1.0 Abstract

Title

A multi-country, OBSERVational, cross-sEctional study to characterize advanced Parkinson's Disease patients in movement disorder centers – OBSERVE-PD

Keywords

Parkinson's disease, advanced vs. non-advanced, classification

Rationale and Background

Parkinson's disease (PD) is an incurable, progressive, neurological disorder that develops gradually, and eventually may become severely disabling despite treatment [1, 2]. Currently, there is no clear consensus on how to define the stages of PD.

In the advanced stage, continuous infusion therapies (apomorphine s.c. and intraduodenal levodopa) and stereotactic surgery with deep brain stimulation come into consideration [3]. The switch from conventional PD treatment to a more invasive treatment is mainly made in centers that can provide comprehensive and timely treatment by a multidisciplinary expert group. Such centers are often labelled as Movement Disorder Centers/Clinics (MDC).

Various studies have reported different percentages of patients with Advanced Parkinson´s disease (APD) in Movement Disorder Centers (MDC) [4-11]. Identifying the number of APD patients in MDC is crucial for the centers to be able to provide sufficient resources for appropriate invasive treatments.

The purpose of this cross-sectional, multi-country, observational study was therefore to increase the understanding of the proportion and patient characteristics of APD patients in MDC in different regions and to observe any regional differences. In addition, classification of patients as "advanced" based on a) investigator personal judgment and b) consensus criteria, derived from a Delphi project, were compared.

Research Question and Objectives

The primary objective of this observational study was to evaluate the proportion of PD patients identified as advanced Parkinson's disease (APD) patients according to physician's judgment in all participating movement disorder centers (MDC) across the study.

The secondary objectives were

- To evaluate clinical characteristics of advanced versus non-advanced PD patients
- To assess the percentage of APD patients considered for invasive therapies (i.e. LCIG or Apomorphine or neurosurgical treatments) per physician's judgment
- To explore referral practices for APD patients
- To compare the percentage of APD patients identified in routine clinical practice by physician's judgment to the percentage of APD patients identified based on the Delphi method APD criteria
- To analyze all of the above objectives per each participating country
- To assess any country-based variations in the definition of APD patients according to physician's judgment.

Study Design

This observational study was conducted in a cross-sectional, non-interventional, multi-country, multi-center format in 18 active countries across different geographical regions. Data for this observational study were collected during a single patient visit.

Setting

Active participating countries were Austria, Australia, Belgium, Canada, Croatia, Czech Republic, Germany, Greece, Hungary, Ireland, Israel, Italy, Romania, Russia, Slovenia, Slovakia, Switzerland, and Turkey. Saudi Arabia was also included but due to local regulatory delays this country was not able to include patients before the end of the study.

Subjects and Study Size, Including Dropouts

There were 2627 patients documented. The full analysis set (FAS) consisted of 2615 patients, 12 patients were excluded from the FAS as they were known to be preselected (and not enrolled consecutively) or as they were missing physician's judgment on the stage of the disease.

Variables and Data Sources

In addition to the classification into APD vs. non-APD according to physician's judgment which was available for all of the 2615 patients in the FAS, patients received a classification according to 11 APD-questions which were developed by the Delphi method. Current PD status was assessed with the Unified Parkinson's Disease

Rating Scale (UPDRS) parts II, III, IV, and V (Modified Hoehn & Yahr staging). Non-motor symptoms were assessed using the Non-Motor Symptoms Scale for PD (NMSS), and quality of life was assessed with the PD Quality of Life Questionnaire (PDQ-8).

Patient data were documented on data report forms (DRF). In addition, each center was asked to fill out a form to describe each center.

Results

Overall, 51.3% (95%-confidence interval [49.4; 53.2]) of the PD patients were judged as APD by the physicians. The percentage of patients classified as APD in the single countries ranged from 24.4% to 82.2%.

Clinical characteristics (APD vs. Non-APD)

On average, patients in the FAS were 67 years old (ranging from 30 to 94 years). Most of the patients (98.5%) were white. The percentage of males was 60.9% in the APD group and 57.7% in the Non-APD group. In APD patients, the average time since diagnosis was considerably higher (11.0 years vs. 4.3 years), and the percentage of patients with motor fluctuations was higher (87.0 % vs. 23.2%) compared to Non-APD patients.

As could be expected, the following mean scores showed a significantly higher impairment in APD patients as compared to non-APD patients: UPDRS II (16.5 vs. 8.4 points), UPDRS III (30.2 vs. 21.1 points), UPDRS IV Q32 (1.0 vs. 0.2 points), Q33 (0.8 vs. 0.1 points), Q34 (0.4 vs. 0.1 points), Q39 (1.2 vs. 0.3 points), UPDRS V (2.9 vs. 2.0 points), NMSS (58.6 vs. 34.4 points), and PDQ-8 (36.6 vs. 20.7 points).

Consideration for invasive therapies

From the APD patients 65.7% (compared to 10.0% in Non-APD patients) were considered to be eligible for invasive treatment options. However, for 42.2% of the patients eligible for invasive therapies (i.e. 65.7% of APD patients) no invasive treatment was ongoing or planned. From patients on ongoing invasive treatment 57.4% received neurosurgical treatments, 38.3% were treated with levodopa-carbidopa intestinal gel, and 8.3% were treated with Apomorphine s.c. infusion.

Referral practices for APD

Overall, 76.4% of the patients were referred to the movement disorder center and most of these patients were referred by a neurologist (53.4%) or by a general practitioner (32.7%). The mean time since referral to the center was 3.5 years.

APD criteria questions / prognostic model

The highest agreement between physician's judgment and classification by APD-questions was achieved by question 8 (limitations in activities of daily living, Cohen's Kappa: 0.440), followed by question 1 (level of motor fluctuations, Cohen's Kappa: 0.425) and question 7 (at least 5 times daily oral levodopa dosing, Cohen's Kappa: 0.410). With a Cohen's Kappa of 0.441 the cumulative APD classification (i.e. at least one of the 11 questions would classify the patient as APD) did not show a much better performance than question 8 alone.

Variable selection was performed in order to find a prognostic model for APD (vs. Non-APD) with optimal predictive performance. Among 32 potential prognostic factors, the following APD criteria were chosen as predictors in the final 13-variable model: APD question 4 (≥ 2 hours of the day with troublesome dyskinesia), question 6 ("off" times at least every 3 hours), question 7, and question 8. In addition, the following variables were included in the final model: UPDRS II score, UPDRS V score, time since diagnosis, current invasive PD treatment, gender, motor fluctuations, caregiver support, geographic region, and type of residence.

Discussion

Many APD patients cannot be managed by conventional PD treatment (oral/transdermal) alone as the disease progresses [3]. Within this study, 43.6% of patients with APD were on ongoing invasive treatments. Arguably, the actual rate of patients benefiting from invasive therapy may be higher, as many patients in this study, despite being considered eligible, did not receive invasive treatment (42.2%).

Real-life experience suggests that neurosurgical treatment (deep brain stimulation) is the most commonly used invasive PD treatment [12]. In this study, however, the choices for neurosurgery and LCIG were made in similar frequency – in 47.0% neurosurgical treatments were planned, and in 45.9% LCIG was foreseen in patients who were not yet on invasive therapies. The relatively high proportion of LCIG treatment of the centers is striking, and may give proof of the fact that LCIG treatment is increasingly adopted as treatment modality. Another reason may include that MDC within the study had less often access to neurosurgical treatments (58.7%) than to LCIG (92.9%). As well the relatively low percentage of access to Apomorphine s.c. infusions (67.5%) is striking. In this context, the fact that the site selection was performed by AbbVie (the sponsor of this study) must be taken into account as a potential source of bias.

In this study, a statistical model based on the collected data was created in order to elucidate the parameters which best correlate with the physician's judgment of assessing a patient as having APD. Not all parameters identified as predictors seem to be equally adequate. Demographic parameters such as the geographical region or gender are obviously not useful as a predictive marker as they may be influenced by

various confounding factors. Therefore, the fact that certain geographical regions (EEMA/JAPAC) were correlated with a higher likelihood of APD may highlight different healthcare standards (e.g. later referral to MDC etc.), or medical practices rather than a higher prevalence of APD in these regions. Many parameters in this statistical model, however, seem to have face validity and to be consistent among each other: Parameters such as longer time since diagnosis, dyskinesias, and limitations of activities of daily living conclusively rank among the best predictors for the diagnosis of APD. The fact that 87.0% of APD (vs. 23.2% in non-APD) patients were reported as suffering from motor fluctuations may hint at the fact that physician's judgment was strongly based on motor fluctuations. As compared to the questionnaire generated by use of the Delphi method, which subsumes a broader range of symptoms under the diagnosis of APD, physicians' judgment has potentially been too narrow. Eventually, the development of universally accepted criteria for diagnosis and disease management of APD would be helpful in diagnosing APD more reliably.