1.0 Abstract

Title

Canadian Advanced Parkinson DUODOPA-Treated Patients Observational Study Evaluating Long-Term Health Outcomes in Centers of Excellence (CADENCE)

Keywords

Levodopa/carbidopa intestinal gel, Parkinson's Disease, health outcomes, patient's quality of life (QoL) and health care resource utilization (HCRU) and safety

Rationale and Background

Information is lacking on the health outcomes in Canadian patients with advanced Parkinson' disease (aPD) treated with Levodopa-Carbidopa intestinal gel (LCIG) in a usual clinical setting. Medical management of aPD patients in Canada does not include apomorphine infusion and therefore differs from patient management in European countries where apomorphine infusion is a well-established treatment option. Therefore, extrapolation of European data to Canada must be approached with caution.

Research Question and Objectives

Primary Research Question: What are the health outcomes and safety findings in Canadian patients with advanced Parkinson Disease (aPD) treated with LCIG long-term within the setting of usual clinical practice?

Primary Objective: To document health outcomes, including caregiver burden, work productivity, activity impairment, patient's quality of life and health care resource utilization and safety findings in Canadian patients with aPD treated with LCIG long-term.

Study Design

This open-label observational study was conducted as a non-interventional, prospective, observational post market authorization study. This post-marketing, observational study

(PMOS) was conducted to document health outcomes in Canadian patients with aPD and long-term treatment with LCIG. The primary aim of this PMOS was to assess real-life health outcomes of treatment with LCIG. This study was conducted alongside routine medical care in aPD patients and consisted of a 2- year observational follow up phase and an optional extended 2 year follow up phase. Follow up assessments were recommended at Day 1, and month 1, 3, 6, 12, 18, and 24 months and optionally at 30, 36, 42, and 48 months. Due to the observational nature of this study, the assessment schedule was left to the judgement of the treating physician.

Setting

This was a national Canadian non-interventional, observational study conducted in routine medical care in advanced aPD patients.

A total of 12 Canadian Movement Disorder Centers specialized for treatment of patients with aPD participated in this PMOS observational study.

Patients and Study Size, Including Dropouts

A total of 88 patients were enrolled from 11 sites over a 4- year time period. All study sites were Canadian Movement Disorder Centers which specialize in management and treatment of aPD.

Variables and Data Sources

Source data for this study were patient data files collected by investigators throughout during this prospective study, including the following:

- Hospital and medical records
- Assessment tools and scales
- Data forms completed by physicians, study nurse(s), patients, and patient caregivers

- All questionnaires completed by patients and patient caregivers

The following efficacy assessments were collected during the study:

- Unified Parkinson's disease rating scale (UPDRS)
    - Parkinson's disease stage (UPDRS V; Hoehn & Yahr "on")
    - Activities of daily living (UPDRS II score "on")
    - Motor examination (UPDRS III score "on")
    - Complication of therapy (UPDRS IV; items 32, 33, 34, 35, and 39 modified according to Movement Disorder Society [MDS]-UPDRS)
- Freezing of Gait Questionnaire (FOGQ)
- Parkinson's Disease Sleep Scale-2 (PDSS-2)
- Non-motor symptoms scale (NMS) ScaleS)
- Patient quality of life (PDQ-39) questionnaire
- Level of cognition according to the Montreal cognitive assessment (MoCA)
- Caregiver burden assessed by the Zarit care giver burden scale
- Impact on caregiver work assessed by the work productivity and activity impairment (WPAI) questionnaire
- Healthcare resource utilization (HCRU)

The following information and evaluations were performed and collected during the study:

- LCIG treatment
- Vital signs

- Concomitant disease
- Pharmacological and non-pharmacological treatment of PD
- Laboratory parameters
- Vitamin supplementation
- Adverse events (AEs) and serious adverse events (SAEs)
- AEs leading to discontinuation of LCIG treatment
- Product quality complaints (PQCs)

Results

Because of the early study closure, the target enrollment of 200 treated patients was not reached. Therefore, caution should be taken in the interpretation of the study results.

Patient population

A total of 88 patients (All Subjects Consented Population [ASCP]) were consented to the study and 82 patients were allocated to treatment (Subject Allocated to Treatment Population [SATP]). All 82 of these patients who underwent PEG-J tube placement, were treated with LCIG, and were included in the Safety Analysis Set Population (SASP) and Full Analysis Set Population (FASP).

The six patients that did not receive LCIG treatment were discontinued after Visit 1.

The initial 2-year study was completed by 39 (47.6%) patients. Forty-three (52.4%) patients were terminated before completing the 2-year study. Of these patients, six (7.3%) ended participation due to AE, five (6.1%) ended participation due to withdrawal by patient, and five (6.1%) patients ended participation due to another reason. The remaining

26 (31.7%) patients stopped due to the early completion of the study by the sponsor. Further data from these patients were not collected by the sponsor.

The mean (SD) age of patients at baseline was 69.21 (7.2) years. There were 51 (62.2%) male and 31 (37.8%) female patients and patients were predominantly white (72 [87.9%]). The mean (SD) duration of disease since initial PD diagnosis was 11.72 (4.5) years (range: 3.7 to 24.2; 95% CI 10.7 to 12.7).

Baseline disease characteristics

Freezing of gait was experienced by 18.3% of the patients in the ON state at baseline.

Using 5-2-1 analysis the following characteristics were found in patients at baseline:

- 31.7% of patients experienced troublesome dyskinesia
- 36.6% of patients were taking five or more daily doses of oral levodopa at baseline
- 82.6% of patients were experiencing 2 or more hours of off time a day at baseline
- 80.5% of patients were experiencing 1 or more hours of troubling dyskinesia per day at baseline

The most common class of previous PD medications taken by the patients in the study were as follows: 84.1% of patients had taken DOPA and DOPA derivatives, 65.9% of patients had taken dopamine agonists, 62.2% of patients had taken monoamine oxidase B inhibitors, 52.4% of patients had taken entacapone, and 50.0% of patients had taken amantadine derivatives.

LCIG was titrated using a temporary NJ tube in 24.4% of patients. In total 32.9% of patients underwent at least one PEG-J tube replacement procedure for a total of 51 replacements.

Efficacy and Health Outcomes Results

Due to early closure of the study, only 82 patients were treated with LCIG and 39 patients completed the initial 2 year study period. Because of this, only statistically significant trends in outcomes results are summarized below.

ADL Total Scores (UPDRS II) increased over time indicating worsening of the score with statistically significant increases from Day 1 at Months 12, 18, and 24.

Motor Examination Total Scores (UPDRS III) increased over time indicating worsening of the score with statistically significant increases from Day 1 at all time points.

Complication of Therapy scores (UPDRS IV) showed statistically significant improvement from Day 1 in several questionnaire items at multiple time points. Changes in Complication of Therapy Scores indicated improvements in the items dyskinesia and time spent in the OFF state.

Parkinson's Disease Stage (UPDRS V) had a small, statistically significant worsening for patients from Day 1 to Month 24.

FOGQ scores showed statistically significant improvement from Day 1 to Month 12, but was not significant at other time points.

PDSS-2 scores showed statistically significant improvement from Day 1 at all time points.

NMSS Scores showed a statistically significant improvement from Day 1 at Month 3, but was not significant at other time points.

PDQ-39 QOL Total Scores showed statistically significant improvement from Day 1 at Month 3 and statistically significant worsening from Day 1 to Month 6 suggesting an initial improvement followed by a subsequent worsening while changes in Total Scores from Day 1 to Month 12 and 24 were not significant.

Mean MoCA Total Scores showed little change from Baseline through Month 24. All patient scores were normal, mild, or moderate and no patient had severe cognitive impairment at any time in the study.

HCRU information was collected from the study patients covering the areas of Occupational Status, Health Care Coverage, Nursing and Home Health Care, and Medical Care.

Change from Baseline in Zarit Caregiver Burden scores did not achieve a statistical significance at any time point.

WPAI scores change from Visit 1 showed initially worsening followed by a plateau of scores. Change in percent presenteeism had significantly worse scores from Visit 1 at all time points, but there was not significant worsening after Month 3. Change in percent absenteeism showed statistically significant worse scores from Visit 1 at all time points, but there was also no significant worsening after Month 3. Change in percent total work productivity impairment had significantly worse scores from Visit 1 at all time points, but there was also no significant worsening after Month 3. Change in percent total activity impairment scores from Visit 1 were statistically significant at Months 3 and 12, but not at other time points.

LCIG Treatment Results

Average morning bolus doses of LCIG remained consistent over the 2-year initial study period. Mean average morning boluses doses ranged from 180.9 mg L-DOPA at Month 18 to 197.7 mg L-DOPA at Month 1.

Average daily continuous LCIG dose increased over time. Mean average daily continuous doses ranged from 873.5 (448.24) mg L-DOPA per day at Day 1 to 1178.0 mg L-DOPA per day at Month 24.

The average daily duration of infusion increased slightly over time. Mean average daily duration of infusion ranged from 13.9 hours per day at Day 1 to 15.9 hours per day at Month 24.

The average number of extra boluses per day was consistent over time. Mean average daily number of extra boluses per day ranged from 2.3 extra doses at Month 24 to 3.0 extra doses at Month 18.

The average dose of extra boluses was consistent over time. Mean average dose of extra boluses ranged from 30.7 mg L-DOPA per bolus at Month 1 to 31.7 mg L-DOPA per bolus at Month 18

The mean average daily dose from extra boluses per day increased slightly over time. The mean average daily dose from extra boluses per day ranged from 92.1 mg L-DOPA per day at Month 1 to 107.1 mg L-DOPA per day at Month 12.

The mean average total daily dose (infusion and bolus) also increased slightly over time. The mean (SD) average total daily dose was 1071.0 (461.4) mg at Day 1 and increased to 1454.2 (518.5) mg by Month 24. The only period in which the mean average total daily dose decreased was a slight decrease between Month 12 and Month 18.

Safety Results

Patient safety was assessed by patient study drug exposure, vital signs and weight, AEs and SAEs, abnormal laboratory values, and PQCs. All safety data presented was taken from the EDC system with the exception of AE and SAE data. Due to limitations in the entry of AE and SAE data in the EDC system, it was decided to use the pharmacovigilance database for these data rather than the EDC system. All efficacy and outcomes data were also taken from the EDC system. The safety results were as follows:

- Twenty-eight (34.1%) patients experienced 98 SAEs
    - Six (7.3%) patients experienced SAEs related to the study drug, although no individual related SAE occurred in more than one (1.2%) patients
    - Fifteen (18.3%) patients experienced an SAE that led to discontinuation of treatment
- Two deaths occurred during the study
    - The deaths were not related to study drug (LCIG). One was due to congestive cardiac failure and one was associated with a PEG-J tube PQC.

- Forty (48.8%) patients had at least one PQC
    - The majority of the complaints were due to malfunction or deterioration of PEG or intestinal tubes

Discussion

Because of the limitations of the study, conclusions are difficult to make. Recruitment challenges resulted in a smaller than anticipated number of patient participants with most patients not completing the initial 2-year study. While some of the efficacy and health outcomes seemed to have positive effects (e.g., UPDRS III, IV, V, and FOGQ), others had negative (e.g., UPDRS II) or mixed (e.g., PDQ-39 QOL scores) effects. Additionally, the relationship of the treatment with LCIG and the changes in the health outcomes is not clear. Therefore, no significant positive or negative effects can be attributed to LCIG treatment in this study.

Conclusion

The primary objective of this study was to document health outcomes and safety in Canadian patients with aPD treated with LCIG long-term. While limited by the relatively small number of patients reaching the targeted 24-month endpoint, this study provides information on the safety profile of LCIG when used in a real-world setting. The outcomes assessments did not have sufficient data to provide meaningful conclusions regarding benefit to patients and their caregivers. The study did demonstrate that the out-patient PEG-J tube placement procedure could be safely performed by Canadian Movement Disorder Centers, and that outpatient LCIG treatment using a drug-device pair could be safely managed by the patients and their caregivers.

LCIG continues to have a positive benefit to risk ratio in the treatment of aPD. No new safety concerns were identified in this study.

Marketing Authorization Holder(s)

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