An update of opicapone in Parkinson's disease: evidence-based results of recent trials

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Abstract

The purpose of this report is to recall the evidence from recent clinical trials and observational studies supporting the efficacy and safety of opicapone as an adjunct to levodopa therapy in patients with Parkinson's disease (PD). This report will include the latest findings from a phase 2 clinical trial (the opicapone-203 trial), demonstrating that, despite using a lower levodopa dose, opicapone can significantly increase the bioavailability of levodopa and improve motor function in patients with Parkinson's disease. Results from this new study further suggest that a combination of catechol-O-methyltransferase (COMT) inhibition, together with an adequate levodopa daily dosing, may provide optimal dopaminergic delivery and consequently stimulation in patients with PD.

KEYWORDS: PARKINSON'S DISEASE, COMT INHIBITION, OPICAPONE-203 TRIAL, LEVODOPA, BIOAVAILABILITY, MOTOR FUNCTION

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Background

PD is the second most common neurodegenerative disorder worldwide, with a global incidence estimated at 9.4 million in 2020.[1,2] It is characterised by a gradual degeneration and loss of dopaminergic neurons in the substantia nigra pars compacta, leading to a reduction in the brain's ability to form, store and regulate the release of dopamine, a neurotransmitter essential for the control of motor function.[3] This results in motor disturbances, namely a resting tremor, rigidity and bradykinesia, as well as non-motor symptoms, including depression and anxiety, impaired cognition and sleep disturbances. With disease progression, these symptoms become increasingly debilitating and have a profound negative impact on patients' quality of life.[1,3]

The incidence of PD has more than doubled in recent years, rising by 55% between 2016 and 2020[2] and there is a need for improved treatments to safely and effectively manage this disease. Levodopa (3,4-dihydroxy-L-phenylalanine, L-dopa), developed in the 1960s, is the 'gold standard' treatment for PD.[4] It can cross the blood-brain barrier and, on reaching the brain, is converted by dopa decarboxylase (DDC) into dopamine, which stimulates dopaminergic receptors and provides rapid and effective control of motor symptoms in the early stages of disease.[5] However, with disease progression, a patient's response to levodopa becomes less evident and both motor and non-motor complications return.[6] The most common type of complication to develop is an 'end-of-dose deterioration' or 'wearing-off'.[6] This can be defined as a decrease in the duration of effect of each individual dose of levodopa with increasing disease progression and duration of drug treatment. Wearing-off symptoms are experienced by 40–50% of patients treated for five years and affect approximately two-thirds of patients after 10 or more years of levodopa therapy.[7] Importantly, wearing-off can also develop

very early in PD, within a few years or even months of treatment initiation.[8-11] Once motor complications develop, cumulative daily OFF time (when symptoms persist despite levodopa) can account for up to 50% of a patient's waking day, presenting a significant physical and psychological burden to patients and their caregivers.[12]

A number of factors are thought to contribute to wearing-off in patients with PD. The therapeutic response to levodopa consists of a short-duration response (SDR) and a long-duration response (LDR). The SDR provides an improvement in motor disability lasting a few hours after administration of single doses of levodopa, whereas the LDR provides a more sustained antiparkinsonian effect derived from prolonged levodopa administration that can last up to two weeks after cessation of drug treatment.[11] Both types of response are present from the initiation of therapy, although the SDR is largely unnoticed as it is masked by the LDR. However, with disease progression, loss of dopaminergic neurons leads to loss of neuroplasticity; the LDR diminishes and the magnitude of the SDR increases.[11,13] Patients become more dependent on the SDR to levodopa, manifested clinically by a less stable, more fluctuating, levodopa response.

A key factor contributing to the SDR is the complex pharmacokinetic profile of levodopa. Levodopa is a large neutral amino acid (LNAA) principally absorbed by the small bowel via a saturable facilitated LNAA transport system, and distributed from the intestine into the circulating blood.[14] Distribution is severely impaired by extensive peripheral metabolism so that only a small percentage of levodopa enters the systemic circulation and it has a very short plasma half-life (60–90 min).[15] The ubiquitous enzyme DDC, extensively converts levodopa to dopamine in the gut, liver and kidneys.[15,16] As dopamine cannot cross the blood-brain barrier, the action of levodopa is rendered ineffective. Drugs that inhibit DDC, namely carbidopa and benserazide, were developed to block this metabolic pathway and improve levodopa plasma levels. However, despite some significant improvements, the short plasma half-life of levodopa remains even in the presence of DDC inhibitors (DDCI), with only a small fraction (5–10%) of levodopa reaching the brain.[15,16]

This is thought to be due to "shunting" of levodopa metabolism to a second metabolic pathway, namely the COMT pathway. COMT is another ubiquitous enzyme with highest activities in the liver, kidney and gastrointestinal tract.[17,18] It converts around 90% of peripheral levodopa into the levodopa metabolite 3-O-methyldopa (3-OMD) which, unlike levodopa, has a long plasma half-life of approximately 15 hours. 3-OMD accumulates during chronic levodopa therapy to reach concentrations that are several times higher than levodopa. Furthermore, it can competitively inhibit levodopa absorption at the blood-brain barrier.[17,18] In the presence of DDCI, levodopa metabolism occurs primarily through this pathway. Together, the combination of poor absorption and extensive peripheral metabolism means that intermittent administration of levodopa/DDCI results in fluctuating levodopa levels with high peaks and troughs and a corresponding non-physiological 'pulsatile' stimulation of dopamine receptors in patients.

A promising new strategy for optimising levodopa delivery are drugs that inhibit COMT.[18,19] By blocking both major pathways of peripheral levodopa metabolism, using a combination of DDCI and COMT inhibitors, levodopa pharmacokinetics can be optimised to provide a smoother, more continuous supply of levodopa, and ultimately dopamine, to the brain. Tolcapone and entacapone, the first commercially available COMT inhibitors developed in the 1990s have been shown to be very effective, significantly increasing the plasma half-life of levodopa and reducing OFF time in patients with advanced PD.[18-21] However, the practical use of these drugs is limited. Tolcapone requires extensive monitoring due to several notable side effects including liver toxicity.[22] Entacapone has a very short half-life, and to be clinically effective, frequent daily doses are required by patients, often up to 10 doses per day.[22]

Opicapone, a third-generation COMT inhibitor, was approved by the European Committee in 2016 and by the FDA in 2020.[23] Opicapone is a potent, selective and long-acting peripheral COMT inhibitor with a low toxicity profile.[24] Despite having a relatively short half-life, it has sub-picomolar binding affinity to S-COMT in peripheral tissues, where strong binding and slow complex dissociation characteristics result in prolonged COMT inhibitory activity that outlasts drug clearance from the systemic circulation.[25,26] It can be administered as a once-daily dose, meaning that administration is not tied to the timing of levodopa dosing. This flexibility makes it much easier and more convenient for patients to use and avoids any potential inference with levodopa absorption.[23]

Pharmacokinetic studies in healthy volunteers and patients with PD, have demonstrated that opicapone, given as an adjunct to levodopa/DDCI, significantly increases minimum plasma levels of levodopa (Cmin) with a lesser effect on peak plasma levels (Cmax).[19,25,27] Opicapone also dose-dependently increases total systemic exposure to levodopa (assessed by area under the curve, AUC)[25,28-32] and reduces peak-to-trough fluctuations.[19,27] In this way, it helps to improve levodopa bioavailability as well as providing smoother, less pulsatile increases in levodopa concentrations. Notably, troughs in plasma levodopa levels that occur between doses were found to directly correspond with OFF symptoms in patients with PD,[33] suggesting that the beneficial effects of opicapone on levodopa pharmacokinetics may be clinically relevant.

Two pivotal phase 3 trials, BIPARK I and BIPARK II, assessed the clinical efficacy and safety of opicapone as an adjunct to levodopa/DDCI therapy in patients with PD.[34,35] These international, randomised, double-blind, placebo-controlled trials evaluated the effects of a once-daily dose of opicapone versus placebo on mean daily OFF time in patients with PD with end-of-dose motor fluctuations. Both trials recruited adult patients aged 30–83 years with a minimum disease duration of three years, and who had received levodopa treatment for at least one year. The trials contained a double-blind phase lasting 14–15 weeks, followed by an open-label phase where all patients received opicapone for 52 weeks. In both trials, opicapone was well tolerated; adverse events were rare and comparable with control groups. In BIPARK I (N=600), opicapone (50 mg) significantly reduced OFF time by -60.8 minutes (95% CI, -97.2 to 24.4, p=0.0015, n=115) compared with placebo (n=120).[34] Similarly, in BIPARK II (N=427), OFF time was reduced by -54.3 minutes (95% CI, -96.2 to -12.4 minutes, p=0.008) in the interventional group (n=154) versus the control group (n=144).[35] A corresponding increase in ON time without troublesome dyskinesia was also reported in patients in intervention groups in both trials.[34,35] Importantly, clinically relevant improvements in ON and OFF time were maintained throughout the one-year extension phase of these studies[35,36] and a pooled analysis of the BIPARK trials and their open-label extensions confirmed the long-term efficacy and safety of opicapone in fluctuating patients with PD.[37] More recently, the COMFORT-PD study evaluated the effects of opicapone in 437 Japanese patients with PD and motor fluctuations.[38] This phase-2b trial, which had a similar design to the BIPARK trials, found that opicapone consistently reduced OFF time, increased total ON time and increased ON time without troublesome dyskinesias over a 15-week period. In accordance with previous results, a long-term open-label extension of this study demonstrated that opicapone-induced reductions in OFF time, improvements in ON time and also tolerability were consistently maintained over 52 weeks.[39]

The clinical efficacy and safety of opicapone have also been demonstrated in a real-world setting in the OPTIPARK study.[40] This was a prospective, open-label, single-arm trial conducted across 68 clinical practice centres in Germany and the UK. A total of 506 patients with PD and motor fluctuations received a once-daily dose of opicapone (50 mg) for three (Germany) or six (UK) months in addition to their current levodopa and antiparkinsonian medications. After three months of treatment, 71.3% of patients showed clinical improvement, as judged by investigators on the Clinicians' Global Impression of Change Scale (CGI-C). This was confirmed by patients with 76.9% reporting improvements on the Patients' Global Impression of Change Scale (PGI-C). Opicapone therapy was generally well-tolerated and led to clinically relevant improvements in Unified Parkinson's Disease Rating Scale (UPDRS) scores for for activities of daily living during OFF time and motor scores during ON time (by 3.0 and 4.6 points, respectively), as well as improving patient quality of life using the Parkinson's Disease Questionnaire (PDQ-8).[40] These real-world results suggest that opicapone not only increases ON time but can also improve the quality of ON time in patients with PD. Recent sub-analyses of the German and UK cohorts demonstrated comparable results to the overall study cohort, confirming the efficacy, safety and tolerability of opicapone in these patient populations.[41,42] Notably, in the UK cohort, clinical improvements were sustained at six months, supporting the long-term efficacy of opicapone under real-world conditions.[42]

Recent findings from a new pharmacokinetic study: the opicapone-203 trial

Although the beneficial effects of opicapone in patients with PD are well recognised, what is less clear is how opicapone may be used to tailor daily levodopa dosing to best meet patients' needs. Improved understanding of this relationship is important to optimise adjunctive treatments and offer greater flexibility in the management of PD. A new phase 2 study by Ferreira JJ and colleagues[43] investigated the effect

of a levodopa treatment regimen (daily dose and frequency of intakes) on the clinical efficacy of opicapone in 24 patients with PD with end-of-dose motor fluctuations and signs of wearing-OFF. This was an exploratory, open-label, modified cross-over trial. The investigators specifically evaluated the effects of a once-daily dose of opicapone on levodopa plasma pharmacokinetics and motor fluctuations when added to two different, lower dosing, regimens of levodopa/carbidopa (LD/CD), compared to LD/CD administered alone.

Following screening, all patients received 500/125 mg LD/CD (as 5 daily intakes of 100/25 mg) for two weeks. They were then randomised 1:1 to two treatment regimens for an additional two weeks. The first group received 50 mg opicapone plus 400/100 mg LD/CD (as four daily intakes of 100/25 mg). The second group received 50 mg opicapone plus 400/100 mg LD/CD (as five daily intakes of alternating 100/25 mg and 50/12.5 mg doses). After completing the regimens, patients were followed up for a further 2 weeks. Pharmacokinetic assessments were carried out over 12 hours after two weeks of each treatment (at the end of the initial treatment with LD/CD alone and at the end of the LD/CD plus opicapone regimen). Clinical outcomes of tolerability and patient-rated ON and OFF times were measured as exploratory secondary outcomes. The timing of ON and OFF states was monitored in real time by investigators during the matching 12-hour pharmacokinetic evaluation, and patients also completed 24-hour patient Hauser ON/OFF diary charts during the three days before each pharmacokinetic visit.

Results showed that, despite using a 100 mg lower dose of levodopa, opicapone increased levodopa plasma half-life and minimal plasma concentrations (Cmin) in both treatment regimens, when compared to treatment with 500/125 mg LD/CD alone. Notably, these effects were slightly more prominent in the 5-daily LD/CD intakes plus opicapone group. In the 5-intake group, there was a >2-fold increase in levodopa half-life and a 2.5-fold increase in levodopa Cmin ($p<0.0001$) whereas in the 4-intake group, plasma levodopa half-life and Cmin ($p<0.005$) were doubled. Opicapone also led to a significant increase in total levodopa exposure (assessed by AUC), with a 29% increase in AUCtotal in the 5-intake group ($p<0.0001$) and a 27% increase in the 4-intake group ($p=0.0003$), compared to treatment with LD/CD alone. Maximal plasma levodopa levels (Cmax) remained 'controlled' in both groups, with no significant changes, compared to LD/CD alone. This 'controlled' Cmax, together with an increased Cmin, led to a significant 40% lower levodopa fluctuation index (FI) ratio in opicapone-treated patients ($p<0.0001$). This observation was made in the 5-intake group, with a smaller non-significant reduction in the 4-intake group. In addition, consistent with the known mechanism of action to reduce the peripheral metabolism of levodopa by COMT, opicapone reduced plasma 3-OMD levels (AUCtotal) by 86% in both groups ($p<0.0001$).

Secondary analyses showed that opicapone-related improvements in levodopa pharmacokinetics were associated with significant clinical outcomes. In 24-hour diary ratings, the 5-daily LD/CD intake plus opicapone group reported a 24% decrease in total OFF time ($p=0.0056$) and a 20% increase in ON time ($p=0.0007$) compared to LD/CD treatment alone. The 4-intake group reported smaller but significant changes, with a 12% decrease in total OFF time ($p=0.0336$) and 11% increase in ON time ($p=0.0015$). In 12-hour patient monitoring, time to ON and time to best ON decreased by 34% ($p=0.0420$) and 15% ($p=0.117$), respectively, in the 5-daily LD/CD intake plus opicapone group, compared to treatment with LD/CD alone. Similar effects were observed for the 4-intake group, with a 12% decrease in time to ON ($p=0.375$) and an 18% decrease in time to best ON ($p=0.0439$). Opicapone was well tolerated, with no significant adverse effects, consistent with previous studies.

By 'controlling' levodopa Cmax and increasing levodopa Cmin leading to a reduction in the FI, opicapone increased levodopa bioavailability despite a lower levodopa dose. These pharmacokinetic effects were associated with significant clinical improvements in this patient population.

Discussion

Results from the recent opicapone-203 study[43] confirm data from previous trials, supporting opicapone as a valid adjunct therapy to improve levodopa bioavailability and treat wearing-off in patients with PD. Other pharmacokinetic studies have also demonstrated that opicapone can increase levodopa bioavailability, raise levodopa trough concentrations and decrease peak-to-trough fluctuations in healthy volunteers and in patients with PD.[25,27-30,32] Similarly, the clinical efficacy of opicapone in decreasing OFF time and prolonging ON

time in patients with PD has been previously demonstrated in both clinical trials and real-world settings,[34-40] and a recent meta-analysis of studies from the BIPARK I, II and COMFORT-PD trials confirmed the significance of these effects.[44]

What is novel in the opicapone-203 study is that the beneficial effects of opicapone were observed despite using 100 mg less of levodopa. Furthermore, there appeared to be an interaction between the efficacy and the levodopa treatment regimen (daily dose and frequency of intakes). Specifically, optimal effects on levodopa pharmacokinetics and motor fluctuations were observed when the levodopa dose was fractionated into more frequent doses with shorter intervals.[43]

Previous strategies aimed at improving levodopa bioavailability in patients with PD have included increasing the overall levodopa dose and/or increasing the frequency of levodopa doses.[45,46] However, despite some benefits, these strategies were limited as they did not improve the pharmacokinetic profile of levodopa. Higher levodopa doses were associated with an increased severity of dyskinesias, whereas fractionating the levodopa dose resulted in very low plasma trough levels and re-emergence of symptoms due to suboptimal levodopa exposure.[45,46] Importantly, in the healthy brain, dopaminergic neurons originating from the substantia nigra fire tonically, producing a steady baseline concentration of dopamine that acts as a natural buffer ensuring constant striatal stimulation.[11,47] However, in PD, with nigrostriatal degeneration, this buffering capacity is progressively lost. In the short-term, this leads to abnormal patterns of striatal function. In the long-term, it leads to profound destabilisation of striatal output and ultimately alters the way in which the basal ganglia processes motor information.[11,47,48] Administration of levodopa/DDCI alone is associated with peaks and troughs of plasma levodopa and ultimately dopamine, with non-physiological stimulation of dopamine receptors; this could potentially lead to further perturbation of basal ganglia processing.[49] It can thus be argued that smoothing out the delivery of levodopa in early PD, using a combination of opicapone and low dose/high frequency levodopa, may help to avoid exacerbating the already destabilised basal ganglia processing and thereby prevent and/or delay the emergence of motor symptoms.[19,49]

Growing evidence supports the benefits of an earlier rather than later use of opicapone in the levodopa-DDCI-COMT inhibitor treatment strategy for PD.[19] Wearing-off, traditionally viewed as a complication of advanced PD, is now thought to occur much earlier in some patients, with a re-emergence of symptoms in the first few years or even months of levodopa treatment.[11] A pooled analysis of the BIPARK double-blind trials and open-label extensions revealed OFF time reductions at the end of the open-label phase were larger for patients in the opicapone group versus placebo (with subsequent switch to opicapone) group (change from baseline, -141.1 min vs -114.7 min, respectively.) Furthermore, a recent post-hoc analysis of these studies found that patients with wearing-off who were at an earlier stage of PD and levodopa treatment, experienced numerically greater efficacy when using opicapone than those in 'later' stages.[50] So far, the only 'formal' trial to investigate the long-term effects of early COMT inhibition during levodopa therapy in patients with PD, is the STRIDE study.[51] Here, early use of entacapone with levodopa/DDCI failed to demonstrate any delay in dyskinesia development in patients with PD over 134 weeks. However, a better understanding of levodopa pharmacokinetics at that time would have significantly improved the study design. Furthermore, currently available opicapone has several advantages over entacapone.[19]

The maintained efficacy of opicapone in the 203-trial, despite using a lower levodopa dose, is in line with previous results showing that opicapone can stabilise the required levodopa intake in patients with PD. In the BIPARK I and II trials, the majority of patients treated with opicapone in the double-blind phase, remained on the same dose of levodopa throughout the one-year extension period, despite investigators having the freedom to adjust dosing according to clinical need.[34,35] Similarly, in the OPTIPARK study, patients treated with opicapone maintained their levodopa dose for up to six months with sustained benefits in symptomatic control.[40] The potential for keeping and/or lowering levodopa doses in the presence of opicapone may be clinically advantageous as well as more cost-effective. A post-hoc analysis of the STRIDE study demonstrated that the risk of patients developing dyskinesia and wearing-off over a period of 2–4 years increased in a levodopa dose-dependent manner ($p<0.001$ for both), with those patients receiving higher total levodopa doses at greatest risk of motor complications.[52] Similar findings were previously reported in a shorter, 9-month trial, examining the effect of levodopa on the rate of PD progression.[9] The goal would be to use a low dose of levodopa and optimise

clinical efficacy with concomitant medication. A sub-analysis of the OPTIPARK study found that as well as improving clinical outcomes in levodopa-treated patients with PD, opicapone significantly reduced treatment costs by an estimated 3719 GBP over six months across UK clinical practices.[42] Thus, combined levodopa/DDCI/opicapone therapy may also help to alleviate the significant financial burden experienced by patients and their caregivers.

Conclusion

Taken together, evidence from the latest opicapone-203 trial provides another piece of the puzzle in the re-positioning venture around COMT inhibitor use in PD (levodopa-DDCI-COMT inhibitor treatment strategy). Specifically, the evidence further supports a shift of opicapone treatment to an earlier stage of PD, where it may be particularly beneficial in the symptomatic treatment of motor symptoms in patients with stable PD. Studies aimed at understanding the complex pharmacokinetics of levodopa and the interaction with COMT inhibition, will help to fine-tune the levodopa/COMT inhibitor dosing regimen to achieve optimal clinical efficacy and relief of symptoms. Prospective studies are now required to test whether this 'fine-tuning' of levodopa delivery at early-stage PD will translate into long-term clinical benefits. Although such studies are not anticipated at the present time, the rationale and partial evidence indicates that early concomitant treatment with opicapone could prevent and/or delay levodopa-induced motor complications in patients with PD.

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