Parkinsonism and Related Disorders 19 (2013) 339–345

Contents lists available at SciVerse ScienceDirect

Parkinsonism and Related Disorders

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

Levodopa–carbidopa intestinal gel in advanced Parkinson's disease open-label study: Interim results

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ARTICLE INFO

Article history:
Received 2 August 2012
Received in revised form
12 November 2012
Accepted 29 November 2012

Keywords:
Parkinson's disease
Levodopa–carbidopa intestinal gel
Motor fluctuations
PEG-J procedure
Pump administration

ABSTRACT

Levodopa–carbidopa intestinal gel (LCIG) delivered continuously via percutaneous endoscopic gastrojejunostomy (PEG-J) tube has been reported, mainly in small open-label studies, to significantly alleviate motor complications in Parkinson's disease (PD). A prospective open-label, 54-week, international study of LCIG is ongoing in advanced PD patients experiencing motor fluctuations despite optimized pharmacologic therapy. Pre-planned interim analyses were conducted on all enrolled patients ($n = 192$) who had their PEG-J tube inserted at least 12 weeks before data cutoff (July 30, 2010). Outcomes include the 24-h patient diary of motor fluctuations, Unified Parkinson's Disease Rating Scale (UPDRS), Clinical Global Impression-Improvement (CGI-I), Parkinson's Disease Questionnaire (PDQ-39), and safety evaluations. Patients (average PD duration 12.4 yrs) were taking at least one PD medication at baseline. The mean (±SD) exposure to LCIG was 256.7 (±126.0) days. Baseline mean "Off" time was 6.7 h/day. "Off" time was reduced by a mean of 3.9 (±3.2) h/day and "On" time without troublesome dyskinesia was increased by 4.6 (±3.5) h/day at Week 12 compared to baseline. For the 168 patients (87.5%) reporting any adverse event (AE), the most common were abdominal pain (30.7%), complication of device insertion (21.4%), and procedural pain (17.7%). Serious AEs occurred in 60 (31.3%) patients. Twenty-four (12.5%) patients discontinued, including 14 (7.3%) due to AEs. Four (2.1%) patients died (none deemed related to LCIG). Interim results from this advanced PD cohort demonstrate that LCIG produced meaningful clinical improvements. LCIG was generally well-tolerated; however, device and procedural complications, while generally of mild severity, were common.

1. Introduction

Dopamine replacement with levodopa was first shown to reduce clinical signs and symptoms of Parkinson's disease (PD) in the 1960s [1], and since then has been the mainstay of PD treatment [2,3]. However, the majority of patients who respond to levodopa eventually experience a narrowing of the therapeutic window, resulting in motor complications, including "Off" time (when medication has worn off and parkinsonian symptoms re-emerge) and levodopa-induced dyskinesias [2]. These complications can be a major source of distress and disability for patients and are difficult to treat [4,5]. "Off" time is of particular interest, as this is arguably the biggest contributor to functional impairment in patients with advancing PD [6–9]. Hence, the ability to reduce "Off" time without an associated increase in dyskinesia is an important goal of therapy development.

The mechanisms behind levodopa-associated motor complications are not fully understood, but are hypothesized to be related to the inability of conventional levodopa regimens to provide physiologic, continuous dopaminergic stimulation [2,5,10]. Levodopa is rapidly metabolized and has a short plasma half-life of approximately 90 min (when administered with carbidopa), thus requiring frequent, repeated dosing and producing fluctuations in drug

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http://dx.doi.org/10.1016/j.parkreldis.2012.11.020

plasma levels [2,11]. It is absorbed mainly in the proximal small intestine, and gastric emptying plays an important role in determining the absorption of conventional oral levodopa formulations. Impaired gastric emptying is common in PD, and likely contributes to the unpredictable motor responses observed with orally-dosed levodopa [12,13]. Levodopa–carbidopa intestinal gel (LCIG) is a carboxymethylcellulose aqueous gel delivered directly to the proximal jejunum via a percutaneous endoscopic gastrojejunostomy (PEG-J) tube connected to a portable infusion pump [14,15]. Continuous infusion of LCIG bypasses gastric emptying, thereby avoiding this potential cause of suboptimal levodopa response [16].

Early studies used differing preparations of levodopa for intestinal infusion, but yielded consistent results. Stocchi and colleagues [17] reported that continuous nasoduodenal-tube administration of levodopa methyl ester for 6 months in 6 advanced PD patients significantly reduced trough plasma levels of levodopa, total "Off" time and "On" time with dyskinesias. Similarly, 24 patients with advanced PD who received daytime levodopa intestinal infusion showed a significant improvement of PD symptoms and quality of life (QOL) measures compared to standard oral therapy [18].

The LCIG (Duodopa®) formulation of levodopa is approved for clinical use in more than 30 countries and has been used in approximately 2800 patients world-wide. The French Duodopa Study Group recently reported retrospective safety and efficacy data from all patients in France who had received LCIG [19]. Of the 75 patients assessed for efficacy, motor fluctuations improved in 96.0% and dyskinesia improved in 94.7%. Only 1 patient reported worsening of motor symptoms leading to discontinuation. Adverse events (AEs) related to technical problems, gastrostomy procedure, and levodopa treatment were reported by 62.6%, 19.8%, and 2.2% of patients, respectively. Of the 91 patients assessed for safety, 18.7% ($n = 17$) discontinued treatment [19]. A recent meta-analysis focusing on LCIG infusion in advanced PD patients reported a consistent efficacy pattern in the reduction of levodopa-related motor complications, including improvement in motor scores and QOL scores [20]. While the AE profile of LCIG was similar to that of oral levodopa, technical problems with the infusion system occurred in up to 70% of patients [20]. However, most of these problems were mild to moderate in severity, of short duration, and led to only small numbers of discontinuations. These technical complications and AE profile remain to be substantiated by a controlled, long-term prospective study.

We present here the interim results of a large, open-label, international, safety trial of LCIG in patients with advanced PD and motor fluctuations despite optimized standard therapy. The study was primarily designed to collect long-term safety data to support the registration of LCIG in the United States, while also providing long-term efficacy data. The study represents the largest cohort of advanced PD patients treated with LCIG to date.

2. Patients and methods

2.1. Study design

A phase 3, open-label, 54-week trial of LCIG in patients with advanced PD and motor fluctuations despite optimized standard therapy is ongoing (Study start: January 2008; CT.gov identifier NCT00335153). There are 86 study sites in 16 countries world-wide, with planned enrollment of 320 patients. The study protocol was approved by each institution's respective internal review board or ethics committee, and written informed consent was obtained from each patient prior to any procedure being performed. The interim analysis was primarily conducted to ensure that the operational aspects of the study were adequate and optimized for the ongoing pivotal trials of LCIG. The primary time point for the evaluation of efficacy is Week 12, to reflect the primary efficacy time point defined in the randomized, active-comparator pivotal trials.

2.2. Patients

The interim analysis presented here includes all patients who had their PEG-J tube inserted 12 weeks before the data cutoff date of July 30, 2010. Major inclusion criteria include: age $\geq$ 30 years; diagnosis of PD according to United Kingdom PD Society Brain Bank criteria; levodopa-responsive, with significant motor fluctuations despite optimized PD therapy, as judged by the investigator; recognizable "Off" and "On" states, with a minimum 3 h "Off" time per day at baseline, and the ability (by patient or caregiver) to competently maintain a standard PD diary. Major exclusion criteria include: unclear PD diagnosis, or suspicion of a Parkinson-plus syndrome or other neurodegenerative disorder; history of surgical treatment for PD; Mini-Mental State Examination score $<$ 24; presence of sleep attacks and clinically significant impulsive behaviors during the 3 months prior to screening; current primary psychiatric diagnosis of acute psychotic disorder, bipolar disorder, or major depressive disorder; or a history or presence of any condition that might interfere with absorption, distribution, metabolism, or excretion of study drug or any contraindication to placement of intrajejunal PEG-J tube.

2.3. LCIG dosing

LCIG contains 20 mg/mL levodopa and 5 mg/mL carbidopa and is supplied in cassettes containing 100 mL of gel solution, a sufficient daily dose for most patients [15,21,22]. LCIG is administered with a portable infusion pump (CADD-Legacy® Duodopa, Smiths Medical, MN, USA). Individually-optimized dosing of LCIG was delivered over a 16-h period, administered as a morning bolus followed by continuous infusion, and if needed, intermittent extra doses (patient-initiated based on symptom experience). The volume of the morning bolus was individualized for each patient based initially on the total oral levodopa dose during the screening period. The total morning dose was usually 5–10 mL, corresponding to 100–200 mg levodopa, and did not exceed 20 mL (400 mg levodopa). Extra doses were adjusted individually during the titration period and remained fixed unless adjusted by the investigator. Extra doses were permitted at intervals of no less than 2 h. A maximum of 8 extra doses was possible during a 16-h treatment day. However, the use of 5 extra doses per any given 16-h period resulted in an adjustment of the following day's continuous rate.

Initially, LCIG was administered via nasojejunal (NJ) tube (Bengmark Nutricia Ch10, Cook NJFT-10, or Stabilife Ch10 nasointestinal tube) for 2–14 days to assess the response to LCIG. If LCIG was tolerated and a clear treatment response was observed, patients underwent PEG-J tube placement for long-term administration. PEG (15 Fr FREKA) and J-tubes (9 Fr J-extension) were placed in a single procedure under local anesthesia using endoscopic and/or fluoroscopic guidance. Patients were hospitalized for NJ-tube insertion (with the option of returning home after initial LCIG dose optimization) and for PEG-J tube placement with dose optimization based on hourly monitoring of the patient's motor state.

2.4. Concomitant medication

Except for LCIG, all other PD drugs (including dopamine-agonists, apomorphine, and catechol-O-methyl transferase inhibitors) were stopped prior to the NJ treatment period; these medications could be re-initiated after 28 days at the investigator's discretion. Oral levodopa–carbidopa medication (immediate-release tablets) could be used at night, when the LCIG pump was turned off for 8 h, but was not allowed within 2 h of the morning bolus.

2.5. Efficacy

Baseline motor symptoms were assessed using a 24-h diary (Hauser diary [8]) for 3 consecutive days prior to NJ-tube insertion. Patients recorded motor symptom status every 30 min throughout the waking day. Due to the variation in waking hours among patients and of individual patients across days in this advanced PD cohort, PD symptom diary data were *normalized* to a 16-h waking time. The normalization was calculated as (observed hours per day) $\times$ (16/waking hours). For example, a patient with 12 h of awake symptom diary data had their "Off" time adjusted by a factor of 1.33 (16 h/12 h). Alternatively, a patient with 20 h of awake symptom diary data had their "Off" time adjusted by a factor of 0.8 (16 h/20 h). All non-waking hours were denoted as "sleep" time. For the 3 days before each scheduled visit, patients were instructed to record motor symptoms using the diary. All variables describing diary-based motor symptoms represent the average of three days' results and were normalized as above. At the time of NJ-tube placement, investigators rated patients on the Clinical Global Impression (CGI) – Severity (scored 1 [normal] to 7 [most extremely ill]).

"Off" time is the study's primary efficacy measure. Secondary efficacy measures include: "On" time without troublesome dyskinesia, which is a sum of two diary entries ("On" time with non-troublesome dyskinesia and "On" time without dyskinesia); "On" time with troublesome dyskinesia; the Unified Parkinson's Disease Rating Scale (UPDRS) scores – Total (sum of Parts I, II, and III), Part I (mentation, behavior, and mood), Part II (activities of daily living), Part III (motor examination; measured in the "On" state and 1–4 h after the LGIC morning bolus); CGI-Improvement (scored 1 [very much improved] to 7 [very much worse])