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Review article

Can suitable candidates for levodopa/carbidopa intestinal gel therapy be identified using current evidence?

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ABSTRACT

Advanced Parkinson's disease (APD) is characterized by increased functional disability, caused by motor complications, the presence of axial symptoms, and emergent disease- and drug-related non-motor symptoms. One of the advanced therapies available is intrajejunal infusion of levodopa/carbidopa intestinal gel (LCIG); however, patient selection for this treatment is sometimes difficult, particularly because of overlapping indications with other alternatives.

In recent years, strong evidence has supported the use of LCIG in treating motor fluctuations associated with APD, and several clinical studies provide emerging evidence for additional benefits of LCIG treatment in certain patients. This article provides an overview of the published literature on the benefits, limitations, and drawbacks of LCIG in relation to PD symptoms, the psychosocial impact of the disease, and the quality of life of patients, with the aim of determining candidates for whom treatment with LCIG would be beneficial. According to current evidence, patients with APD (defined as inability to achieve optimal control of the disease with conventional oral treatment), a relatively well-preserved cognitive-behavioral status, and good family/caregiver would count as suitable candidates for LCIG treatment. Contraindications in the opinion of the authors are severe dementia and active psychosis.

1. Introduction

The aim of currently available conventional drug treatments of Parkinson's disease (PD; levodopa, dopamine agonists [DAs], and enzyme inhibitors) is to enhance dopaminergic transmission [1]. These treatments greatly improve symptoms of PD in the early and middle stages of the disease [2–6]. Due to the progressive nature of PD, however, the benefits are gradually reduced as the symptoms worsen [7,8]. The concept of advanced PD (APD) is broad, but it is generally associated with motor complications (fluctuations and dyskinesia that cannot be adequately controlled by standard medications), increased functional disability, the stage of the disease [9], by the presence of axial symptoms (gait and balance impairment), and by emergent disease- and drug-related non-motor symptoms (NMS; mainly neuropsychiatric complications, including cognitive impairment) [10,11],

Abbreviations: APD, Advanced Parkinson's disease; DBS, Deep brain stimulation; ICD, Impulse control disorders; LCIG, Levodopa-carbidopa intestinal gel; NMS, Non-motor symptoms; NMSS, Non-motor symptoms scale; PD, Parkinson's disease; PDSS, Parkinson's disease sleep scale; PEG, Percutaneous endoscopic gastrostomy; QoL, Quality of life

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Table 1
Summary of improvement in OFF time, ON time and dyskinesia with LCIG as reported in the literature.

Study	Change in OFF time	Change in ON time without dyskinesia	Change in ON time with dyskinesia
Antonini et al. 2007 [44] 9 patients Observational prospective	At 12 months, 9.5-fold reduction. (mean reduction from 284 to 30 min; $p < 0.01$)		Reduced by nearly 4-fold at 6 and 12 months (mean reduction from 156 to 40 min; $p < 0.01$)
Antonini et al. 2008 [45] 22 patients Observational prospective	UPDRS IV item 39 Baseline: 2.6 ± 1.2 After 1 year 1.28 ± 0.5 After 2 years: 1.48 ± 0.8 ($p < 0.05$)	No changes in dyskinesia duration	No changes in dyskinesia duration
Eggert et al. 2008 [46] 13 patients Observational prospective	Percentage of time Baseline: 50 ± 14% After 6 months: 11 ± 7% ($p < 0.01$)		Percentage of time Baseline: 17 ± 15% After 6 months: 5 ± 6% ($p < 0.01$)
Santos-García, 2010 [48] 9 patients Observational retrospective	90.9% improvement	Daily ON time showed 66.6% improvement	
Puente et al. 2010 [49] 9 patients Observational retrospective	Reduced from 9.4 ± 2.1 h to 3.1 ± 2.7 h ($p < 0.05$)	Daily ON time increased from 6.1 ± 1.9 to 12.0 ± 3.4 h ($p < 0.05$)	
Fasano et al. 2012 [52] 14 patients Observational retrospective	UPDRS IV item 39 unchanged (−7.6%) Off duration reduced by 48.6% ($p = 0.00001$)		Reduced by 38.5% ($p = 0.001$)
Antonini et al. 2013 [59] 73 patients Observational prospective	UPDRS IV item 39. OFF time duration Baseline 1.59 ± 0.96 Month 6: 0.85 ± 0.63 ($p < 0.05$) Month 12: 1.06 ± 0.73 ($p < 0.05$)		UPDRS IV item 32. Dyskinesia duration Baseline: 1.72 ± 0.98 Month 6: 1.15 ± 0.87 ($p < 0.05$) Month 12: 1.45 ± 0.83 ($p < 0.05$)
Foltynie et al. 2013 [23] 12 patients Observational prospective	Percentage of time Baseline: 29.4 ± 13.2% Follow-up 16.7 ± 22.2% ($p = 0.06$)		Percentage of time Baseline: 16.6 ± 18.6% Follow-up 8.2 ± 10.3% ($p = 0.22$)
Caceres Redondo et al. 2014 [62] 29 patients Observational retrospective	UPDRS IV item 39. OFF time duration Baseline: 58.1 ± 11.5 Follow-up: 24.6 ± 7.2 ($p < 0.05$)		UPDRS IV item 32. Dyskinesia duration Baseline: 60.6 ± 37.8 Follow-up: 48.8 ± 28.7 ($p < 0.05$).
Olanow et al. 2014 [37] 35 patient allocated to LCIG Prospective, double-blind trial	Decreased by 4.04 ± 0.65 h	Increased by 4.11 ± 0.75 h	Decreased by 1.8 ± 1.3
Slevin et al. 2015 [38] Open-label extension of ref. [37] LCIG-naive: 29 patients LCIG continuing: 33 patients	LCIG-naïve: Decreased 2.34 ± 2.78 h ($p < 0.001$) LCIG-continuing: Sustained reduction 0.42 ± 2.67 h ($p = 0.377$)	LCIG-naïve: Increased 2.19 ± 3.70 h ($p = 0.005$) LCIG-continuing: Increased 1.00 ± 2.58 h ($p = 0.036$)	
Pickut et al. 2014 [22] 37 patients Observational prospective	UPDRS IV item 39 89.5% of patients experienced improvement		UPDRS IV item 32. Dyskinesia duration 60–70% of patients experienced improvement
Sensi et al. 2014 [35] 28 patients Observational prospective	UPDRS IV item 39. OFF time duration Baseline: 2.3 ± 0.9 24 months: 48% improvement ($p < 0.00001$)		UPDRS IV item 32. Dyskinesia duration Baseline: 2.2 ± 1.1 Significant improvement after 24 months
Zibetti et al. 2014 [66] 59 patients Observational retrospective	UPDRS IV item 39. OFF time duration Baseline: 1.8 ± 0.7 Follow-up: 0.9 ± 0.5 Duration reduced by 49%($p < 0.001$)		UPDRS IV item 32. Dyskinesia duration Baseline: 1.7 ± 0.9 Follow-up: 1.2 ± 0.0.7 Duration reduced by 30% ($p = 0.002$)
Antonini et al. 2015 [70] 56 patients with data for this analysis Observational prospective	Baseline: 7.1 ± 3.5 h 12 months reduced by 4.7 ± 3.4 ($p < 0.0001$)		Baseline: 5.2 ± 4.5 h 12 months reduced by 1.7 ± 5.0 ($p = 0.023$)
Buongiorno et al. 2015 [74] 72 patients Observational prospective	Baseline: 6.8 ± 2.8 h (45% of day) Last visit: 3.0 ± 3.5 h (20% of day)		Patients with < 50% at baseline: increased from 18% to 35% at last visit Patients with > 50% at baseline: no change
Calandrella et al. 2015 [81] 35 patients	UPDRS IV item 39. OFF time duration Baseline: 2.4 ± 0.6 Follow-up 1.1 ± 0.6 ($p < 0.001$)		Dyskinesia score (UPDRS IV items 32–33) Baseline: 2.2 ± 0.7 Follow-up 1.5 ± 0.7 ($p < 0.001$)

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