1.0 Abstract

Title

COSMOS - COmedication Study assessing Mono- and cOmbination therapy with levodopa-carbidopa inteStinal gel

Keywords

LCIG, levodopa-carbidopa intestinal gel, advanced Parkinson's disease, monotherapy

Rationale and Background

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder with a worldwide estimated prevalence of 0.3% in the general population 40 years of age and older. The most effective symptomatic therapy for PD remains levodopa, a precursor of dopamine. However, within several years of levodopa therapy initiation, a considerable number of patients develop complications, and after 5 to 10 years of treatment at least 50% of patients develop motor fluctuations and abnormal involuntary movements (dyskinesia).

As PD progresses, even complex oral drug regimens may become insufficient for symptom control. Therefore, other therapeutic strategies have been developed, including treatments based on continuous drug delivery. Among the enteric continuous drug delivery formulations, levodopa-carbidopa intestinal gel (LCIG) is the only formulation of levodopa and carbidopa which has been found to be suitable for continuous long-term intestinal infusion so far.

However, so far, no systematic, comprehensive and homogeneous real-world data are available – neither on LCIG monotherapy or LCIG in combination with add-on PD medication, nor on the management of add-on PD medications before or upon LCIG initiation, or during long-term LCIG maintenance therapy.

The present study attempts to fill this knowledge gap and generate relevant data from routine clinical practice on the usability of LCIG as a monotherapy and in combination with add-on PD medications.

Research Question and Objectives

The primary objective of the study was to evaluate the percentages of Advanced PD patients on LCIG monotherapy right after LCIG initiation and at 3, 6, 9, and 12 months, respectively.

The secondary objectives of this study were:

- To describe PD medication management, and the main reasons justifying their use, directly prior to LCIG initiation, at LCIG initiation and during long-term LCIG treatment
- To describe LCIG infusion settings and substantial dose adjustments and the respective reasons
- To describe the Healthcare Resource Utilization (HCRU)
- To identify the physician's and patient's/caregiver's overall preference for the pharmacological treatment approach using LCIG as monotherapy vs. LCIG plus add-on PD medication
- To identify predictors for achieving long-term monotherapy with LCIG vs. LCIG plus add-on PD medication, based on the patient's profile and the physician's profile
- To describe the latency from LCIG initiation until LCIG is given as a monotherapy and the average duration of LCIG monotherapy
- To describe the latency from the initiation of LCIG therapy until the introduction or tapering of each PD medication, or until substantial dose adjustments of LCIG
- To evaluate the percentage of patients who are on LCIG monotherapy, PD medication management and HCRU for the participating countries who have enrolled a minimum of 20 study subjects

Study Design

This is a multi-country, retrospective and cross-sectional, post-marketing observational study (PMOS) of patients with APD (advanced Parkinson's disease) treated with LCIG in a routine clinical setting. It was planned to be conducted in approximately 15 countries.

The study population comprises adult patients diagnosed with APD, on current treatment with LCIG, and treated with LCIG for at least 12 months prior to study inclusion. The participating sites were to be hospitals or clinics experienced in treating patients with APD, and with experience in LCIG treatment. Participating physicians should have been involved in the respective patient's management since initiation of LCIG therapy.

Two definitions of LCIG monotherapy were used:

1. LCIG monotherapy 1 (yes, no) at LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation with the following definition:
   LCIG monotherapy means that the patient is not on any add-on PD medication or PD therapy at the respective time point (only rescue medication is allowed).
2. LCIG monotherapy 2 (yes, no) at LCIG initiation and at 3, 6, 9, and 12 months after LCIG initiation with the following definition:
   LCIG monotherapy means that the patient is allowed to take an add-on PD medication or PD therapy at the respective time point, however, only in the evening after the daily LCIG infusion hours are completed.

This study consists of one single visit. The observational period is mainly retrospective and includes one cross-sectional study visit. Data gathered were derived from the time prior to initiation of LCIG therapy until the day of the study visit.

Setting

In this analysis the following countries were included: Austria, Bulgaria, Canada, Czech Republic, Estonia, Spain, Greece, Croatia, Hungary, Ireland, Israel, Netherlands, Romania, Sweden

Subjects and Study Size, Including Dropouts

In total, 412 patients were enrolled. Three patients did not fulfill the inclusion criteria and, thus, the full analysis set (FAS) comprises 409 patients.

Variables and Data Sources

Patient data and site characteristics were to be documented on the electronic data recording form (eDRF). In addition, patients were asked to complete the following questionnaires: Parkinson’s Disease Quality of Life Questionnaire (PDQ-8), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease - Rating Scale (QUIP-RS), Parkinson's Disease Sleep Scale-2 (PDSS-2), and Beliefs Medication Questionnaire (18-item BMQ). Physicians should complete the following questionnaires: Unified Parkinson's Disease Rating Scale (UPDRS), Non-Motor Symptoms Scale for Parkinson’s Disease (NMSS), Mini-Mental State Examination (MMSE), and Healthcare Resource Utilization Questions (HCRU). Data from questionnaires were also to be recorded on the eDRF.

Results

Site characteristics

Patients were recruited from 49 sites, which were mainly composed of university hospitals (56.5%) or public hospitals (34.8%). The majority of participating physicians were neurologists specialized in movement disorders (60.8%). In the majority, international treatment guidelines were followed (55.4%). National guidelines were used by 44.6%. Only local treatment algorithms (17.6%) were heeded to a lower extent.

Patient characteristics

Out of 412 enrolled study participants, 409 patients were included in the FAS. Almost two thirds (65.3%) of the patients were male. Almost all patients were white (99.0%), which may be mainly explained by the choice of included countries. The majority of included patients came from urban centers or from towns larger than 10.000 inhabitants (70.9%).

Mean patient age was 69.1 years (range 42-86). Patients had been diagnosed with Parkinson's disease on average 12.8 years before LCIG initiation, at a mean age of 55.5 years (range: 27-74). Notably, motor fluctuations, the pathognomonic symptom of advanced Parkinson's disease, started on average 7.3 years after diagnosis, i.e. markedly earlier. The majority of patients also suffered from additional motor symptoms: wearing-off occurred in 92.6%, and started almost at the same time (7.5 years) as motor fluctuations. Morning akinesia occurred in more than two thirds of patients (68.8%) and started on average shortly thereafter, 7.7 years after diagnosis. Dyskinesia occurred on average the latest (after 8.4 years), but also occurred in the majority of patients (82.8%). The various motor phenotypes of Parkinson's disease occurred similarly often: akinetic rigid phenotype was documented in 38.7%, tremoric phenotype in 27.0%, and the mixed phenotype in 32.4%.

Historical treatment of Parkinson's disease included the majority a dopamine agonist (52.6%), and in 7.3% device-aided therapy (other than LCIG); 4.9% had been treated with apomorphine infusions, and 2.7% had received deep brain stimulation. LCIG was on average initiated 12.8 years (3-36) after diagnosis, i.e. for many patients several years after many of the above described motor symptoms had emerged, yet.

Clinical status upon initiation of LCIG

Immediately before starting LCIG therapy, patients had a considerable burden of motor symptoms, with a mean duration of 3.7 h of dyskinesia, and an "off" time of 6.1 h per day. In more than two thirds of all patients (67.2%), dyskinesias were reported to be at

least mildly disabling. In addition, almost all patients suffered from bradykinesia (97.8%) and rigidity (95.1%), and almost three fourths suffered from gait impairment (74.8%).

The wide majority (85.6%) initiated LCIG therapy with a nasojejunal test phase. In patients who were on strict monotherapy with LCIG (monotherapy 1) after 12 months, a nasojejunal test phase had been used considerably more frequently.

Status at patient visit

At the time of the patient visit, i.e. after treatment of LCIG of at least 12 months, the majority of patients still reported motor symptoms such as bradykinesia (88.0%), rigidity (77.0%), or gait impairment (68.9%). However, the prevalence of those symptoms had markedly decreased compared to the time before LCIG initiation. Treatment-related side effects had remained largely unchanged in comparison to the status before LCIG initiation, with the exception of punding, which was reported more often (10.8%; before LCIG initiation: 7.8%).

After LCIG initiation 39.1% of the patients needed less help with daily activities or home care, 20.3% of the patients needed more help. For 23.5% of the patients the amount of help needed did not change since LCIG initiation.

Patient-reported outcomes

Several PROs were assessed at the patient visit by use of various questionnaires. Results largely pointed to a low- to mid-grade symptom burden.

Physician-reported outcomes

Total UPDRS score and scores of different parts of the UPDRS were documented as available before start of LCIG and at the patient visit as part of physician-reported assessments. Most physician-reported outcomes were stable or showed improvements after at least 12 months of treatment with LCIG.

LCIG monotherapy

Patients were on average on treatment with LCIG for almost three years (35.8 months) at the time of the study visit. After LCIG initiation, the percentage of patients on monotherapy increased 3 months after LCIG initiation to approximately the double rate, from 13.2% to 28.1% (monotherapy 1) and from 24.7% to 51.6% (monotherapy 2). Thus, focusing on monotherapy 1, more than a fourth of patients did not require additional PD medication (except for rescue medication) anymore. In accordance,

considerably fewer patients had add-on medication documented at month 3 (62.3% to 38.6%) and thereafter during ongoing LCIG treatment as compared to before LCIG initiation. Patients initially requiring add-on therapy, who then changed their regimen to monotherapy took on average approximately 3 months (89.5 days) until monotherapy was achieved.

The percentage of patients on monotherapy 12 months after LCIG initiation, i.e. the primary endpoint, was even higher, i.e. 29.3% (monotherapy 1) and 52.3% (monotherapy 2). The percentage of patients with add-on PD medication 12 months after LCIG initiation was 40.1%. Also in the years thereafter, the percentage of patients on monotherapy 1 remained largely stable, and only decreased slightly in year 5 (27.5%). Patients reaching monotherapy remained on monotherapy (monotherapy 1) for approximately 2.0 years; also monotherapy with night medication was on average maintained for approximately 2.1 years.

Levodopa was the co-medication that was administered most frequently: before LCIG initiation, almost all patients who took a PD medication other than LCIG were on levodopa (93.9%); at month 12, fewer than two thirds (63.8%) still received levodopa. Similar decreases occurred in the other, most frequently documented drugs such as dopamine agonists (decrease from 42.2% to 40.4%) and MAO inhibitors (decrease from 22.5% to 16.9%).

As expected, the total levodopa equivalent daily dose (LEDD) increased over time, from 1585.4 mg before LCIG initiation to 2148.9 mg at month 12 after LCIG initiation.

Infusion details

At LCIG initiation, the mean total LCIG dose per day was 65.6 ml (range 19.0-167.7 ml), which then increased only slightly by the time point 12 months (69.2 ml). Also the morning dosages (8.6 ml vs. 8.5 ml), the continuous dosages (3.5 ml/h vs 3.6 ml/h) and the infusion duration (15.7 h/d vs. 16.1 h/d) at LCIG initiation and after 12 months remained largely similar. Changes of LCIG dosage was mainly undertaken due to lack of efficacy (48.9%), followed by side effects (35.5%), or the need to improve a specific symptom (34.5%). A substantial change of LCIG dosage, defined as a change of at least 20%, was on average conducted not before 409.2 days, i.e. more than an entire year, after LCIG initiation.

Safety results

The retrospective design of the study did not allow identification of comprehensive safety data. However, previously adverse reactions, and adverse events, product

complaints and pregnancies occurring after patient authorization were reportable within this study. All ADRs that occurred previously were merely to be collected within the eCRF. The most frequently documented ADRs by SOC were Product issues (27 affected patients; 6.6%), followed by Injury, poisoning and procedural complications (25 affected patients; 6.1%), Nervous system disorders (23 affected patients; 5.6%), and Infections and infestations (22 affected patients; 5.4%). In 21.5%, an ADR led to a LCIG dose decrease, in 4.7% of the cases LCIG was temporarily stopped. After patient authorization, no AE, and no pregnancy occurred. Three product complaints were reported that were all device-related (PTs: device connection issue, device kink, device dislocation).

Discussion

The patient cohort reflected a valid sample of patients diagnosed with advanced Parkinson's disease. The male preponderance is in accordance with most, albeit not all epidemiologic studies. Also the relatively high patient age in line with known increase of prevalence of Parkinson's disease; in addition, development of advanced Parkinson's disease over time results naturally in a higher patient age.

Data indicated that a substantial rate of patients could be managed with LCIG monotherapy. Overall percentage of patients on LCIG monotherapy increased over time until month 12 and remained largely beyond, with data points up to 5 years of LCIG treatment. Consistently, the percentage of patients on LCIG with add-on therapy decreased over time. Thus, LCIG therapy provided many patients relief from polypharmacy, while at the same time ensuring effective treatment: many patients appeared to be well controlled, with most symptoms scores showing stable disease burden.

The management of LCIG initiation, along with placement of the PEG-J tube was managed in various ways at the respective sites, which was an expected finding in this international study, with obvious national and local differences. The majority of patients was hospitalized not only during PEG-J placement, but also during the titration phase (78.7%). On the other hand, approximately 1 in 10 patients (9.8%) were not hospitalized at all. Of note, while the mean duration of titration was approximately one week (7.5 days), the mean time between titration start and discharge from hospital was much longer (22 days). Possible explanations for such extended hospitalizations include the possibility that management of PEG-J related issues may have required more long-term hospital care.

Notably, infusion details, including total dose per day, morning dosages and infusion durations remained largely similar throughout treatment. Substantial treatment changes

were performed rarely, on average for the first time after more than a year after treatment initiation.

Being on monotherapy 1 had significant associations with several parameters, including, most notably, fewer motor symptoms, prior use of dopamine agonists, and on the physician's end, a higher approximate number of APD patients treated with LCIG per year. Thus, physician's experience and training appeared to be an important factor in managing patients on LCIG treatment alone.