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DOCTORAL THESIS

CLINICAL-THERAPEUTIC ASPECTS IN ADVANCED PARKINSON'S DISEASE

A B S T R A C T

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INTRODUCTION

Parkinson's disease is an extremely important neurodegenerative disease in terms of its increasing prevalence and its long-term socio-economic implications. As the disease progresses, the effectiveness of conventional oral / transdermal medication decreases progressively and the therapeutic response becomes inconsistent and unpredictable. Motor complications that occur as a result of uneven absorption of oral medication, with fluctuations in levodopa plasma concentrations and a progressively narrowing therapeutic window, greatly affect the motor performance of patients, with significant impairment of work capacity, quality of life and self-confidence. Even if the motor symptoms are defining both in the diagnosis and in the staging of the disease, the non-motor symptoms (some of them even preceding the motor ones by several years) are extremely important, especially in the advanced stages of the disease. Among the non-motor symptoms, gastroparesis and consecutive erratic gastric evacuation have a special importance due to the major impact on the predictability of the conventional therapeutic response and motor complications. The heterogeneity of clinical picture makes it often difficult to recognize a patient in advanced stages of the disease.

LD treatment remains the "golden" standard in PD therapy, but its long-term administration generates motor complications (motor fluctuations and dyskinesias), which will affect the patient's quality of life. Despite the fact that in the last 10 years important advances have been made in APD therapy, a series of clinical and therapeutic aspects remain unresolved, which represent real challenges for both general neurologists and those specialized in movement disorders.

The doctoral thesis is structured in four studies.

STUDY I:

PROFILE OF PATIENTS WITH ADVANCED PARKINSON'S DISEASE SUITABLE FOR DEVICE AIDED THERAPIES: RETROSPECTIVE DATA OF A LARGE COHORT OF ROMANIAN PATIENTS

1.1. OBJECTIVES AND METHOD

The lack of clear criteria for defining APD in many cases delays the indication for device-aided therapies (DAT) in a significant number of patients who could benefit from them. In recent years, there have been a large number of scientific articles published with expert recommendations trying to provide practical approaches for the various stages of PD. The biggest challenge seems to be to establish the optimal moment in the evolution of APD, when it is necessary to initiate advanced phase therapies (invasive therapies, assisted by device). They use the concept of continuous drug delivery (CDD), in order to obtain a continuous dopaminergic stimulation (CDS) or deep brain stimulation (DBS), which is thought to be effective due to the continuous compensation of dopaminergic deficiency. Hence the need for a consensus in defining APD has born. Following the recommendations of the experts, the concept of "5-2-1" has already emerged (patient who despite the administration of at least 5 doses of LD / day has at least 2 hours of OFF / day and / or at least one hour of unsettling dyskinesia), a relatively simple tool and easy to apply in everyday practice. However, clinical practice has shown that this recommendation is not comprehensive enough to assess the complex clinical picture of patients in the advanced stages of PD and especially in establishing the indication / eligibility for device-aided therapies - DAT (apomorphine pump, deep brain stimulation - DBS and intestinal infusion with levodopa-carbidopa gel - LCIG). In our center, the only DAT option available is LCIG (since 2011). The initiation of LCIG therapy in our country is recommended to be performed in university clinics with dedicated training, with experience in PD management and LCIG treatment. Thus, multidisciplinary teams with expertise (neurologist, gastroenterologist, psychiatrist, dedicated nurse) rigorously evaluate, preferably in conditions of continuous

hospitalization, each patient to establish eligibility for DAT in general and LCIG treatment in particular. The same multidisciplinary collaboration is needed after performing PEG-J to maintain the long-term safety and efficacy of the therapy.

Identifying the “optimal time” to start treatment with LCIG is extremely important, so that the patient with APD can fully and for a long period of time benefit from the best possible quality of life, with adequate socio-familial insertion, without being a burden for the family. Rigorous selection of PD patients with maximum benefits from LCIG, complex, multidisciplinary assessment, the presence of an involved and adequately trained family member in the care of the patient with APD following device-aided therapy, are key elements in long-term maintenance, effectiveness and safety of treatment and appropriate adherence.

In the near future we expect new clarifications / recommendations from experts on how to evaluate patients with APD. It is expected that as other options of combination therapy (opicapone, safinamide, pre-filled apomorphine pens, inhaled levodopa powder, extended-release amantadine, etc.) and other DAT solutions become widely available, the management of patients in different stages of APD will be further improved. At present, there are no concrete data in the literature on the upper limits of dopaminergic medication, especially LD (dosage and posology), the way in which they are influenced by access to various add-on therapies or device-aided therapies (DAT), regarding the proportion of patients considered eligible for DAT in tertiary centers and the spectrum of motor and non-motor complications in patients with APD.

Considering the experience of the 2nd Neurology Clinic from Târgu Mureș in the treatment with LCIG, accumulated since 2011, we decided to retrospectively evaluate all patients with APD referred to our clinic in order to establish eligibility for DAT within the last 6 years (a period between June 1, 2011 and May 31, 2017). The objectives of our research were represented by:

- identification of patient profile with APD eligible for LCIG therapy,
- the importance of assessing gastrointestinal complaints in these patients,
- management of motor fluctuations and severe complex dyskinesias in patients treated with LCIG
- identification of the factors that may lead to the discontinuation of LCIG treatment.

The eligibility criteria of the patients included in our analysis were:

- at least 2 hours / day off period, with ≥ 2 distinct episodes of off, except for early morning akinesia, both anamnestic and subsequently documented in 24-hour journals, completed at the patient's home
- with / without dyskinesias
- levodopa responsive patients with at least 4 doses of LD / day
- with various drug combinations (add-on therapies): dopamine agonists (DA), monoamine oxidase-B inhibitor (MAOI-Bs), catechol-O-methyltransferase (COMT) inhibitor and / or amantadine.

During the 6 years of analysis a number of 311 patients with APD, diagnosed according to the UK Brain Bank Criteria, met the eligibility criteria listed above.

All patients have signed the informed consent of the hospital regarding the confidentiality of personal data, according to the regulations in force.

The study protocol was approved by the Ethics Commission of the University of Medicine and Pharmacy Târgu Mureș, approval no.94/19.05.2017 (<https://w.w.w.umfst.ro/universitate/comisii-de-etică/comisia-de-etică-a-cercetării-stiințifice/avize/2017.html>).

The study was conducted according to the recommendations of the Helsinki Declaration.

The aim of the first study of the thesis was to assess the profile of the patient with APD suitable for DAT.

1.2. RESULTS

Of the 311 patients initially examined, only 125 patients were considered to have reached the limits of conventional oral / transdermal therapy and were considered eligible for DAT, and of these 89 followed the PEG-J procedure for initiating LCIG therapy.

Following the analysis of the data, we found that the doses and posology of LD used in patients who were considered for DAT therapy were higher. Thus, in patients with a daily dose between 750-1000 mg / day, divided into at least 5 doses, with motor complications (at least 2 hours of OFF / day and / or at least one hour of disturbing dyskinesia) should be evaluated in order to establish DAT. We use for evaluation of motor status of the patient diaries of 24 hours/day (30 minutes periods) for 3 consecutive days before clinical evaluation, to obtain a correct and accurate picture of the motor fluctuations of the patient during the entire day, with regard to timing of administration of antiparkinsonian medication. This diaries reflects in an objective manner the real motor status of the patient. It is important for neurologists and general practitioners to refer the patients with APD to a center specialised in movement disorders with a multidisciplinary approach when the daily LD doses are above 700-1000 mg/day, given for at least 5 times/day, with motor complications (at least 2 hours OFF / day, at least 1 hour / day of disabling dyskinesia), despite of maximal optimisation of oral treatment. In this situation the patients should be evaluated for advanced therapeutic strategies (DBS, LCIG pump, subcutaneous apomorphine pump).

1.3. CONCLUSIONS

Patients with APD can have a variety of symptoms, and because symptoms and therapeutic efficacy can be manifested in many different combinations, it is not possible to decide using a single, rigid, set of criteria which APD patient is eligible for DTA. According to our data, patients with APD received lower and fewer doses. Nevertheless, the use of additional therapies was more prevalent when compared with the literature. We consider that referral of APD patients by the treating physicians (neurologists, general practitioners) to a specialised movement disorder center with a multidisciplinary approach should be considered when the average daily dose of LD is at least 750-1000 mg/day, administered at least 5 times daily or, in justified cases even 4 times/day (poor compliance, severe burden of caregiver, limited availability of add-on therapeutic options, severe forms with rapid clinical progression), if motor complications (daily minimum 2 hrs off periods and/or more than one hr troublesome dyskinesia), that significantly reduce the quality of life despite maximal complementary therapies, persist.

STUDY II:

THE IMPORTANCE OF EVALUATION OF GASTROINTESTINAL SYMPTOMS IN ADVANCED PARKINSON'S DISEASE

2.1. INTRODUCTION

Gastrointestinal disorders occur in all stages of Parkinson's disease, often years before diagnosis. In advanced Parkinson's disease they can worsen the quality of life and may limit both conventional and device aided therapies.

2.2. AIM AND METHOD

The objective of our research was to assess the importance of gastrointestinal complaints in patients with APD. In this retrospective study, we analyzed the 6-year data of all levodopa-responsive patients with PD, with at least 2 hours per day off status, at least 3 on the Hoehn-Yahr scale during on phase, and at least four doses of levodopa per day. Gastrointestinal symptoms were evaluated on the basis of yes/no answers given to questions about dysphagia, inappetence, epigastric discomfort, bloating, early satiety, nausea, vomiting and constipation.

2.3. RESULTS

Of the 311 patients evaluated, 286 patients were assigned according to the presence/absence of gastrointestinal symptoms. The 181 of them had at least one gastrointestinal symptom. Those had a longer disease duration (10.13 ± 4.03 vs 7.4 ± 2.42 years), more severe clinical picture (longer off: 4.03 ± 1.32 vs 2.91 ± 1.02 hours, more lasting dyskinesias: 2.76 ± 0.91 vs 1.83 ± 0.61 hours, higher Hoehn-Yahr score) and received higher levodopa doses at higher dosing frequencies. Constipation and bloating were the most common gastrointestinal complaints. Most of the complaints occurred more frequently in dyskinetic patients.

2.4. CONCLUSIONS

Gastrointestinal complaints are common in advanced Parkinson's disease. Their assessment should be a part of routine examination. The gastrointestinal profile should be determined by interdisciplinary approach with appropriate clinical and instrumental methods. The analysis of the data showed that the association between gastroparesis and dyskinesia may be an important link in the pathogenic mechanism of advanced Parkinson's disease. Impairment of gastrointestinal function (gastroparesis and erratic gastric emptying) in patients with PD, especially in advanced stages of the disease, is common, generating by significant fluctuations in plasma LD levels that, together with the evolutionary nigro-striatal neurodegenerative process lead to motor complications. In the case of patients with suboptimal control of motor fluctuations continued administration of levodopa / carbidopa intestinal gel (LCIG) to the small intestine results in more stable plasma levels compared to oral administration of levodopa. Data from published randomized and open label clinical trials show that LCIG infusion is also effective in the treatment of dyskinesias.

STUDY III.

MANAGEMENT OF ADVANCED PARKINSON DISEASE WITH MOTOR FLUCTUATIONS AND COMPLEX, SEVERE DYSKINESIAS: DATA FROM A LARGE COHORT OF PATIENTS TREATED WITH LEVODOPA-CARBIDOPA INTESTINAL GEL

3.1. INTRODUCTION

Regarding the long-term follow-up of patients with severe motor fluctuations and complex, disabling dyskinesias, including biphasic dyskinesias (DID) treated with LCIG, we are not aware of the existence of dedicated studies in this regard. Thus, we considered it necessary to perform a retrospective evaluation of all patients with APD with severe motor fluctuations and disabling dyskinesias (peak dose dyskinesias, biphasic, dystonia) treated with LCIG in the records of our clinic and which materialized in the form of study III of this thesis.

3.2. OBJECTIVES AND METHOD

We conducted a retrospective evaluation of all patients with APD treated at the 2nd Neurology Clinic in Targu Mures with LCIG during 6 years period. Our main purpose was to identify patients with severe motor fluctuations and complex, disabling dyskinesias (peak dose dyskinesia, diphasic dyskinesia and end of dose dystonia, treated with LCIG, as well long term follow-up after LCIG therapy initiation.

This retrospective analysis follows a separate group of patients with APD that is less studied in dedicated clinical trials. The inclusion criteria were: at least 30 minutes of diphasic dyskinesia (DID) on 3 consecutive days, considered responders and treated with LCIG. The patients were evaluated at discharge, after initiation of LCIG therapy, and at 6, 12, 18 months, respectively (\pm one month), and whenever needed. At each visit the change in therapy were recorded (add-on medication, changes in LCIG doses and daily duration of LCIG treatment). In order to facilitate the evaluation of the patients and the quantification of dyskinesias, especially DID, we trained the patients and/or their relatives regarding the

recognition of their different phases. Thus, to differentiate peak dose dyskinesia from diphasic dyskinesia, we used the concept of early incomplete on with dyskinesia and late incomplete on with dyskinesia (we considered this concept necessary given that, after initiation of LCIG, the recognition of dyskinesias according to the oral administration of LD was no longer possible).

3.3. RESULTS

Of the 311 patients with motor fluctuations initially examined, 125 cases were considered suitable for DAT out of which, 83 (66.45) also presented dyskinesias, and 43 (34.4%) were enrolled in the group with complex, severe, disabling dyskinesias (peak-dose dyskinesia, diphasic dyskinesia and end of dose dystonia) associated with severe motor fluctuations. At the end of the study (18 months period), only 34 patients remained in the study. We had observed that after PEG there was a slight increase of moderate dyskinesia (h/day) coupled with a near-lack of severe forms of dyskinesias. Off hours/day, as well as diphasic dyskinesias, dystonia and early morning akinesia, were also significantly reduced. Although the standard duration of treatment with LCIG is 16 hours / day, clinical observations suggest that administration of levodopa / carbidopa intestinal gel 24 hours / day may further improve symptoms (levodopa-resistant freezing, poorly controlled nocturnal fluctuations by conventional medication or morning akinesia) as well as troublesome dyskinesias that can be greatly improved by continuous 24-hour administration of LCIG infusion (despite increasing daily dose of LD).

This improvement could be due to better LD pharmacodynamics and more stable plasma / intracerebral levels beyond the obvious aspects of improved pharmacokinetics due to intrajejunal administration. In parallel, we found an increase in moderate dyskinesias, which indicates a change in their profile, a phenomenon maintained throughout the follow-up of 18 months. This phenomenon, to our knowledge, is not described in the literature. We consider that the improvement resulting from the decrease of the OFF periods and the increase of the ON periods with non-superior dyskinesias (even if we found the change of the dyskinesia profile as we showed above) is consistent and lasting. However, a number of new challenges arise, given the tendency to change the profile of motor complications despite continuous dopaminergic stimulation. Regarding the recommended daily doses of LCIG, there are currently no studies on the safety and efficacy of high doses of LCIG (≥ 2000 mg / day) and information on the use of high doses is limited. In the group of patients evaluated by us, 17 patients received ≥ 2000 mg LD / day, and the actual doses of LCIG at discharge were higher than the theoretical ones.

The incidence of adverse events in these patients was comparable to data in the literature. The conclusions of this substudy are that patients with APD and complex dyskinesias require a special therapeutic approach and should be tested / titrated in continuous hospitalization conditions. Doses and daily duration of LCIG administration combined with a properly adapted add-on medication provides an improvement in symptomatology and the quality of life of patients with APD who require DAT.

3.4. CONCLUSIONS

Patients with APD with complex dyskinesias need a special therapeutic approach, ideally tested in hospitals. A properly adapted LCIG treatment regarding the dose and time of administration completed with well-selected add-on medication should offer improvements for patients who want to or can choose this DAT. Targeted, clinical trials are needed to assess the changes observed in the dyskinesia profile and to identify possible additional measures that could further improve the quality of life of those patients and could increase the efficiency and safety of LCIG.

STUDY IV: FACTORS THAT CAN LEAD TO LCIG TREATMENT DISCONTINUATION

4.1. OBJECTIVE

The last study of the thesis (the forth) aims to identify the factors that can lead to the discontinuation of LCIG treatment.

4.2. METHOD

In this sense, we analyzed the data of all discontinuation cases that occurred among the 204 patients with APD whom LCIG therapy was initiated until the end of 2018, in two university centers in Romania with a large turnover of patients with PD: Timisoara (TM, 90 patients) and Târgu Mures (MS, 114 patients). Both centers are university clinics with comparable characteristics: they have consistent experience in therapy with LCIG, they have an average of 9-10 initiations / year, they work according to the same protocols, they have multidisciplinary teams with dedicated training, they benefit from the same dedicated home care system, testing and initiation of LCGI therapy is done in conditions of continuous hospitalization.

Both centers had a total of 43 discontinued patients, of which 33 cases due to the death of patients (cardiac arrest, stroke, neoplasia, intestinal-mesenteric infarction, pneumonia, deterioration of the general condition). Disease duration until LCIG infusion was significantly longer (11.67 ± 4.98 vs 9.44 ± 3.44) and the overall clinical picture more severe (both regarding motor symptoms and cognitive decline) in dropout patients (compared to patients who continued treatment). The dropout patients also presented significant differences regarding the incidence of polyneuropathy (32.5% vs. 11.18%). The main cause of discontinuation was death. A predictor of mortality in patients treated with LCIG in addition to age and comorbidities could be an MMSE score < 26 before initiating therapy. The most common predictors of discontinuation of LCIG treatment are complications related to the administration system, lack of treatment efficiency, unrealistic expectations from the patient and relatives, recurrent psychotic manifestations despite antipsychotic treatment, worsening of dyskinesias, severe polyneuropathy. The discontinuation rate in our study group was 21%, a low / reasonable rate compared to the data in the literature. The conclusions of this study (the forth) are that defining the profile of the patient with APD who would benefit most from LCIG treatment is very important, as well as identifying the optimal time to start therapy. The existence of a well-trained and involved caregiver along with ensuring an aftercare system, are vital for the long-term maintenance of the benefits of LCIG therapy. A more severe stage of the disease, significant cognitive impairment at the time of initiation, and the association of polyneuropathy can be considered predictive factors for discontinuation.

4.3. CONCLUSIONS

The causes of discontinuation from LCIG therapy in Romanian patients are similar to those from other centers; however, the rate of dropout is somewhat lower. The clinician's experience in selecting and treating the patients at advanced stages of PD can increase therapeutic adherence. Also the presence of a well trained caregiver along with the availability of a proper aftercare system is mandatory for maintaining the long-term benefits of the therapy and the overall best outcome possible.

It should be mentioned once again that in Romania a number of preparations with LD and some combination therapies (safinamide, opicapone, amantadine with prolonged release, subcutaneous injections of apomorphine for sudden off episodes) with indication in the treatment of APD, are not available, as well as the fact that the only DAT option available in our region is LCIG. Targeted prospective studies are needed to confirm whether a more severe stage of the disease and cognitive impairment at the time of initiation, respectively, the association of polyneuropathy can be considered as predictive factors for dropout.

Therefore, we believe that all these factors, taken as a whole, reflect the limitations, challenges and difficulties in the long-term management of LCIG treatment in APD not only in Romania, but probably also in Central and Eastern Europe.

The limitations of this research are given by the method of retrospective analysis of data, the difficulty of assessing the impact of the involvement of a family member, some incomplete data or lack thereof. Thus, we could not properly document a number of adverse effects such as weight loss, polyneuropathy (electrophysiological study could not be performed in all patients, taking into account for diagnosis only subjective charges and clinical manifestations) lack of dosage of serum vitamin B12, homocysteine and methylmalonic acid. We also could not rigorously document the exact causes of death (especially in institutionalized patients) and we likely have an underreporting of the total number of side effects and other relevant complications related to the LCIG administration system.

FINAL CONCLUSIONS

1. Patients with BPA may have a wide variety of symptoms and complications that, similar to therapeutic efficacy, may manifest differently. Thus, daily practice has shown that it is currently impossible to use a single rigid set of criteria to determine eligibility for TAD.
2. The first consensus of the experts (the one that later became "rule 5-2-1") and which stipulates that if despite the administration of 5 doses of LD, the patient presents at least 2 hours of OFF and / or 1 hour of dyskinesia annoying, the use of TAD must be considered, it is a relatively simple and easy way to apply. However, daily clinical practice has shown that in reality, patients with BPA who end up being selected for the available TAD options are at a more advanced clinical stage.
3. Patients in whom we considered that the limits of conservative treatment were not reached had an average of 2.8 ± 0.8 hours OFF while patients considered eligible for TAD had 4.7 ± 1.1 hours OFF (with an average of 3.62 ± 1.3 hours for the whole group of patients evaluated).
4. The evaluation of the use of substitution treatment in APD patients showed that the LD doses used are at the lower limit of the therapeutic range which is outlined according to the data in the literature, but the use of combination therapy options (AD, MAOI-B, I-COMT and amantadine) is significantly more common. It is difficult to assess whether the need to use "more sophisticated" therapeutic formulas and implicitly some tendency to "delay" in the implementation of TAD is due to the reluctance of patients / relatives and / or physicians. At the same time, it is difficult to assess the impact on the long-term efficiency of the various TAD options.
5. We consider that referral of patients with BPA to a center specializing in movement disorders should be considered when the daily doses of LD are at least 750-1000 mg, administered at least 5 times / day or, in justified cases, even 4 times / day (poor compliance, significant caregiver burden, limited availability of add-on treatment options, severe forms with rapid evolution and clinical progression), if despite the use of maximal complementary therapies, motor complications persist that significantly reduce quality of life (at least 2 hours OFF and / or at least one hour of severe dyskinesia).
6. Appropriate assessment and classification of gastrointestinal symptoms in patients with Parkinson's disease should be an integral part of routine examination, but is mandatory in centers of expertise.

7. The gastrointestinal profile of patients with Parkinson's disease, but especially in the advanced stage, must be determined in a multidisciplinary approach. The association between gastroparesis and dyskinesia appears to be an important link in the complex pathophysiological processes of advanced Parkinson's disease, which needs to be clarified in targeted clinical trials.
8. LCIG treatment may also be a feasible option in patients with BPA and complex dyskinesias (peak dose dyskinesias, biphasic dyskinesias, and end-of-dose dystonias). Targeted clinical trials are needed to assess the change in dyskinesia profile observed under LCIG treatment and whether it requires additional therapeutic measures that, in addition to improving patients' quality of life, increase the efficacy and safety of long-term LCIG treatment.
9. It is very important to define the profile of the patient with BPA (both in terms of motor and non-motor complications), who would benefit the most from LCGI treatment, as well as to identify the optimal time to start therapy.
10. Targeted prospective studies are needed to confirm whether the aspects considered by us (a more severe stage of the disease and the cognitive impairment present at the time of initiation, respectively the appearance of polyneuropathy) can be considered predictive factors for discontinuation of therapy.

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