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Treatment of Parkinson's Disease after the Wearing Off Sets in

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Abstract

In 2018, we wrote a paper on the drug treatment of Parkinson's disease. In this article, we obtained that the wearing off was observed in 77%, but the incidence of dyskinesia was 37.7% for the Parkinson's disease patients from the onset of the disease 16-20 years. In this review article, we will discuss some of the newer treatments of Parkinson's disease first, i.e., transplantation with induced pluripotent stem cell-derived cells, gene therapy, deep brain stimulation, levodopa/carbidopa intrajejunal gel infusion, MRI-supported focused ultrasound, and IPX066. Then, we will discuss our opinion on the mechanism of wearing off and dyskinesia, and modifications of levodopa treatment after the wearing off sets in.

Introduction

In 2018, we wrote a paper on the drug treatment of Parkinson's disease (PD)[1]. We observed wearing off (shortening of the levodopa beneficial effects on parkinsonism) to be 77% and the incidence of dyskinesia (abnormal involuntary movements mainly due to the overdose of levodopa) 37.7% for the PD patients from the onset of 16 – 20 years (Table). In this review of the treatment of PD, we will touch on the newer treatments but would not intend to go in, if such treatments would be good or bad to the patients with PD. We believe that newer treatments as described below were introduced for the goodness of patients with PD. Then, we will discuss modifications of levodopa treatment after wearing off sets in.

Newer treatments of PD

Newer treatments have been introduced to the treatment of PD. Most of the newer treatments have developed as to treat the motor fluctuations of the PD.

Induced Pluripotent Stem Cells

Takahashi and Yamanaka[2] were successful inducing pluripotent stem cells (iPS) from mouse embryonic or adult fibroblasts by introducing four factors. Since then PD has become a candidate, which may be benefitted by transplant by dopaminergic neurons derived from the iPS[3]. The first

Table. From reference 1, modified, Data indicate the number of patients who were positive in respective symptoms and the percentage.

From the onset	No.	Wearing off		Dyskinesia		Freezing	
5 years or less	135	24	17.8%	3	2.2%	41	30.4%
6–10 years	158	89	56.3%	28	17.7%	88	55.7%
11–15 years	114	86	75.4%	36	31.6%	67	58.8%
16–20 years	53	39	73.6%	20	37.7%	35	66.0%
21 years or more	38	29	76.3%	21	55.3%	29	76.3%
Total	498	267	53.6%	108	21.7%	260	52.2%

patient of PD was done in autumn of the year 2018. It will take 2 years or more to obtain the result. In addition, as they are using a MHC (major histocompatibility complex)-matching human iPS for this transplantation, they have to use an immuno-suppressor, tacrolimus[4].

It is not known if the treatment using iPS is better than using fetal midbrains for transplantation. Olanow et al.[5] reported on patients with PD by transplantation using the midbrain of the fetus. UPDRS (Unified PD rating scale) of the transplanted patients with PD were better until 15 months after the surgery. But after the 15 months, there was no significant difference with placebo-treated patients.

Gene therapy

The progress of the gene therapy as of 2012 is well described in the review of Nakata et al.[6]. Among them, aromatic amino acid decarboxylase (AADC), glutamic acid decarboxylase (GAD), and neurturin appear to be of worth mentioning. Amino acid decarboxylase activity in the nigrostriatal system in the advanced PD is very low[7].

Muramatsu et al.[8] studied 6 patients with advanced PD for 6 months using adeno-associated virus vector 2 and AADC infusion in the striatum. They found that motor functions in the off-medication state improved an average of 46%. Mittemeyer et al.[9] reported on ten patients the elevated PET signal to be persisted over 4 years. The UPDRS in all patients off medication improved in the first 12 months but displayed a slow deterioration in subsequent years.

Glutamate is an excitatory transmitter in the subthalamus[10]. When the glutamic acid decarboxylase is infused to the subthalamus, it may reduce the excitatory tone by changing glutamate to gamma amino butyric acid (GABA). LeWitt et al.[11] did a bilateral subthalamic infusion of AAV2(adeno-associated virus 2)-GAD (N = 33) compared with sham surgery in patients (N = 22) with advanced PD. At the 6-month, the AAV2-GAD group showed significantly greater improvement from baseline compared with the sham group.

Glial cell-derived neurotrophic factor (GDNF) enhances the function of nigrostriatal dopaminergic neuron[12]. However, a double-blind trial did not show a beneficial effect of GDNF[13]. Using neurturin, a naturally occurring structural analogue of GDNF[14], Olanow et al.[15] reported no significant difference after the infusion of neurturin from the sham surgery group.

Deep Brain Stimulation

Deep brain stimulation (DBS) became a standard procedure in the surgical treatment of PD since 1993[16-17]. Short term effects up to five years are better in surgically treated patients than medically treated patients[18-22]. For the prognosis for more than 10 years, it is not clear. Merola et al.[23] reported that the clinical course of STN-DBS (subthalamic DBS) progressively worsened during the 20 years period; 64% falls, 86% dysphagia, 57% urinary incontinence and 43% dementia. Janssen et al.[24] reported that motor performance was mainly due to a deterioration in bradykinesia and axial symptoms in a study of 5 years on 26 of PD. Rizzone et al.[25] reported that motor complications were well controlled at 11 years from the surgery, but that the UPDRS-II-on score worsened by 88.5%. Bang Henriksen et al.[26] reported that 29 were demented, 19 were in nursing homes, and 24 have died among 79 patients who received STN-DBS 10 years before. Constantinescu et al.[27] reported on 26 men and 7 women operated 15 years before and a sustained benefit was maintained in 19 of them (83%) but STN-DBS was inactivated in four (17%) due to inefficacy. All patients deteriorated slowly, and a majority developed severe non-motor and axial symptoms.

Regarding side effects of the DBS, voice and speech disorders are one of the most important issues[28-29]. Tanaka et al.[29] reported that the STN-DBS group, especially females, showed widespread impairment of voice parameters (n=37) than the medical-therapy-alone group (n=40). Regarding the technical problems, infection, lead migration, skin erosion, and pain over the leads are well known[30].

Thus, a long-term follow-up of more than 10 years is not always good for DBS. These symptoms may be a part of the natural course of PD, but it is important to compare with medically treated patients.

Levodopa/carbidopa Intrajejunal Gel Infusion

Intrajejunal gel infusion of levodopa/carbidopa (LCIG) started in 1988 for the treatment of severe wearing off[31]. This method can be applied to patients 70 years or over with or without mild to moderate dementia[31-32]. This method is also useful in non-motor symptoms of PD[33]. Olanow et al.[34] reported that mean off-time decreased by 4.04 h on 35 patients with LCIG compared with a decrease of 2.14 h for 31 patients allocated to immediate-release oral levodopa-carbidopa at 12 weeks. Regarding side effects, Fernandez et al.[35] reported that the most common were abdominal pain (30.7%), complication of device insertion (21.4%), procedural pain (17.7%), dyskinesia (10.9%), postoperative wound infection (10.4%), and excessive granulation tissue (13.5%) in 168 patients during 54-weeks treatment with LCIG. Wang et al.[32] made meta-analysis on 8 trials with 384 patients of advanced PD with motor fluctuations. They concluded that compared with the control group, LCIG significantly decreased off-time, but more randomized double-blind controlled studies were needed to further confirm the efficacy and safety of LCIG. The device and procedural complications were common in LCIG, and it does not seem a safe treatment of PD.

MRI Guided-Focused Ultrasound

MRI guided-focused ultrasound is a novel technique[36]. It is a treatment for essential tremor, PD, and neuropathic pain. It has been brought into clinical medicine since 2014[36-37]. It seems good for unilateral intermedio-ventral thalamotomy in essential tremor[38] and PD patients with dyskinesia[39]. Although it appears to be promising, long-term studies are needed.

IPX066

IPX066 is a novel extended-release CD–LD (carbidopa-levodopa) formulation. It is designed to achieve rapid absorption and onset of clinical benefit and to provide longer duration of clinical benefit for 4 to 6 hours[40]. Hauser et al.[41] reported that plasma levodopa concentrations increased at a rapid rate and was sustained above 50% of peak concentration for 4 hours in a single dose of IPX066, whereas immediate-release carbidopa-levodopa was sustained 1.4 hours. Hauser et al.[42] reported that 201 patients treated double-blind with extended-release carbidopa-levodopa had greater reductions in off-time than did 192 patients treated double-blind with immediate-release carbidopa-levodopa. Stocchi et al.[43] reported that 84 patients in an advanced stage with motor fluctuations demonstrated a lower percent off time, lower off time, and higher on time without troublesome dyskinesia with IPX066.

Hsu et al.[44] reported that the single-dose pharmacokinetics of ER CD-LD (sustained release levodopa/carbidopa) in healthy subjects sustained for approximately 5 hours and not to decrease to 10% of peak until 10.1 hours, whereas immediate release LD reached peak concentrations at 1 hour; then decreased rapidly. With CD-LD-entacapone, LD Cmax occurred at 1.5 hours, and concentrations were less than 10% of peak by 6.3 hours. Concomitant use of dopamine agonists or monoamine oxidase inhibitors did not interfere with the beneficial effects of IPX0061[45].

Levodopa/Carbidopa Therapy

For the first 5 to 6 years since the start of levodopa treatment, 100 -150 mg of levodopa with carbidopa three to four times a day before or after the meal is suffice to most of the PD patients[1, 46-47]. After 5 years or later since the levodopa was started, a patient with PD may notice worsening of the symptoms. Motor symptoms approximately follow the blood levels of levodopa. Patients of PD may have non-motor symptoms while off.

A Reason why Wearing off and Dyskinesia occur

The blood half-life of levodopa is approximately 2 hours and a half[44]. Why no wearing off in the beginning of levodopa treatment. When the motor symptoms of PD occurs, approximately 50% of nigral neurons may be remaining[48]. Therefore, the ingested levodopa enters the dopaminergic terminals. Here, the dopamine transporters exist. Therefore, dopamine released to the synaptic cleft soon will be picked up into the original dopaminergic neurons after stimulating the dopamine receptors. But the time goes on, most of the dopaminergic neurons have degenerated. Then levodopa may be picked up by the serotonin neurons, which can produce dopamine, because they have aromatic amino acid decarboxylase. These serotonin neurons do not have dopamine transporters. Therefore, once released dopamine cannot be re-up-taken to those serotonergic neurons. Dopamine must be metabolized extracellularly and intracellularly in glial cells. This may be the underlying mechanism of wearing off. Dopamine floating in the synaptic cleft may induce dyskinesia. But the speed of neurodegeneration in serotonergic neurons may be slower than the dopaminergic neurons in PD[49]. Once the serotonergic neurons in the striatum undergo neurodegeneration, neuroglia may take place to produce dopamine. But the neuroglia-induced dopamine will not be sufficing to undertake the motor disturbance of PD. After a long run, patients with PD respond rather poorly to levodopa with less wearing off. This clinical course of PD seems to fit well to what may be going in the brain.

Modifications of Levodopa Treatment after Wearing off sets in

Giving Levodopa/Carbidopa 4 to 9 Times a Day: When the drug on period becomes below 3 hours, we have to give the patients with PD levodopa/carbidopa 5 to 7 times a day. Eventually one may need to give levodopa/carbidopa 8 or 9 times to the patients. Each dose of levodopa may be 75 to 200 mg.

Giving Levodopa/Carbidopa before meals: Giving levodopa/carbidopa before meals may give you somewhat higher blood levels than giving levodopa after meals.

Modify the drug interval: Patients with PD frequently claim that the duration of the drug interval varies a lot. Instruct the patient to take the levodopa at the beginning of the worsening of symptoms to reduce the off time. Most of the patients aware of the effect of levodopa/carbidopa is disappearing. It takes for approximately 30 minutes for levodopa/carbidopa to become effective.

Giving liquid levodopa/carbidopa. When the beneficial effect of levodopa to appear takes more than one hour, try to give the patient water soluble levodopa. Carbidopa/levodopa is easy to water soluble[50]. A levodopa/carbidopa tablet may stick to the esophageal or stomach wall. By the liquid levodopa, this can be avoided. Liquid preparation of levodopa is made to put a levodopa/carbidopa tablet into 50cc of water[51]. It is better to keep it in a refrigerator.

Modify each dose: Usually, patients become worse towards late afternoon. If an usual day dose is 100 mg every 3 hours, try to give 150 mg at 3 o'clock or so.

In case of early morning akinesia: Give levodopa while in a bed, then move one's arms and legs in the bed for 15 to 20 minutes.

In case of dyskinesia: Try to discontinue selegiline or rasagiline if the drug is used. These drugs may worsen dyskinesia. Try to reduce or discontinue a dopamine agonist. These drugs may worsen dyskinesia when dopamine agonists are used together with levodopa. Try to discontinue istradefylline, which may aggravate dyskinesia. Try to decrease or discontinue COMT inhibitors. The incidence of dyskinesia is higher in those who were treated levodopa/carbidopa + entacapone that levodopa/carbidopa + placebo[46]. If all procedures fail to control dyskinesia, reduce the individual dose of levodopa and increase the number of dosages in a day.

In case of hallucination: Decrease individual dose of levodopa/carbidopa and increase the number of dosages in a day. Decrease or stop medication other than levodopa/carbidopa. One may add quetiapine 25 to 150 mg two or three times daily, donepezil 5 -10 mg a day, or both.

In case of freezing: Freeing tends to occur during the off period. Try to keep on as possible. Freezing tends to occur on the corner of the home and changing the position in the bathroom. Instruct the patients to walk on the heels with arms swing lightly, and to raise their heads. Freezing may also occur when she or he is engaged in drying the washing in the sun or to carrying a tray to bring food. In such occasions, nerve impulses going to the lower extremities become weak. Then, freezing or fall sets in. Patients with PD should be instructed that no drug will help freezing and freezing should be avoided by their own mind.

Conclusions

With the meticulous management of levodopa, majority of the patients with PD are managed medically for a long period. Newer treatments such as the gene therapy, DBS, MRI-guided focused ultrasound, and IPX066 are at times good for PD patients. But usually, they do not want surgery or any devices to be put on their bodies.

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