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Treatment strategies in advanced Parkinson's disease: Review of the literature

İleri evre Parkinson hastalığında tedavi stratejileri: Literatürün gözden geçirilmesi

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SUMMARY

Parkinson's disease (PD) is a chronic, neurodegenerative disorder affecting basal ganglia, dopamine-secreting cells in the pars compacta region of the substantia nigra, in particular. It commonly affects people above the age of 50, however younger –onset has also been reported. Since there is an ongoing dopaminergic cell death in basal ganglia, it is a progressive disorder leading to severe disability in the late stages of the disease. The advanced stages of PD are the most challenging part of the disease for clinicians, as well as the patients' themselves due to the motor fluctuations, freezing of gait, dyskinesia, postural instability, falls, autonomic involvement, non-motor symptoms. This symptomatology corresponds to the stage of 4-5 on the Hoehn and Yahr (H&Y) scale, which is commonly defined as advanced PD. The treatment options in the patients with advanced PD are discussed in this review.
Keywords: Parkinson's disease, advanced stage, treatment options

ÖZET

Parkinson hastalığı (PH), özellikle substansiya nigra pars kompakta bölgesindeki dopamine salgılayan hücreler olmak üzere bazal gangliayı etkileyen kronik, nörodejeneratif bir bozukluktur. Sıklıkla 50 yaş üzeri kişileri etkiler. Bununla birlikte daha genç başlangıç da bildirilmektedir. Bazal gangliada devam eden bir dopaminerjik hücre ölümü olduğundan, ileri dönemlerde ciddi özürlülüğe yol açabilen ilerleyici bir hastalıktır. PH' nın ileri dönemeleri, motor dalgalanmalar, yürüyüşte donmalar, diskinezi, postüral instabilite, düşmeler, otonomik tutulum, non-motor semptomlar nedeniyle hastalar için olduğu kadar klinisyenler için de zorlayıcıdır. Bu semptomatoloji, sıklıkla ileri evre PH olarak tanımlanan Hoehn and Yahr (H&Y) skalasında evre 4-5' e karşılık gelir. Bu derlemede ileri evre PH olan hastalarda tedavi seçenekleri tartışılmıştır.
Anahtar sözcükler: Parkinson hastalığı, ileri evre, tedavi seçenekleri

INTRODUCTION

Approximately 50 % of the PD patients suffering from the disease at least for 5 years, experience motor fluctuations. Thus, medical treatment options for the advanced PD can be summarized as the treatment of motor fluctuations which occur as a result of narrower therapeutic window as the disease progresses, where low plasma and striatal levels of dopaminergic drugs lead to "off" periods, and the higher levels lead to dyskinesia[1]. However non-motor symptoms including orthostatic hypotension, sleep disturbances, constipation, urinary incontinence, and cognitive involvement, psychiatric symptoms such as anxiety, depression, and psychosis should also need assistance and management[1, 2].

Treatment of motor fluctuations

The underlying mechanism of motor fluctuations is believed to be the pulsatile stimulation of dopaminergic receptors of the striatal spiny neurons after an oral dose of LD due its' varying concentrations. Since they are likely to occur at the onset of advanced stage of PD, modifications in the regimen of anti-Parkinson drugs at this stage seems to be mandatory [3].

As a well-known entity, the absorption of levodopa (LD) interferes with amino acids. Thus patients suffering from daily off periods should be warned to take levodopa-carbidopa/levodopa-benserazide (LC/LB) formulations at least one –half hour before or after meals. This strategy would be sufficient to reduce off times, in some cases [4]. Additionally, fractionating the doses of LC/LB and changing the time intervals between doses would also be helpful to reduce daily off periods in the patients who are going through the advanced stage of PD. However administering liquid LC with ascorbic acid solution to the patient can be another option in the treatment of motor fluctuations[4-7]. According to the ADVANCE-PD results, extended-Release Levodopa (IPX066, ® RytaryVR) which is a LC capsule containing immediate and sustained release pellets reduced the daily off-time in patients with motor fluctuations [7].

As an alternative option to prevent daily off periods, and/or wearing off, Brooks et al, showed that adding Catechol-O-Methyltransferase inhibitors (COMTI) to LC/LB formulations would be beneficial in reducing the off time in patients with advanced stage PD. Moreover, this strategy should give a chance to reduce the doses of LD, as well as the frequency of the drug [8]. Since tolcapone has a side-effect like liver toxicity, entacapone is widely used which is shown to reduce the off periods approximately 40 minutes in patients with motor fluctuations[9]. However, Kiss et.al, presented a long-acting peripherally selective COMTI "opicapone" in 2010 [10], and the phase III trial results of BIPARK-I study of opicapone was presented in 2015, which revealed that 50mg opicapone remarkably reduced off-time and increased on-time without severe dyskinesia [11].

Adding monoamine oxidase inhibitors (MAOIs) to LD is another way of reducing motor complications. Fox et al., reported that 1 mg/day rasagiline addition to daily LD doses can be effective in the treatment of motor fluctuations, by reducing the off-time approximately 1 hour when adjunct to LD in patients with motor fluctuations [12, 13]. In favor of this hypothesis, the results of PRESTO study also demonstrated a reduction in off time in patients with motor fluctuations who were administered 0.5 mg and 1 mg/day rasagiline with LC/LB formulations [14]. Safinamide (® Xadago) is a reversible MAO-B inhibitor which can be used as an add-on therapy regimen. It also acts via blocking sodium channels and modulating the release of glutamate. This mechanism of action gives a chance to improve OFF episodes without worsening dyskinesia [15].

The administration of long-acting dopamine agonists (DAs) in the treatment of motor fluctuations to maintain continuous dopaminergic stimulation may be another way of treating motor fluctuations[16]. Based on this hypothesis, PREPARED study demonstrated a 20% and more reduction in off time from baseline with ropinirole prolonged release formulation [17].

For unpredictable off periods, apomorphine which is a fast-acting DA can be administered subcutaneously, as a rescue agent[18]. However, the possible side-effects of DAs such as cognitive decline, hallucinations, orthostatic hypotension, as well as impulse control disorder should be kept in mind [19]. While, a recent apomorphine formulation, inhaled apomorphine (VR040) has an advantage of rapid transfer to bloodstream, it did not show a significant decrease in the off-periods according to phase-II trial results in 2013 [20]. However, a new sublingual apomorphine formulation (APL-130277, Cynapsus), has found to be effective in improving the MDS- Unified Parkinson's Disease Rating Scale (UPDRS) Part-III scores according to the phase-II trial results[21].

Recent studies revealed that adenosine A_{2A} receptor antagonists (istradefyllline, tozadenant) can be beneficial to treat motor fluctuations via inhibiting

the indirect basal ganglia pathway in patients with PDE. Regarding this hypothesis, istradefyllline is the first drug that was licensed in Japan as an add-on therapy of wearing-offs [22, 23].

In the highlight of current knowledge, device-aided therapies which are discussed below can be a beneficial treatment option in selected patients with motor fluctuations [24].

Treatment of LD-induced dyskinesia

Dyskinesia is another challenging issue in the course of PD. It is considered to be associated with abnormal glutamate transmission in basal ganglia and defined as involuntary movements that can exist in a variety of phenomenology including chorea, dystonia, myoclonus, and tics, etc., which may increase with anxiety, and stress. While they appear in wakefulness, they can lead to disability in varying degrees, and need appropriate management for the patient to maintain his or her daily activities [25].

Since the most common type of dyskinesia is "peak-dose dyskinesia", the common approaches in the treatment include the reduction or discontinuation of mono-amine oxidase-B inhibitors (MAO-BI), and catechol-o- methyl-transferase inhibitors (COMTI), respectively, in cases of MAO-BI or COMTI use [25, 26]. To reduce the excessive effect of LD leading to dyskinesia, the long-acting LD formulations can be switched to immediate-release forms. In cases of immediate-release forms of LD usage, the individual doses of LD can be reduced and the frequency of doses can be increased in order to prevent wearing-off. A DA can be added to the regimen, in cases of inadequate motor control due to the decreased LD doses. Intestinal LD treatment can be considered in selected patients, as well as deep brain stimulation (DBS) [26].

Amantadine which is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor is another beneficial agent in the treatment of dyskinesia, diphasic dyskinesia which is more challenging, in particular [27]. Per oral use is more common but recently a new formulation is reported as ADS-5102, a-once daily extended release capsule formulation of the drug in the EASED study, and the 340 mg per oral dose of the drug is found to be effective in providing on periods without troublesome dyskinesia [28]. Based on the positive effects of glutamatergic receptor blockage in the treatment of dyskinesia, Rascol and his colloquies revealed that mavoglurant which is a mGlu5 metabotropic glutamate receptor antagonist has also an antidyskinetic effect regarding to the results of the phase II trials [29].

Diphasic dyskinesia is a more treatment resistant form of dyskinesia, in which the reduction or discontinuation of MAO-BI, and COMTI is a treatment option. Adding DA to the regimen can also be considered, as in peak-dose dyskinesia treatment [26]. As other dyskinesia forms, DBS is an option in the treatment of diphasic dyskinesia [26, 30].

"Wearing-off dyskinesia" or "off-period dystonia" can manifest by toe curling, foot flexion and inversion, painful muscle spasms which deteriorates gait. However bent spine, scoliosis can also be seen in some patients with PD [26, 31]. If off-period dystonia is restricted to night time or early morning, switching the standard LD to long-acting formulation, adding baclofen, or botulinum toxin injections can be considered. Meanwhile, adding COMI or MAOBI to the LD doses, or increasing the frequency of LD doses would be more adequate if the off-periods exist prior to the next expected doses of LD. Adding DAs, baclofen or botulinum toxin injections, subcutaneous apomorphine injections should also be considered[32]. Additionally, deep brain stimulation may also be helpful in unpredictable off dystonias[30, 33].

Treatment of non-motor symptoms

Non-motor symptoms of PD are an important burden on patients and their caregivers as well. There is a wide range of symptomatology including pain, orthostatic hypotension, constipation, urinary incontinence, erectile dysfunction, anxiety, depression, apathy, psychosis, sleep disturbances (insomnia, REM sleep behavior disorder, excessive daytime sleepiness), cognitive dysfunction, impulsive and compulsive behaviors. The proposed treatment options for non-motor symptoms of PD are summarized in Table-1 (Table-1) [34-37].

Table-1. Treatment options for non-motor symptoms of PD

Non-motor symptom	Treatment options
Pain	• Range-of-motion exercise • Optimize dopaminergic therapy [a] • Topical treatments • Acetaminophen • Pregabaline, gabapentine (in case of neuropathic pain) • Opioids
Fatique	• Metilphenidate [b] • Modafinil [b]
Orthostatic hypotension	• Midodrine (Maximum dose 3x10 mg/dail) • Fludrocortisone (0.1-0.2 mg/daily)[c] • Droxidopa (Initial dose: 3x100 mg/day; Maximum dose: 6x100 mg/day)
Constipation	• Dietary changes (increase water intake, etc.) • Macrogol, Polyethlene glycol-based bisacodyl suppository • Abdominal massage
Urinary incontinance	• Bladder routine planning (Going to the bathroom and attemptingto void every 2-3 hours) • Anticholinergics [d] • Mirabegron (β3-adrenergic agent)
Erectile dysfunction	• Sildenafil
Sialorrhea	• Muscarinic receptor antagonists - Ipratropium Bromide Spray - Glycopyrrolate per oral • Intraglandular botulinum toxin injections
Depression, anxiety	• Dopaminergic agonists • Selective serotonin reuptake inhibitors[b] (citalopram, sertraline,fluoxetine,paroxetine) • Serotonin and norepinephrine reuptake inhibitor (venlafaxine) • Tricyclic antidepressants[d] (amitriptyline, nortriptyline, desipramine) • Trazodone • Cognitive behavioral therapy • Transcranial magnetic stimulation
Apathy	• Cholinesterase inhibitors (Rivastigmine transdermal) • Psycho-stimulants • DAs, in selected patients
Psychosis	• Rule out iatrogenic and medical causes (delirium, toxic-metabolic disturbance) • Avoid anticholinergic medications, MAOIs and DAs, respectively. • Cholinesterase inhibitors • Atypical antipsychotics (Clozapine [f], quetiapine, pimavanserin)
Sleep problems	• Insomnia - Maintain sleep hiygiene - Melatonine (1-12 mg) - Zolpidem (5-10 mg) - Trazodone (25-75 mg) - Doxepin (10 mg) • Restless legs syndrome,periodic leg movements - Maintain sleep hiygiene - Dopaminergic agonists - α2δ ligands (pregabalin, gabapentin) - Low dose opioids - Clonozepam • Parasomnias - Cognitive behavioral therapy - Clonozepam • REM sleep behavior disorder - Withdraw or reduce MAOIs, antidepressants, beta blockers, opioids, centrally acting alpha-agonists - Clonozepam (per oral, 0.25–2 mg, 30 minutes prior to bed time) - Melatonine • Excessive daytime sleepiness - Maintain sleep hiygiene - Regular daytime physical activity - Reduce dopaminerjik load, if any - Swith LD+DA combination to DA+MAO-BIs - Try modafinil

Cognitive problems	• Cholinesterase inhibitors [e] (Rivastigmine, donepezil, memantine) • MAO-B inhibitors (Rasagiline) • Memantine [b]
Impulsive and compulsive behaviors (Punding, pathological gambling, hyper sexuality, hyper shopping, hyper eating, hobbyism)	• Reduce dopaminergic therapy • Cognitive behavioral therapy • Clozapine • DBS • Intrajejunal levodopa • Topiramate, valproic acid • Quetiapine • Amantadine

[a] May not be appropriate in patients with advanved PD due to adverse-effects. [b] Insufficient evidence for the efficacy. [c] Potassium should be monitored to avoid hypokalemia. [d] Beware of confusion, delirium, and cognitive deterioration. [e] Rivastigmine has superiority over donepezil. Data for the use of memantine for cognitive dysfunction in PD remain unclear. [f] Watch out the risk of agranulocytosis.

DEVICE-AIDED TREATMENT STRATEGIES IN ADVANCED PD

Since motor complications in the middle and late stages of PD is a result of fluctuating plasma concentrations and a shorter half-life of LD with oral formulations, more continuous dopaminergic stimulation can be provided with device-aided therapies including continuous subcutaneous apomorphine infusion (CSAI), or continuous duodenal/jejunal levodopa/carbidopa jel infusion (LCJI) pump, and DBS[38, 39].

Continuous subcutaneous apomorphine infusion (CSAI)

CSAI is one of the device-aided treatment options in advanced PD patients which can be considered as an effective choice in the management of peak-dose dyskinesias that limit further therapy optimization, off-period non motor symptoms, and in patients who need too frequent rescue doses of intermittent apomorphine. More likely, it can also be benefical in patients with impaired gastric motility, and absorbtion. Contraindications to CSAI are severe neuropsychiatric symptoms, dementia and severe biphasic dyskinesias. However advanced age is not a contraindication and the procedure is reversible and less invasive than continuous duodenal/jejunal LCJI or DBS [40, 41].

Prior to the application of CSAI in suitable patients, apomorphine response test must be done to assess the appropriate, beneficial dose of subcutaneous apomorphine treating the symptoms of PD [42]. A subcutaneous (SC) catheter and a pump device are needed to administer CSAI. Patients wear a portable apomorphine pump on a belt or around the neck which is connected to the SC catheter. For continuous delivery of apomorphine with the effective dose which was determined in the apomorphine response test, delivery doses of the pump can be adjusted in a range of 12 to 24 hours a day, and can be programmed for varying infusion speeds. Even though it is generally a well-tolerated therapy, adverse effects can be seen as nausea, injection site reactions, postural hypotension, confusion, impulse control disorders commonly, and hemolytic anemia, eosynophilic syndrome rarely[43]. Since nausea is the most common adverse effect, peripheral blocking of dopamine receptors with domperidone, which is a peripherally acting DA, should be helpful to reduce the risk of nausea. Initiating oral domperidone three times daily, several days before apomorphine test is considered to be effective in reducing the risk of nausea [44].

Continuous duodenal/jejunal levodopa/carbidopa jel infusion (LCJI)

Since LD is the main drug in the treatment of PD and the response to LD decreases with complications including unpredictable motor fluctuations and dyskinesia as the disease progresses, the continuous LD secretion and more stabilized LD plasma concentrations become mandatory[45]. Additionally, as the therapeutic response is highly dependent on intestinal absorption and gastric motility, which decrease as the PD progresses, there is a growing need for continuous duodenal/jejunal LCJI[46]. It is a device-aided therapy which consists of a carboxymethylcellulose aqueous gel administered via a portable infusion pump attached to a cassette. A transabdominal tube is attached to this cassette, and the drug can be delivered through a permanent endoscopic gastrostomy (PEG) tube, or by an internal jejunostomy tube (PEJ) [45, 46]. LCJI provides continuous and more stable plasma concentrations than oral formulations via bypassing gastric emptying problems, and therefore can be helpful in treating motor complications in selected patients[47].

IPD patients with levodopa-responsive but experiencing motor fluctuations and/or dyskinesia with inadequate oral control are good candidates for LCJI. Contraindications for this therapy include cognitive or psychiatric disturbances, orthostatic

hypotension, and severe hepatic-renal or cardiac comorbidity. Side-effects can occur such as skin lesions/irritations/nodules, nausea and vomiting, sedation, orthostatic hypotension, somnolence, dopamine dysregulation syndrome, and intolerability, as well [48].

Deep Brain Stimulation

Deep brain stimulation is an effective treatment option in patients with IPH whose motor symptoms and fluctuations, dyskinesias are disabling or insufficiently controlled despite adequate medical treatment. Since the best response to DBS is generally equivalent to the best response seen with levodopa, the most important marker in candidate selection is LD response of the patients, except tremor. The other factors which have to be taken in the account for candidacy are cognitive and psychiatric state of the patients, as well as their comorbid diseases, brain magnetic resonance imaging (MRI) findings, age, and the duration of IPD[30, 49]. Krack and his colloquies reported that ''off'' dystonia, followed by diphasic dyskinesias and peak-dose dyskinesias respond well to DBS; however deterioration in gait or balance can be seen after DBS[49, 50]. The most common targets of DBS in IPH are reported to be subthalamic nucleus (STN), and globus pallidus interna (GPi). The question whether there is a superiority of these two targets to each other has been answered as the STN may be superior to GPi in regards to economic profile (fewer battery replacements) and medication reduction, and GPi may be superior to STN in terms of dyskinesia control and medication flexibility, in the literature[51]. However in a recent study comparing these two targets in the means of therapeutic and adverse effects in advanced PD patients, reported that there were no significant changes in the part I-IV scores of the UPDRS between the groups. Based on the sub-scores for gait disturbance/postural instability and dyskinesia, the results were found to be in favor of GPi DBS than STN DBS ($p = 0.024$ and 0.016, respectively), and there were no differences between the groups in terms of serious side-effects including fall, intracranial hemorrhage/infarction, depression, psychosis, suicide attempt, wound adhesion [52]. In compatible with these results, the side-effect profile of GPi DBS was found to be similar to STN DBS, except depression [53], in which postoperative depression is found to be slightly more remarkable in STN-DBS patients [54]. However, a retrospective review of the patients who underwent STN or GPi-DBS revealed that presurgical depression history is an important risk factor for postsurgical depression. 55 Verbal fluency worsening is one of the most common cognitive adverse effects, and can be seen after DBS [56].

CONCLUSION

Since PD is a disabling progressive neurodegenerative disease with a chronic course, the presence of motor and non-motor symptoms and complications in the advanced stages, are the most challenging issues that put a burden on patients' daily lives. To handle this broad spectrum of motor and non-motor symptomatology, the treatment options varying from medical regimens to device-aided therapies should be specified to the patient, based on the dynamic features of the patients as well as the disease itself.

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