Austin Journal of Clinical Neurology

Open Access

Austin Publishing Group

Research Article

TEMP - Therapy Escalation in M. Parkinson - A German Regional Multicenter Survey

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Received: September 20, 2021; **Accepted:** October 19, 2021; **Published:** October 26, 2021

Abstract

Objective: To characterize socio-demographic and disease-specific data of Parkinson's disease patients before and 1 year after therapy escalation with subcutaneous Apomorphine (APO), Levodopa/Carbidopa Intestinal Gel (LCIG), or Deep Brain Stimulation (DBS) in an observation trial under real life conditions.

Methods: Between 2014-2015, patients undergoing therapy escalation were consecutively included in 5 movement disorders centers. Motor and non-motor symptoms were scored recorded before and 1 year following initiation of invasive treatments. Therapy adherence, changes of scores and oral medication were evaluated.

Results: In this open-label, prospective, 12-months, multicenter real life study 63 patients were included. 31 received DBS, 19 were commenced on LCIG, 15 received treatment APO. 16 patients were lost for follow-up. Therapy adherence after one year in STN-DBS was 100%, in LCIG 87.5%, and in APO 47%. Therapy termination in the APO cohort was due to onset of hallucinations, orthostatic hypotension and inflammatory skin lesions and necrosis. After one year, UPDRS-III scores improved for STN-DBS patients. All groups gained ON-time without differences between the 3 arms. STN-DBS patients had less ON-time with dyskinesia compared to APO- and LCIG-patients. Levodopa daily dose was decreased by 50% in STN-DBS patients, and 33% in APO patients, respectively

Conclusion: All three escalation options improved ON-time. Therapy adherence in APO was less than 50% after 1 year, making it a potential bridging option while awaiting a more invasive treatment.

Keywords: Parkinson's disease: Escalation; Apomorphine; Levodopa/carbidopa intestinal gel; Deep brain stimulation

Introduction

In the early stages of Parkinson's Disease (PD), motor symptoms are usually well controlled by oral or transdermal dopaminergic medication. However, with longer disease duration, the incidence of levodopa induced motor fluctuations increases under dopaminergic treatment [1]. Adjustment of levodopa or dopamine agonist single doses and frequency may transiently improve motor and non-motor fluctuations, and a combination with COMT-inhibitors or MAO-B-inhibitors might temporarily suffice to control fluctuations. When adjustment of oral medication however does not satisfactorily control motor problems [2], an escalation of therapy with invasive treatment alternatives are considered as a therapeutic option. Subcutaneous apomorphine Administration with a Pump Device (APO) [3], Levodopa-Carbidopa Intrajejunal Gel-Infusion (LCIG) [4] and Deep Brain Stimulation of the Subthalamic Nucleus (STN-DBS) [5,6] are available. They not only differ in terms of invasiveness, but also in side effect profiles and need for post-interventional caring. These different aspects predispose for a specific invasive therapy option based on an individual decision. There are some therapy recommendations at hand as to which escalation is recommended to what patients [7-9] to date, real life compliance data of patient maintenance are limited. We therefore performed a real-life observational study on PD patients escalated on APO, LCIG, or STN-DBS.

Methods

This study was approved by the Ethics Committee of the Brandenburg Medical Board. All participants provided written informed consent.

Between 5/2014 and 1/2015, PD-patients fulfilling the UK Parkinson's Disease Society Brain Bank Criteria [10] that underwent a therapy escalation with either APO, LCIG, or STN-DBS were consecutively included in five Neurology Departments (two university tertiary medical centers, one tertiary care hospital, one secondary care hospital and one specialized Movement Disorders Hospital) in Berlin and Brandenburg, Germany. Socio-demographic data, Unified Parkinson's disease rating scale (UPDRS)-III and MDS-UPDRS I, II, IV scores to define non-motor, motor impairment and motor complications, percentages of daily OFF-time, daily ON-time and daily ON-time with dyskinesia, Hoehn & Yahr stage [11] to assess the global disease severity, and current dopaminergic treatment were recorded. One year after therapy escalation, patients were followed up, and changes in disease-specific scores and oral dopaminergic medication were assessed.

Statistical analysis was performed using IBM SPSS statistics

Citation: Gandor F, Kübler D, Ebersbach G, Kühn A, Müller J, Klostermann F, et al. TEMP - Therapy Escalation in M. Parkinson - A German Regional Multicenter Survey. Austin J Clin Neurol 2021; 8(3): 1154.

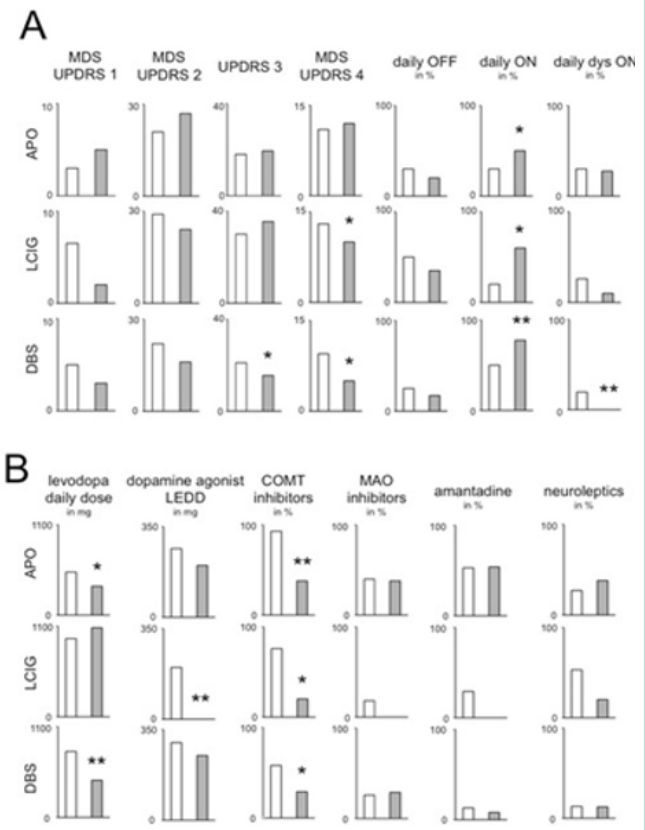

Figure 1: Comparison of disease specific scores (A) and oral dopaminergic medication (B) at baseline (white bars) and one year follow-up (grey bars). Values for levodopa daily dose and dopamine agonist in levodopa equivalent dose in mg, COMT-inhibitors, MAO-inhibitors, amantadine and neuroleptics as percent. *p≤0.05, **p<0.005. APO apomorphine, LCIG: Levodopa/ Carbidopa Intrajejunal Gel; STN-DBS: Deep Brain Stimulation; dys dyskinetic.

software. Distribution was calculated applying Shapiro-Wilk-Test, variance using the F-test. Difference between groups was assessed applying Kruskal-Wallis and post-hoc Mann-Whitney U-tests, since all values were not normally distributed or normally distributed but unequally variant. Alpha was set at 0.05.

Results

Within the survey period, 63 eligible patients consented to participate. 31 (49%) patients were escalated with STN-DBS, 17 (27%) received LCIG, and 15 (24%) were commenced on APO, respectively. 21 patients were lost for follow up (2/15 APO patients, 12/17 LCIG patients, 7/31 STN-DBS patients). One patient in the LCIG-group died of unrelated cause. Therapy adherence after one year in those patients available for follow-up was 100% for STN-DBS and LCIG. 8/13 (62%) APO patients discontinued treatment due to hallucinations (n=5), orthostatic hypotension (n=2), or cutaneous necrosis at the injection site (n=1).

Patients receiving STN-DBS were younger than those escalated with APO or LCIG (STN-DBS 64 [41-75] years *vs.* APO 76 [47-82] years and LCIG 73 [67-79] years; p = 0.04; median [range]) and had a shorter disease duration and a shorter course of motor fluctuations (Table 1). During ON-stage, disease severity, defined by Hoehn & Yahr stage, and motor impairment, objectified by UPDRS-III was lowest in the STN-DBS group, followed by APO, and LCIG (Table 1).

At one-year follow-up, motor impairment improved significantly only in STN-DBS patients (UPDRS III at baseline 21 [9-43] *vs.* follow-up 15.5 [3-45], p<0.05). Motor fluctuations significantly improved in the LCIG group (MDS-UPDRS IV at baseline 13 [9-18] *vs.* follow-up 10 [1-12], p<0.05) and STN-DBS group (baseline 9.5 [0-14] *vs.* follow-up 5.0 [0-13], p <0.05). Non motor function assessed by MDS-UPDRS I and II remained unchanged. When extracting the percentage of ON-time and ON-time with dyskinesia from the MDS-UPDRS IV, patients in all groups gained more ON-time per day at follow-up (LCIG 20% [0-50] *vs.* 60% [9-75], p=0.01; STN-DBS 50% [25-100] *vs.* 75% [43-100], p=0.002; APO 30% [0-76] *vs.* 50% [10-85], p=0.05). In addition, patients escalated with STN-DBS also reported a significant reduction of ON-dyskinesia from baseline to follow-up (baseline 19.5% [0-54] *vs.* follow-up 0% [0-25], p<0.001). This trend was also seen in patients receiving LCIG but did not reach a significant level (baseline 26% [0-80] *vs.* follow-up 10% [0-35], p=0.07).

The levodopa daily dose in STN-DBS patients could be decreased by 47% (800mg [400-1200] *vs.* 425mg [0-1025], p<0.001), in APO patients by 33% (525mg [350-1650] to 350mg [150-825], p=0.01), respectively, but remained nearly unchanged in LCIG patients (at baseline 950mg/d *vs.* at follow-up 1082mg/d; n.s.). On follow-up, all LCIG patients were withdrawn from dopamine agonists, whereas the levodopa equivalent dose of agonist therapy in the APO and STN-DBS groups remained nearly unchanged. Although not significant, LCIG patients received less neuroleptic medication at one-year follow-up in contrast to APO patients, who had a slight increase in neuroleptic's daily dosage.

Discussion

In this open-label, prospective, observational, real-life multicenter trial following up a cohort of 63 PD-patients with motor fluctuations that underwent therapy escalation with Subthalamic Deep Brain Stimulation (STN-DBS), subcutaneous Apomorphine (APO), or Levodopa-Carbidopa Intrajejunal Gel-Infusion (LCIG), we showed that STN-DBS patients were significantly younger than patients that received LCIG or APO. This finding reflects the consideration that younger patients are deemed more suitable to undergo STN-DBS, resulting in less age-related peri-interventional complications [9]. Moreover, this approach might be influenced by results from the Early-Stim study [6].

The therapy adherence in the APO cohort was low. The high rate of discontinuation in the APO group is in line with previous reports [12]. The older age in this cohort seems at first sight counterintuitive for commencing APO treatment, since the prevalence of dopamine agonist driven neuropsychiatric side effects increases with age and disease duration [13-15]. The fact that 5/13 (38.5%) patients discontinued APO due to hallucinations further supports this assumption. Sesar and colleagues observed psychiatric effects under APO resulting in discontinuation of treatment in 15/230 patients (6.5%). In addition, hallucinations significantly worsened with longer APO treatment [12]. These findings contrast a report were APO was found to have beneficial effects on visual hallucinations [13].

In addition to the side effects of visual hallucinations, orthostatic hypotension and cutaneous necrosis that caused APO patients in our

Table 1: Demographic data at baseline. Data in median (range) or n (percent of total).

	Total (n=63)	APO (n=15)	LCIG (n=17)	DBS (n=31)
Age	69 (41-82)	76 (47-82)	73 (67-79)	64* (41-75)
Females	28 (44%)	9 (60%)	9 (53%)	10 (32%)
Disease duration	12 (4-35)	13 (4-31)	14 (6-35)	10* (4-17)
Years fluctuating	3 (0-17)	6 (0-17)	5 (2-15)	2* (0-11)
H&Y On	2.5/4	3*	3	2*
H & Y Off	4	4*	5	3*

Group analysis with Kruskal Wallis test and post-hoc Mann-Whitney U-test. APO: Apomorphine; LCIG: Levodopa/Carbidopa Intrajejunal Gel; STN-DBS: Deep Brain Stimulation; H&Y: Hoehn and Yahr stage.

survey to withdraw from treatment, the unchanged severity of motor fluctuation might further contribute to the low therapy adherence rate of less than 50% at 12 months. In 2017, Sesar and colleagues summarized the results of a 10-year survey of 230 PD-patients that were commenced on APO and found that therapy adherence after 1 year was only 63.5%, with a drop-out rate of 27.0% after only 6 months.

A clear limitation of our observational study is the high rate of patients lost for follow-up in the LCIG group (71%) compared to the STN-DBS group (23%) and APO group (13%). Undoubtedly, the high lost for follow-up rate in the LCIG group does not allow commenting on the therapy adherence in this group, nor comparison with the remaining escalation therapies. This underlines the need to adapt follow-up visits by including video-based consultations to follow a structured reassessment protocol.

Previous studies show adherence to LCIG above 90% after 12 months [18] and around 70% after 24 months [19]. In addition, we found in those LCIG patients available for follow-up an increase in ON-time and reduction in dyskinesia one year after escalation, which is in line with previous reports [4,18,19]. The fact that LCIG patients were significantly older than patients escalated with APO and STN-DBS might reflects the consideration that peri-interventional complications of STN-DBS implantation and psychiatric side effects of dopamine agonists are more prevalent with older age. In addition, non-motor side effects of PD become more prevalent with longer disease duration and older age [1]. Therefore, the withdrawal of psychotogenic dopaminergic medication such as dopamine agonists [20] or amantadine [22] in the LCIG cohort resulted in a reduced number of these patients on neuroleptic treatment and improvement of MDS-UPDRS-I scores after one year.

STN-DBS and APO provided more ON-time per day one year after intervention. The amount of daily ON-time with dyskinesia was reduced in STN-DBS, but not APO patients. Moreover, MDS-UPDRS-IV scores, assessing the severity of motor fluctuation, were only significantly decreased in STN-DBS.

Sesar et al. found no change in dyskinesia in the aforementioned survey on APO patients [12], replicating the findings in our survey. In contrast, the EUROINF study found a significant improvement of UPDRS-III and -IV-scores in PD-patients commenced on APO. However, patients were in comparison significantly younger (62.3±10.6 years), and the observation period was only 6 months [3]. In contrast to a solely dopaminergic effect on motor control with APO, STN-DBS patients, in addition to the prokinetic stimulation effect of the subthalamic nucleus, might further profit from the ability to stimulate areas with antidyskinetic properties, generally aiming at the pallidofugal fiber tracts dorsal of the STN [17].

As expected, levodopa daily dose was significantly lowered in patients with STN-DBS, as found in all major STN-DBS trials [5,6]. Also, patients escalated on APO had significantly lower daily levodopa doses after one year, which is in line with previous findings [12]. In contrast, daily dopamine agonist dose remained nearly unchanged in APO and STN-DBS patients.

To date there is no clear recommendation for which patients to consider for APO as a first line escalation option when addressing symptom fluctuation. Furthermore, an expert panel found no consensus on which escalation therapy to prefer for patients older than 70 years [8]. This reflects the multifaceted picture that needs addressing when considering therapy escalation, taking patient preference, concomitant conditions, the neuropsychiatric history, the social and caregiving environment into account to decide on the best option for the patient [16].

Taken together, no treatment recommendations can be drawn from this study, owed to its open-label observational design and the low patient number. Our findings therefore have to be interpreted with caution. However, our data stress certain points that merit discussion. As previously published, younger PD patients with a shorter disease duration profit from STN-DBS to control motor fluctuation, resulting in more ON-time, less OFF-time, less dyskinetic ON-time and reduced daily levodopa dosage [6]. Since therapy adherence of APO is low over a period longer than 6 months [12], APO might be a suitable bridging option for PD patients awaiting a more invasive therapy escalation.

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