrical energy delivered (TEED = voltage^2 × pulse width × frequency/impedance), prevalence of PD-associated mild cognitive impairment (PD-MCI) and PD associated dementia (PD-D).

To support the classification of PD-MCI and PD-D, patients from the University of Cincinnati received a structured neuropsychological evaluation, Mini-Mental State Examination (MMSE), and Montreal Cognitive Assessment (MoCA); whereas those from the University of Turin underwent MMSE and a battery of cognitive tests assessing reasoning (Raven color matrices), memory (verbal span, spatial span, paired associative learning), language (phonemic verbal fluency, semantic fluency) and frontal executive functions (Trail making B, Nelson's associative categories). Although there were slight differences in neuropsychological instruments between the two centers, the diagnosis of PD-MCI and PD-D was made by an experienced neuropsychologist in accordance with MDS criteria [9,10].

In addition, patients were assessed for dysphagia (score ≥ 2 on item 7 of UPDRS), drooling (score ≥ 2 on item 6 of UPDRS), sleep impairment (score = 1 on item 41 of UPDRS), pain/sensory problems (score ≥ 2 on item 17 of UPDRS), and symptomatic orthostatic hypotension (score = 1 on item 42 of UPDRS). For constipation and urinary incontinence we considered the need of pharmacological treatment as the most consistent indicator of the patient's functional state.

Side effects, complications and hospitalizations were collected and categorized as follows: directly related to the surgical procedure ("perioperative complications"); related to malfunctioning of the devices ("technical complications"); related to therapies and/or stimulation ("treatment-related"); directly or indirectly related to disease progression ("disease-related"); and "maintenance procedures", defined as procedures intended to keep or restore the regular functionality of STN-DBS and LCIG devices.

2.3. Statistical analysis

Continuous variables were described as average ± standard deviation (range). Cramer's V and Kruskal-Wallis tests were used to compare groups at baseline. The Wilcoxon test and repeated-measures ANOVA with Bonferroni's correction for multiple comparisons were used for comparisons between baseline and follow-up data. All tests were performed using SPSS 21.0, considering two-tailed p-values with 0.05 as the statistical threshold. The ethical committee approval was obtained and patients provided written informed consent.

3. Results

3.1. Baseline evaluation

As expected by study design, there were no baseline demographic differences between STN-DBS, LCIG, and OMT cohorts (Table 1). Age at surgical selection ranged from 46 to 70 years and disease duration from 9 to 20 years. Dyskinesia and other motor complications were similar in all cohorts.

3.2. Follow-up evaluation

Follow-up assessments were performed after 5.08 ± 2.26 years in the STN-DBS cohort (range 3–9), 5.15 ± 1.46 years in the LCIG cohort (range 3–8.5), and 5.11 ± 2.25 years in the OMT control (range 3–8.5).

3.3. Primary endpoints

Activities of Daily Living: STN-DBS, LCIG and OMT differed in UPDRS-II scores (+6.1 vs. +5.7 vs. +13.7; $p = 0.005$). The magnitude of worsening was similar in STN-DBS and LCIG ($p = 0.709$), in both cases milder than that observed in the OMT group ($p = 0.010$ for STN-DBS and $p = 0.021$ for LCIG) (Fig. 1; Table 1).

OFF time: OFF time decreased with STN-DBS and LCIG, and increased with OMT (−62.0% vs. −54.5% vs. +78.6%; $p < 0.001$). The improvements observed in STN-DBS and LCIG were of similar magnitude ($p = 0.830$) (Fig. 1).

Dyskinesia: There were differences in dyskinesia duration (−66.1% vs. −9.0% vs. +24.2%; $p = 0.001$) and severity (−68.8% vs. −18.0% vs. +16.7%; $p = 0.002$) in the STN-DBS, LCIG, and OMT cohorts. STN-DBS and LCIG yielded greater improvement on dyskinesia compared to OMT, with relative superiority of STN-DBS over LCIG ($p = 0.004$ for duration; $p = 0.014$ for severity) (Fig. 1).

3.4. Secondary endpoints

Motor severity: There was similar interval worsening in UPDRS-III scores in STN-DBS, LCIG, and OMT cohorts over the duration of follow-up, both in the ON (+3.7 UPDRS-III points [+7.1 UPDRS-III in StimON/MedOFF condition] vs. +4.0 UPDRS-III vs. +5.2 UPDRS-III; $p = 0.345$), and OFF states (+12.6 vs. +12.5 vs. +13.5 UPDRS-III; $p = 0.988$) (Table 1). In addition, the three groups did not show

Please cite this article in press as: A. Merola, et al., Advanced therapies in Parkinson's disease: Long-term retrospective study, Parkinsonism and Related Disorders (2016), http://dx.doi.org/10.1016/j.parkreldis.2016.05.015