1.0 ABSTRACT

Title

EPI PARK

Advanced Parkinson's disease treatment eligibility in France: an epidemiological study.

Keywords

Parkinson's disease, levodopa-carbidopa intestinal gel (LCIG), Duodopa®, epidemiological study

Rationale and Background

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder worldwide which considering the ageing population in France represents a real public health concern. Indeed, in France, this disease affects about 1% of the population aged 65 and over. According to a study, based on data extracted from the public healthcare system database, the prevalence of treated PD in 2000 was approximately 143,000 patients (Bertin et al, 2005) but it was probably underestimated. More recently, the number of patients being registered in the 2013 health care system database as being affected by PD in Metropolitan France was assessed at 195,200. Genetic causes and non-genetic risk factors play important roles in PD but the exact mechanisms underlying these processes are still not completely understood.

PD is a chronic and slowly progressive disease. Indeed, symptoms continue to worsen over a period of years, including motor complications and late stage symptoms that could also include cognitive and psychotic disorders evaluated by the Movement Disorder Society-Unified Parkinson Disease Rating Scale (MDS-UPDRS).

Nevertheless, there is no clear consensus on how to define the stages of Parkinson's disease and no diagnostic codes available to classify advanced progressive disease (APD). It is the reason why a recent study aimed to achieve consensus among movement disorder

specialists treating PD patients, notably to identify the clinically important indicators that could define APD, using the Delphi method (Antonini et al, 2015). However, those criteria are not yet recognized and used as diagnosis criteria for APD.

At this stage of the disease, three invasive therapeutic alternatives can be considered (Giugni et al, 2014): deep brain stimulation (DBS), subcutaneous apomorphine continuous infusion (APO), or continuous intestinal infusion of levodopa-carbidopa gel (LCIG - Duodopa®):

Duodopa® is approved in France from September 14, 2004 in the following indication: treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when available combinations of Parkinson medicinal products have not given satisfactory results (Duodopa® SmPC). In France, the Transparency Committee limited Duodopa® to the patients not eligible for DBS and presenting contra-indication, intolerance or failure to APO. In 2013, in the last Transparency Committee's Opinion, the target population size was estimated to be 360 (lower limit of the confidence interval of the population estimated by the DUOCIBLE study).

Research Question and Objectives

In this context, this new epidemiological study aimed to accurately estimate in a real-life setting the size of the French population of PD patients who would be eligible for Duodopa® therapy, according to the conditions defined by the French Authority for Health in its latest Transparency Committee's opinion (2013) and secondarily to the marketing authorization indication. This study also allowed to describe characteristics of advanced PD patients and to estimate the proportion of PD patients eligible for each invasive therapy (DBS, APO or Duodopa®).

An exploratory objective was also applied to the study population to estimate the size of the population of PD patients eligible for Duodopa® when advanced PD was defined according to the criteria assessed by the Delphi method (Antonini et al, 2015).

Study Design

EPIPARK was designed as an epidemiological, cross-sectional, descriptive, non-interventional, and multicenter study.

Two complementary parts were introduced simultaneously: a « CENSUS » part to count all the idiopathic patients with advanced PD seen consecutively as outpatients by neurologists and a « CORE » part to describe the characteristics of advanced PD patients and identify patients eligible for Duodopa® and for each of the two other invasive therapeutic alternatives available at this stage of disease (DBS and APO).

Extrapolation

For the analysis based on the "raw" datasets no extrapolation factor were applied.

In order to generalize the results to a one-year activity of the observed neurologists and the targeted prescribers and consequently the Metropolitan French population of advanced PD patients the following weighting process was applied on results:

- According to the parameters collected in the CENSUS, to extrapolate the information collected by each participating neurologist on a 6-month period to a full year of activity, a first weighting coefficient was calculated including the level of activity of the participating neurologists, estimated through the number of registered patients in the CENSUS and the duration of the associated reporting phase. This weight was applied to each patient included by the observed neurologist and reflect the number of individuals represented by each recruited patient in the targeted population based on the level of activity of this neurologist
- Another weighting factor/coefficient was calculated including the number of neurologists in each stratum defined by the type of practice and the phone area.

Setting

The study was conducted by neurologists as they are the physicians following up parkinsonian patients through all the disease course and are the key physicians taking the

decisions for treatment at the advanced stage (HAS 2014). Their selection was based on the national IMS One Key reference list, which is provided by an independent entity from AbbVie. At the time of study designing and protocol writing in 2015, 2611 practicing neurologists were identified in Metropolitan France. Hypothesis regarding, the number of centers to be active and the number of patients to be recruited were calculated on this basis. It was assumed calculated that 289 active neurologists would be active in the study to ensure representativeness of the population.

At the time of the study implementation, the most recent update of Onekey reference list was used containing 2841 neurologists who were called.

Patients' selection

Each patient or their legal representatives have received verbal and written information prior to inclusion in the study.

The inclusion criteria for the CENSUS part of the study where adult (≥18 years old) patient presenting advanced idiopathic Parkinson's disease, defined by a duration of levodopa treatment of at least 3 years and the presence of motor complications (motor fluctuations and/or dyskinesia), insufficiently controlled by conventional anti-parkinsonian medications, seen by the neurologist as outpatient either in a hospital or a private office.

Physicians were asked to register in the CENSUS part of the study all their consecutive patients who met the previous criteria during the study period.

Concerning the CORE part of the study the inclusion criteria were patient registered in the CENSUS and who (patient or legal representative) had received verbal and written information about the study and who did not express his/her opposition to personal data collection and processing.

Physicians were asked to include in the CORE part of the study patients who met the previous criteria during the study period up a limit of 20 patients per center.

Subjects and study size

In order to achieve a 95% CI with a margin of error of +/- 5% on either side of the estimated proportion, it was calculated that a total of 384 patients included in the CORE part of the study was required.

In order to take into account non-assessable patients (estimated at 15% of all patients included in the CORE part of the study), a sample of 442 patients in this study part was required to be recruited by 289 neurologists (339 neurologists were required to consider the inactive neurologists, estimated at 15% of all the participating physicians).

To avoid a potential center-effect and to allow the participation of the neurologists having the smaller number of advanced PD patients in their active file, a maximum number of inclusions was fixed per center at 10 first, and then 20 considering the few numbers of participating neurologists.

To take into account of potential duplicates of patients followed up by more than one neurologist who participated in the study and registered by all of them, the number of patients seen for PD by another neurologist than the one who completed the register was taken into account for a sensitivity analysis

Variables and data sources

Concerning physicians, the physician's type of practice, the site location according to the 5 French phone areas, and the reason for non-participation (if applicable) were collected.

- Concerning patients for the CENSUS part, variables collected in the register were: the date of the medical visit, if patient was seen by another neurologist for PD or not, the number of yearly medical visits done by the participating neurologist, inclusion in the CORE descriptive part of the study or not and reasons for non-inclusion if applicable.
- Concerning patients included in the CORE part of the study, the following variables were documented on the eCRF: validation of selection criteria, socio-demographic data, disease history (including number of visits for PD within the last 12 months, follow-up by another neurologist for PD or not, levodopa-responsiveness), prior and ongoing PD treatments and concomitant therapies, clinical data, comorbidities, advanced PD criteria according to Delphi method (for the exploratory objective).

Regarding the eligibility to DBS and the contra-indication, intolerance or failure to subcutaneous apomorphine, the missing data handling planned in the first version of the SAP were in favor of eligibility to Duodopa® rather than to DBS or apomorphine (scenario 1). So it was decided with the Scientific Committee to build up a second scenario of missing

data handling in order to not overestimate the complete eligibility to Duodopa® vs DBS and/or apomorphine (scenario 2).

Analyses have been performed first according to scenario 1 to stick to what was planned by the SAP and then complementary analyses of primary and secondary endpoints regarding eligibility to Duodopa® have been analyzed according to the scenario 2 in order to confront results.

Results

Physicians' disposition:

In the end, 118 neurologists agreed to participate, due to the high number of physicians not available or who were not effectively contacted nor reached during the study sites recruitment period (n=1275, 44.9%) or "out of scope"and, i.e. having confirmed at first contact that they were not involved in the management of PD patients (n=528, 18.6%) or who refused to participate (n=920 (32.4%)).

Among the 118 neurologists who agreed to participate, 38 (32.2%) were ready to include and among them, 33 (28.0%) were active and 5 (4.2%) didn't include any patient. Of these 33 neurologists, 21 (63.6%) practiced exclusively in hospital, 11 (33.3%) in a private structure and 1 (3.0%) in both structures (mixed activity). The 33 active neurologists registered 1 to 93 patients in the CENSUS with a mean number of 20.8 patients. All of them included at least 1 patient in the CORE part of the study (1 to 20 patients).

Methods to overcome this bias were implemented.

Patients' disposition:

A total of 688 patients were registered in the CENSUS and 425 (61.9%) were included in the CORE descriptive part of the study. Among the 425 patients included in the CORE part of the study, 410 (96.5%) were retained for data analysis.

Demographics of patients and other baseline characteristics:

Patients with advanced PD were mainly male (58.3%), with a mean age of 71.1 ± 9.4 years and 56% were over age 70. Mean time since diagnosis was 12.5 ± 5.9 years and mean time since onset of motor complications was 5.9 ± 4.5 years. Overall 70.5% of patients had an excellent or good general health status. The majority of patients (N=374, 91.2%) had between 1 and 4 visits with the same neurologist within the last year. The time since initial diagnosis, patients were comparable according to the type of neurologist activity with an overall mean time since diagnosis of 12.5 ± 5.9 years. The mean time between initial diagnosis and onset of motor complications was 6.6 ± 3.6 years.

Regarding clinical assessment of the disease,

- The Hoehn and Yahr stage was available for 223 (54.4%) patients and 54.7% of them had a ≥3 stage at last assessment
- The Schwab and England score was available for 123 (30.0%) patients with an overall mean score of 67.3 ± 20.0%
- The MDS-UPDRS score was available for 130 patients (31.7%) and mean scores were as follows according to the different subscales: UPDRS: I 3.9 ± 2.9, UPDRS II: 14.6 ± 7.6, UPDRS III 'on' 18.9 ± 9.6, UPDRS 'off': 33.0 ± 13.7, and UPDRS IV: 7.8 ± 4.1.

Regarding PD signs and symptoms,

- At time of inclusion, almost all of the 410 advanced PD patients (N=394, 96.1%) had motor fluctuations, with troublesome 'off' phases for more than 25% of waking time in 60% of the cases
- Dyskinesia were observed on 75.1% (N=308) of patients at the time of inclusion and this symptom was present for more than 25% of waking time in 61% of the cases, was assessed as severe during 'on' time response in 35.4%, and had at least minimal impact on functional activities in 78.6%.
- Dystonia was reported in 29.5% (N=121) of the patients, and it was assessed as severe during 'on' phase in 28.9% of the cases.

All of the 410 patients had current motor fluctuations and/or current dyskinesia at the time of inclusion.

Almost all patients (N=408, 99.5%) had at least one ongoing antiparkinsionan treatment at the time of inclusion. All patients had history of levodopa per OS and most of them (N=394, 97.0%) were still treated with levodopa at the time of inclusion. Of the 394 patients with ongoing levodopa, the type of levodopa-based regimen was combination with dopamine agonists for 32.2% (N=127), with dopamine agonists and IMAO-B for 17.3% (N=68), with IMAO-B only for 10.4% (N=41) and other combinations counted for 40.1% (N=158). Contraindications to second line treatment and hypersensitivity were rarely reported. Indeed, regarding the three second line therapies, 30.2% of the patients had history of APO and 7.1% of DBS. Moreover 2.2% of the population (9 patients) had an history of Duodopa®. Two-third of them (66.7%) were still ongoing at the time of inclusion.

Main results

The primary objective was to estimate, in Metropolitan France, the size of the population of PD patients eligible to Duodopa® in accordance with the conditions defined by the French Authority for Health in its last Transparency Committee's opinion. After extrapolation from data collected in advanced PD patients and exclusions related to predefined non-eligibility criteria, our 1-year estimate for France is between 7 344 and 9 108 PD patients eligible for Duodopa® (from July 2017 to July 2018). These two sizes of the target population correspond, respectively to 16.5% (95%CI [16.17 - 16.79]) and 13.3% 95%CI [13.01 - 13.58]) (determined according to the two pre-planned data missing handling scenario) of the 55 258 PD patients estimated to have advanced disease stage over this period

The first secondary objective of the study was to estimate the proportion of patients eligible to Duodopa® according to the indication defined in its market authorization. Among the 55,258 estimated patients with advanced Parkinson's disease in France, according to the first missing data handling scenario, after application of the weighting factors to the analysis 2768 patients [5.0%] were eligible for DBS. 20,633 patients [37.3%] presented no contra-indication, intolerance nor failure to APO, 49,214 (89.1%, 95%CI [88.80 - 89.32]) had no contra-indication for Duodopa® use, 18,034 (32.6%, 95%CI [32.25 - 33.03]) had severe motor fluctuation and hyper/dyskinesia and 53,288 (96.4%, 95%CI [96.28 - 96.59]) were levodopa-responsive. Eligibility to Duodopa® according to its market authorization was observed for 14,732 (26.7%) patients. Accordingly, following scenario 2, after application of the weighting factors to the analysis population, 14,802 patients [26.8%] were eligible for DBS, 24,525 patients [44.4%] presented no contra-indication, intolerance nor failure to APO, 49,214 (89.1%, 95%CI [88.80 ; 89.32]) had no contra-

indication for Duodopa® use, 18,034 (32.6%, 95%CI [32.25 ; 33.03]) had severe motor fluctuations and hyper/dyskinesia and 53,288 (96.4%, 95%CI [96.28 ; 96.59]) were levodopa-responsive. Eligibility to Duodopa® according to its market authorization was observed for 14,731 (26.7%) patients.

Exploratory endpoints:

Regarding the advanced PD criteria defined by the DELPHI method, all patients should meet at least one motor symptom indicator or at least one non-motor symptom indicator. On the overall weighted population, 99.6% (N=55,043) analysis population had at least one top 3 clinically relevant most important indicator.

Conclusion

After the previous DUOCIBLE study conducted in 2012 to define the population of PD patients eligible to Duodopa®, the EPIPARK study was set up to provide new data based on a more robust method.

The generalizability of our results is supported by:

- The multicenter design of the study which has been carried out throughout France even if the number of active physicians was limited (the management of advanced PD patients may differ according regions)
- The number of analyzed advanced PD patients which was consistent with the planned sample size
- The help of the members of a Scientific Committee comprising neurologists considered in France as clinical experts, who maximized the reliability of the definition of the target population for Duodopa®
- The rigorous methods used to prevent and control potential biases throughout the study, from study implementation to statistical analysis, in accordance with the study Scientific Committee comprising one methodologist-epidemiologist.

In the end, the EPIPARK findings could be generalized to the overall French population of PD patients, with the limitation of a potential selection bias of participant neurologists related to their limited number.

Based on a sufficiently robust method, the non-interventional EPIPARK study provided new data on the French population of PD patients eligible to Duodopa®, with a minimum 1-year estimate at 7 344 patients. This estimate is based on a proposal regarding the definition on advanced disease stage, as there was a lack of consensus on such a definition.

Considering the lack of epidemiological data on the advanced stage of PD, this study also provides consistent information on the characteristics of advanced PD patients and on the size of this population in France.