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ABSTRACT

Objectives: To report the results of a national survey aimed at quantifying the current level of diffusion of Levodopa/carbidopa intestinal gel (LCIG) in Italy.

Methods: Sixty Parkinson's Disease (PD) specialists in Italy were invited to complete a survey covering issues on clinical and practical aspects of LCIG therapy.

Results: Clinical features of 905 patients were collected retrospectively. The majority of centres reported the use of a multidisciplinary team, biochemistry testing, neurophysiological and neuropsychological tests before and after treatment, in addition to caregivers' training and patient's follow as outpatients. Most centres (60%) used internal guidelines for patient selection. The overall rate of adverse events was 55.1%. Weight loss, chronic polyneuropathy and stoma infection were the most frequently reported. 40% of centres used replacement therapy with Vitamin B12 and Folic acid from the start of LCIG and continued this for the duration of treatment. The rate of discontinuation was of 25.7 % overall, with 9.5 % of cases occurring in the first year. The main causes of withdrawal were device-related complications, disease progression (comorbidity, severe dementia) and caregiver and / or patient dissatisfaction.

Conclusions: In Italy LCIG infusion is managed in a uniform manner at a clinical, practical and organizational level even though the selection criteria are not standardized through the country. The high percentage of patients remaining on treatment in the short- and long-term follow-up confirms effectiveness of treatment, careful follow-up, and appropriate patient and caregivers training.

Background

Levodopa/Carbidopa intestinal gel (LCIG) is currently approved in 30 European countries and Italy was one of the first countries to implement this in 2005. LCIG is effective and safe in advanced Parkinson's Disease (PD) [1-2], but the reported rate of withdrawal varies and often causes of discontinuation are not clearly addressed [1-4].

Organization of the centres on comprehensive therapy management is critical in achieving a good long-term outcome and preventing discontinuation. Proper patient selection criteria are essential in managing this device-aided therapy, but other issues may be crucial, for instance, appropriate involvement and training of the caregiver [5].

The aim of this survey was to identify the current level of LCIG diffusion across Italy, assess clinical practice and evaluate the current rate of complications and discontinuations.

Methods

An expert panel in device-aided management of advanced PD identified areas of clinical interest and developed 25 key questions about clinical, organizational and reimbursement aspects of LCIG therapy (Supplementary data). In Autumn 2015 the survey was sent via e-mail to 50 PD Centres, the most representative of current use of LCIG therapy in Italy, and which had reported at least 5 implanted patients during the observational period.

Results

The survey was completed by 43 of the 50 centres, and the clinical features of 905 patients were reported. Most centres (37/43) were also involved in other device-aided therapies: use of apomorphine

pumps and deep brain stimulation. In most centres an average of 2-4 patients were started on LCIG treatment each year. Many centres (60%) relied on internal guidelines. Multidisciplinary teams consisted of a neurologist, a gastroenterologist and a psychologist. In 35% of the centres there was a nurse with special expertise in PD device-aided therapies; nutritionists were involved in 17% of multidisciplinary teams. About 87% of the centres performed a preliminary nasal-duodenal test phase during hospital admission. Biochemical analyses, neurological examinations, neurophysiological and neuropsychological tests (standard screening included Mini Mental State Examination, Frontal Assessment Battery and Trial Making Test) were performed in all centres before Percutaneous Endoscopic Gastrojejunostomy (PEG-J) implantation. Neurological assessment were carried out after 1-3 months (2.3 ± 1.2) and every 6 months (± 3.2) thereafter. PEG-J revisions were scheduled within the first 1-6 months (4.4±3.2) and every 6 months. Neurophysiological assessment were repeated every 6-8 months (8.8 ± 3.2), biochemical analyses every 6 months (5.2 ± 3.6) and cognitive testing at least once a year (10.8 ± 4.9).

The rate of overall non-serious adverse events and complications was 55.1%. Weight loss (14.7 %), with an average of almost 10.8 Kg from the start of treatment, chronic polyneuropathy (10.6%), and stoma infection (8.9 %) were the most frequently reported (Table 1). The tube was replaced on average every 12 months (12 ± 3.9); the most frequent causes of replacement were: deterioration of the device (31/43 centres), device occlusion (17/43), device infection (5/43). About 40% of centres used replacement therapy with Vitamin B12 and Folic acid from the start of LCIG and for the duration of the treatment.

All centres had at least one case of discontinuation of therapy. The rate of withdrawal was 25.7% (mean centre follow-up was 6.1 yrs. ±3.0). 9.5 % of cases occurred in the first year post implant. The main causes of discontinuation were device related complications (19.6.%), dissatisfaction of caregivers and/or patients (15.0%), death (11.6%), acute and chronic polyneuropathy (9.4%), lack of

efficacy (8.1.%), hallucinations/confusion (7.2%), post-surgery-related peritonitis (within 1-3 months in 8/9 patients) (3.8%), comorbidities (2.7%), worsening of dyskinesias (2.6%) and excessive weight loss (2.1%). (Table 2).

Discussion

In this study, we collected retrospective data on the long-term follow-up of LCIG treatment in a large sample of 905 patients from 43 neurological centres, representing routine care (real life care) setting. Our results indicate that even though there are no shared and uniform selection criteria in Italy, evaluations are standardized throughout the country.

In terms of safety, our data are consistent with those reported in previous studies [1-4]. The most frequent non-serious adverse events were related to infusion therapy and/or device. We noted a significant rate of weight-loss (14.7%) which is higher than previously reported [6]. These data emphasize that malnutrition should not be underestimated and nutritional intervention should be promptly organized, including the presence of a nutritionist in the multidisciplinary team.

We observed a prevalence of approximately 11% of chronic neuropathy. Although our study was retrospective and as such could not properly address the problems related to polyneuropathy, it can be assumed that the systematic integration of the use of vitamin B12 and folic acid, adopted by many centers, may have contributed to reduce the number of patients with acute neuropathy (2.5%) and/or chronic cases (10.6%). Indeed, the total number of incident cases was smaller than that previously reported, considering the high prevalence of neuropathy (up to 55%) in patients on high levodopa doses (infusion or tablets) reported by previous studies [7-9].

Our dropout rate (25.7%) is quite low compared to other series [3,4] where it reached nearly 40% and occurred most frequently during the first year of treatment. By contrast, we report a dropout rate of only 9.5% during the first year of treatment. Lack of patient's improvement in autonomy in the

early phase is one of the main factors contributing to dissatisfaction in patients and caregivers. Patient's discontinuation in this phase was mostly related to lack of efficacy (8.1.%), especially when axial symptoms (gait disturbances and falls) were the predominant pre-existing features. Worsening of dyskinesia, because of a narrow therapeutic window, was a secondary, minor cause (2.6%) of patient dropout, in line with recent report by Antonini et al. [10] and in contrast with previous cases series [3,4]. The most troublesome dyskinesias reported were of the choreiform type. Their increased duration (> 50% waking time), despite LICG dose adjustment strategies (increase/reduction of the morning dose and/or continuous one), modification of dopamine agonist therapy, and/or combination with amantadine was the main cause of discontinuation.

The caregiver figure also appears to be of central importance [3,4]. An inadequate selection process in some patients and caregivers with unrealistically high expectations probably contributes to early discontinuation. Discussing device-aided treatment should be a stepwise process, and full, detailed information may contribute to a better outcome in this selected population [5].

The majority of treatment discontinuations occurred during long-term follow-up. The most frequent causes were device dysfunction (19.6%), difficulty in device management by elderly people and caregivers (15.0%), and progression of cognitive decline not related to infusion therapy (14.1%). Furthermore, new onset and/or worsening of hallucinations and/or confusion (reported mainly as attention/processing speed disorder), reported after initiation of infusion therapy, were a significant (7.2%) cause of withdrawal in our study population.

As reported by Sensi et al. [11] and recently by Fabbri et al. [12], in late PD, cognitive decline and axial symptoms become more prominent and the continuous delivery of dopaminergic therapy may also exacerbate these symptoms. In this late stage of the disease the caregivers' burden increases in part due to having to manage the pump, but especially due to increasing supervision needed by patients with severe cognitive decline. The inclusion of such patients may be due to the lack of uniform selection

criteria in Italy. Especially in the first years of LCIG treatment the criteria for qualifying for LCIG therapy were broad in the real-world setting. This probably explains why a number of patients with cognitive impairment or dementia, who would not have qualified to participate in the clinical trials leading to regulatory approval, were part of the cohorts at each of the contributing sites.

This study has limitations owing to the nature of its design. Firstly, the survey methodology limited obtaining data to the recollection of investigators rather than collecting healthcare outcomes. This may have led to biases in recall that may have altered the magnitude of the outcomes reported. Secondly, the study includes only about 80% of all Italian centres that deliver LCIG treatment. Thirdly, although the strength of this multicentre study consists of mirroring the real life care setting, the lack of standardized guidelines may restrict interpretation of results. This is particularly critical when evaluating cognitive outcome: the lack of uniform neuropsychological evaluation has limited the interpretation of these data. However we believe that, considering the size of the sample and the amount of data reported, this survey can be the starting point from which to develop uniform national guidelines to help healthcare staff and administrators in optimizing therapeutic management of PD patients. Our findings confirm the good profile of safety and efficacy of long-term LCIG achieved in our country.

For the first time, we have carefully assessed the main causes of patient dropout and found that late disease stage and associated dementia associated with increased caregiver burden are the major causes of discontinuation. Implementation of LCIG therapy at an earlier stage, before the patient is overwhelmed by the preponderance of non-dopaminergic symptoms, may provide the greatest benefit of this strategy.

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Table 1

NON SERIOUS ADVERSE EVENTS	No of patients (%)
POLINEUROPATHY	
Acute (GBS like)	2.5
Chronic	10.6
WEIGHT LOSS	14.7
HALLUCINATIONS/CONFUSION	4.8
ABDOMINAL PAIN	4.4
NAUSEA/ INNAPETENCE	3.0
PERISTOMAL INFECTION	8.9
OTHERS	6.1
TOTAL	55

Table 1: Non - serious adverse events associated with Levodopa-Carbidopa Intestinal Gel infusion reported by 43 centres (905 patients)

EVENTS	No. Patients (DS)	%
Surgery-related		
Duodenal perforation	2 (±0.6)	0.8
Pain	7 (±0.4)	3.0
Peritonitis	9 (±0.5)	3.8
Device Related		
Tube occlusion	19 (±0.6)	8.1
Stoma infection	27 (±1.2)	11.5
Infusion related		
Weight loss	5 (±0.4)	2.1
Worsening of dyskinesias	6 (±0.5)	2.6
Hallucinations /confusion	17 (±0.6)	7.2
Inefficacy	19 (±0.9)	8.1
Peripheral neuropathy	22 (±1.0)	9.4
Unrelated to procedure/infusion		
Comorbidities	5 (±0.8)	2.7
Death	27 (±1.8)	11.6
Worsening of cognitive decline	33 (±0.9)	14.1
Caregiver's not compliance	35 (±1.0)	15.0
TOTAL	**233**	**25.7**

Table 2: Main causes and frequency of Levodopa Carbidopa Intestinal Gel Infusion discontinuation in 43 Centres (905 patients).

- It is a long term follow up on more than 900 levodopa-carbidopa intestinal gel patients
- Provides an overview of the causes and rates of withdrawal in the short and long term.
- The main causes of discontinuation were: device-related complications, disease progression, caregiver/patient's dissatisfaction.
- The overall rate of discontinuation was of 25.7 %, 9.5 % in the first year post implant.