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Initiation and dose optimization for levodopa-carbidopa intestinal gel: Insights from phase 3 clinical trials

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ABSTRACT

Background: Levodopa-carbidopa intestinal gel (LCIG) provides continuous infusion and reduces "off" time in advanced Parkinson's disease (PD) patients with motor fluctuations despite optimized pharmacotherapy.
Methods: Clinical experience with 2 LCIG dosing paradigms from phase 3 studies was examined. In an open-label, 54-week study, LCIG was initiated as daytime monotherapy via nasojejunal (NJ) tube then switched to percutaneous endoscopic gastrojejunostomy (PEG-J) tube; adjunctive therapy was permitted 28 days postPEG-J. In a 12-week, double-blind, placebo-controlled, double-dummy trial, patients continued stable doses of existing anti-PD medications, but LCIG replaced daytime oral levodopa-carbidopa and was initiated directly via PEG-J.
Results: In the open-label study, 92% of 354 patients received monotherapy at post−PEG-J week 4; mean titration duration was 7.6 days; dosing remained stable post-titration (mean total daily dose [TDD] was 1572 mg at last visit). In the double-blind trial, 84% received polypharmacy; mean titration took 7.1 days for the LCIG arm (TDD post-titration: 1181 mg; $n = 37$). At post−PEG-J week 4, mean "off" time with LCIG was reduced by 3.9 h (open-label/monotherapy study) and 3.7 h (double-blind/polypharmacy trial). NJ treatment (open-label study only) required an additional procedure with related adverse events (AEs) and withdrawals. The most common AEs during PEG-J weeks 1−4 in the open-label/monotherapy and double-blind/polypharmacy trials, respectively, were complication of device insertion (35%, 57%) and abdominal pain (26%, 51%). Discontinuations due to nonprocedure/nondevice AEs were low (2.2%, 2.7%).
Conclusion: These results support the option of initiating LCIG with or without NJ and as either monotherapy or polypharmacy.

1. Introduction

Although levodopa has been established as the gold standard therapy for Parkinson's disease (PD) [1–5], disabling motor complications emerge with ongoing oral levodopa treatment [2–7]. Levodopa-associated motor complications are thought to develop at least in part due to pulsatile dopaminergic stimulation arising from oral levodopa's short half-life and oral route of administration [8–10]. In advanced PD patients, continuous drug delivery with levodopa-carbidopa intestinal gel (LCIG) significantly decreased

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"off" time versus standard oral levodopa-carbidopa immediate release (LC-IR) tablets in randomized [11–13] and open-label studies [14–19].

In countries where LCIG is currently approved, it is typically initiated as monotherapy for advanced PD via a temporary nasojejunal (NJ) tube. However, prior LCIG studies have generally been small, often retrospective, and provided limited information regarding initiation and titration methodology [13,20,21]. We, therefore, retrospectively examined clinical experiences with LCIG initiation and titration, along with efficacy and safety data, from the recent phase 3 studies supporting United States registration, in advanced PD.

One study was an international, open-label, long-term safety, 54-week study of LCIG first as monotherapy via NJ tube followed by percutaneous endoscopic gastrojejunostomy (PEG-J) tube in 354 patients [14,15]. The other registration study was a 12-week, randomized, double-blind, double-dummy, pivotal trial, with direct-to-PEG-J titration along with stable adjunctive therapy, in 71 patients [11]. These studies provided an opportunity to evaluate LCIG initiation (1) as monotherapy or as adjunctive therapy (polypharmacy), and (2) via NJ prior to PEG-J or directly via PEG-J.

2. Methods

These studies of LCIG (levodopa 20 mg/mL, carbidopa monohydrate 5 mg/mL) had similar eligibility criteria and safety and efficacy endpoints [11,14,15]. All patients had advanced, levodopa-responsive PD with severe motor fluctuations (≥3 h of "off" time/day) despite optimized anti-PD pharmacotherapy. Patients were titrated for dose optimization, maximizing functional "on" time without troublesome dyskinesia (i.e. without dyskinesias that interfere with function or cause meaningful discomfort) while minimizing "off" episodes and troublesome dyskinesia. Initial titration periods were up to 2 weeks; completion was defined as 2 consecutive days with no dose adjustments. The key efficacy endpoint was change in "off" time from baseline assessed by patient diaries [22].

In both studies, after a 16-h daily infusion, the pump was turned off at night and oral LC-IR was permitted. For this report, "LCIG monotherapy" is defined as LCIG alone during the 16-h infusion day with or without LC-IR at night. Other levodopa formulations and apomorphine were not permitted. Efficacy and safety analyses presented are per individual study protocol unless otherwise noted. No formal statistical comparisons between studies were performed.

2.1. Study designs

2.1.1. Open-label study

Patients were to discontinue all adjunctive anti-PD medications (e.g. dopamine agonists, amantadine, catechol-O-methyl transferase inhibitors) prior to receiving LCIG (Fig. 1A) [14,15]. LCIG was initiated via a temporary NJ tube to confirm levodopa response and to optimize LCIG dosing before PEG-J placement. LCIG was titrated as monotherapy (with only LC-IR tablets permitted at night). At the investigator's discretion, adjunctive anti-PD medications could be reinitiated after 28 days of treatment via PEG-J. Rescue medication, if needed, was extra LCIG doses (or LC-IR if LCIG was interrupted).

2.1.2. Double-blind trial

LCIG infusion, initiated via PEG-J, plus placebo capsules was compared with encapsulated LC-IR tablets plus placebo gel infusion (Fig. 1B) [11]. LCIG/LC-IR was titrated during the first 4 weeks, followed by an 8-week treatment period with a stable regimen. All concomitant anti-PD medications (except apomorphine/other levodopa formulations) were continued and kept stable throughout the 12-week study. Rescue medication, if needed, was open-label LC-IR tablets.

2.2. LCIG titration schemes

2.2.1. Open-label study

The NJ and PEG-J titration phases each were to be completed 2–14 days. For the initial NJ phase, patients were hospitalized ≤14 days as needed for titration. The starting LCIG dose was calculated from the total daily dose (TDD) of LC-IR taken the day before NJ placement. The LCIG TDD consisted of individually adjusted morning, continuous maintenance, and extra doses.

The initial morning dose was calculated as a proportion of the patient's usual morning dose of oral levodopa (typically 60–80%,

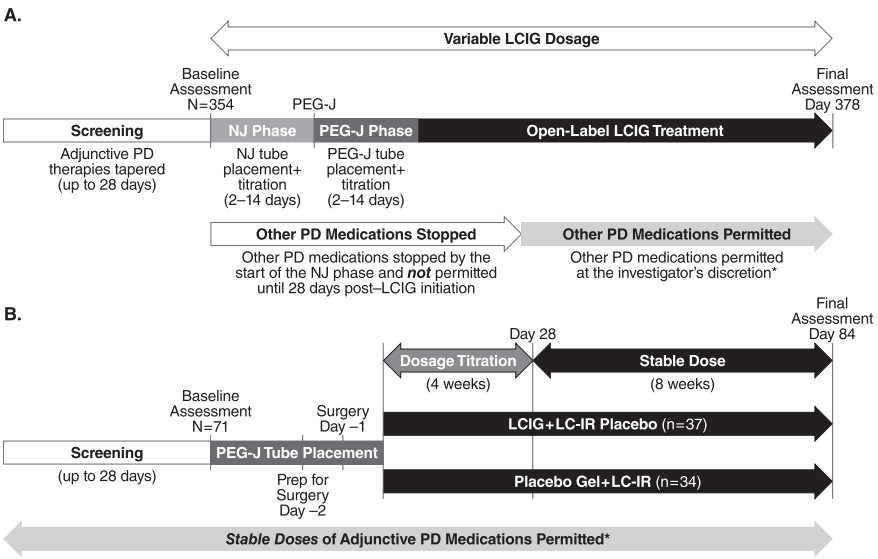

Fig. 1. Study designs: A. Open-label study. B. Double-blind study. *Sustained-release levodopa-carbidopa, other levodopa formulations, and apomorphine excluded. Levodopa-carbidopa intestinal gel (LCIG); levodopa-carbidopa immediate release (LC-IR); nasojejunal (NJ); Parkinson's disease (PD); percutaneous endoscopic gastrojejunostomy (PEG-J).

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