Basal Ganglia 5 (2015) 95–99

Contents lists available at ScienceDirect

Basal Ganglia

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

New developments in continuous jejunal infusion of levodopa/carbidopa in advanced Parkinson's disease

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ARTICLE INFO

Article history:
Received 20 July 2015
Received in revised form 1 October 2015
Accepted 1 October 2015

Keywords:
Duodopa®
Duopa®
Motor complications
Non-motor symptoms
Quality of life
Treatment adherence

ABSTRACT

Levodopa-associated motor fluctuations and dyskinesia in patients with Parkinson's disease (PD) are often difficult to control by the oral administration of levodopa. Continuous infusion of a levodopa/carbidopa intestinal gel (LCIG) may represent a feasible treatment option for this patient population. To start LCIG infusion, a temporary nasoduodenal/nasojejunal tube should be considered to show that the patient responds favorably, before a permanent percutaneous endoscopic gastrostomy with jejunal tube (PEG-J) is placed. The present review focuses on recently published key studies on the efficacy and safety of LCIG treatment in advanced PD. The results provide robust evidence of a marked reduction of OFF-fluctuations and dyskinesia, thereby also improving the quality of life of these severely disabled patients. LCIG treatment is therefore a promising alternative to continuous subcutaneous apomorphine infusion or deep brain stimulation in advanced PD patients with severe motor fluctuations.

Contents

1. Introduction

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder and characterized by the motor symptoms akinesia, rigidity, rest tremor, and postural instability as well as a range of non-motor symptoms. Although the oral symptomatic treatment of motor symptoms in PD has been improved during the previous decades, the gold standard for the therapy of motor symptoms remains levodopa in combination with an inhibitor of aromatic amino acid decarboxylation such as carbidopa. However, levodopa-associated motor fluctuations and dyskinesia often pose a major challenge in advanced PD and are difficult to control by the oral administration of levodopa. Alternatives include, e.g., continuous subcutaneous apomorphine infusion (CSAI), deep brain stimulation, and continuous intestinal infusion of levodopa/carbidopa by means of a gel (LCIG, Duodopa® in Europe; Duopa® in the US) [1]. Apart from the continuous drug delivery achieved with LCIG by the direct administration into the small intestine, the stomach passage can be avoided, which may otherwise lead to insufficient active substance absorption due to PD-related irregular gastric emptying [2]. The placement of the intestinal tube (i.e., PEG-J) for LCIG requires surgery with only local anesthesia by most gastroenterology departments. The PEG-J is usually performed after a test phase with a transnasal jejunal tube over several days. Nasal titration is not required in Europe and in the recently issued

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http://dx.doi.org/10.1016/j.baga.2015.10.001
2210-5336/

FDA approval for Duopa®, but recommended in Switzerland [3–5]. Duodopa®/Duopa® is indicated for the treatment of advanced levodopa/responsive PD with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results. The present review focuses on new developments with respect to LCIG infusion in advanced PD with special emphasis on four recently published clinical trials.

2. Olanow et al. [6]

The randomized, double-blind, double-dummy, double-titration HORIZON study included 71 patients with advanced PD, who did not achieve satisfactory control of OFF-times with optimized drug therapy (oral levodopa/carbidopa, dopamine agonist and at least one other PD medication) (Table 1) [6]. Participants received stable doses of levodopa for at least 4 weeks before enrolment in the study and had at least 3 h of OFF-time per day as measured by a home diary. Subjects receiving sustained-release levodopa/carbidopa, Stalevo® (Orion Pharma, Finland), or other formulations of levodopa were permitted after conversion to equivalent doses of immediate-release levodopa/carbidopa at least 4 weeks before study entry. Additional PD medication was permitted, provided that its dosage had remained stable for 4 weeks prior to randomization and no dose adjustments were made during the study.

Subjects were randomized to treatment with LCIG plus oral placebo or to oral levodopa/carbidopa plus placebo intestinal gel. Compared to baseline, the mean daily OFF-time as primary outcome measure was reduced by 4.04 h/d (standard error [SE] 0.65) in the LCIG group and by 2.14 h/d (SE 0.66) in the placebo group. This difference was highly significant in favor of LCIG treatment ($p = 0.0015$). At the same time, ON-time without troublesome dyskinesia as secondary outcome measure was increased in the LCIG group by 4.11 h/d (SE 0.75) vs. 2.24 h/d (SE 0.76) in the placebo group ($p = 0.0059$). The Parkinson Disease Questionnaire-39 (PDQ-39) Summary Index values were reduced as compared to the baseline value by 10.9 points (SE 3.3) in the LCIG group and by 3.9 points (SE 3.2) in the placebo group ($p = 0.0155$). Furthermore, the mean score on the Clinical Global Impression-Improvement (CGI-I) scale (7-point scale from 1 = very much improved to 7 = very much worse) was 2.3 points (SE 0.4) in the LCIG group and 3.0 points (SE 0.4) in the placebo group at the final examination ($p = 0.026$). Although almost all study subjects experienced adverse effects (95% in the LCIG group, 100% in the placebo group), that occurred mainly as a result of the tube placement, most were temporary and limited to the first week following PEG-J tube placement. Four of the 71 patients showed signs of polyneuropathy (1 in the LCIG group, 3 in the placebo group). No cases of Guillain-Barré syndrome were observed [6].

3. Slevin et al. [8]

In contrast to the HORIZON study design, in which no dose adjustments were permitted after the titration phase, continuous adjustment of the LCIG dose is standard practice in Europe. This practice corresponds to the protocol of the 1-year, open-label HORIZON extension study published by Slevin et al. [8] (Table 1). Prior to a new titration phase, the LCIG-naive group that received placebo during the HORIZON study was switched to LCIG. Due to tapering of the other PD medication and the continuous LCIG dose adjustment, 65% of all patients were treated with a levodopa monotherapy consisting of LCIG with or without oral levodopa during the night at the end of the study. In the LCIG-naive patients, start of LCIG infusion led to a mean OFF-time reduction of 2.34 h/d (SD 2.78; $p < 0.001$) starting from BL 5.08 h/d (SD 2.03), while in the LCIG-treated group (patients treated with LCIG during the HORIZON study), continuation of LCIG resulted in a moderate mean reduction from BL 3.11 h/d (SD 2.56) of 0.42 h/d (SD 2.67; $p = 0.377$). Interestingly, the combined effect on OFF-time in the pivotal trial plus extension was the same for both groups irrespective of early versus later start of LCIG-treatment. During both consecutive studies, OFF-time with 6.3 h/d (SD 1.7) at BL decreased 4.04 h/d (SE 0.65) and 0.42 h/d (SD 2.67) in the LCIG-group versus the LCIG-naïve group where OFF-time with 7.0 h/d (SD 2.1) at BL decreased 2.14 h/d (SE 0.66) and 2.34 h/d (2.78), respectively.

The mean increase of ON-time without troublesome dyskinesia was 2.19 h/d (SD 3.7; $p = 0.005$) in the LCIG-naive and 1.0 h/d (SD 2.58; $p = 0.036$) in the LCIG-treated group. The improvement in the LCIG-treated group is possibly explained by the fact that the LCIG dose was optimized at the start of the extension study and that dose adjustments were now permitted throughout the entire study duration (Table 1).

No significant changes to quality of life were observed during the extension study. However, the CGI-I score showed significant improvement in both groups (by 2 points each; $p < 0.001$) and the majority of patients improved very much (~40%), much (>27%) or minimally (>13%).

It was possible to assess the safety of LCIG independently of complications caused by the tube placement, as the duodenal tube had already been placed during the HORIZON study, 12 weeks prior to the start of the extension study [6]. With regard to the incidence of potential levodopa-associated adverse effects such as dyskinesia, hallucinations and orthostatic hypotension, no difference was observed between the LCIG-treated and LCIG-naive groups during the first 4 weeks. 77% of patients experienced adverse effects possibly or probably related to the treatment. However, these were generally mild to moderate. The incidence of adverse effects continuously decreased over the course of the study duration (from 52% to 24%, evaluation every 30 days). The most common serious adverse effects were complications associated with the tube placement (5%), abdominal pain (3%), asthenia (3%) and pneumonia (3%). A not severe polyneuropathy was observed in 9.7% of patients (3 LCIG-naive, 3 LCIG-treated), which is within the normal rates of polyneuropathy in PD [8]. Treatment adherence was high at 89% over the course of a year.

4. Fernandez et al. [9]

The study design of the largest prospective open-label LCIG study ($n = 354$) by Fernandez et al. reflects standard procedure in Europe (Table 1) [9]. In this study, the initial LCIG monotherapy dosage was determined via nasal titration. Additional PD medication was only permitted after subsequent dose titration (in this case, 28 days after PEG-J placement) and dose adjustments were permitted throughout the entire study duration. The final data confirm the results of the HORIZON study. The mean daily OFF-time was reduced by 65.6%, i.e., by 4.4 h/d (SD 2.9; $p < 0.001$), and the ON-time without troublesome dyskinesia increased by 62.9%, i.e., by 4.8 h/d (SD 3.4; $p < 0.001$). These improvements persisted throughout the entire treatment duration of 54 weeks. Furthermore, the CGI-I score showed that 22.4% of patients were very much improved, 55.5% were much improved and 13.7% were minimally improved. 3.1% of patients showed no change; 2.8% reported to be minimally worse and 1.0% to be much worse. The mean PDQ-39 Summary Index was 6.9 ± 14.1 points lower than the baseline value. A statistically significant mean improvement was achieved in seven of the eight PDQ-39 dimensions, social support being the only exception [9]. It should also be noted that the daily dose remained stable after initial nasal titration (mean LCIG dose of 1572 mg/d at last visit), which indicates that no obvious LCIG