Carbidopa-Levodopa Formulations in Patients with Advanced Parkinson's Disease – A Review of AAN 2016

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Abstract:

Parkinson disease is the second most common neurodegenerative disease worldwide. Although no available therapies alter the underlying neurodegenerative process, symptomatic therapies can improve patient quality of life. IPX066 is an oral, extended-release, capsule formulation of carbidopa-levodopa. Author aimed to assess this extended-release formulation versus immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations. The objective of this review was to highlight the pharmacokinetics, motor effects, and safety of IPX066, a novel extended-release formulation of carbidopa-levodopa, with an immediate-release carbidopa-levodopa formulation in advanced Parkinson's disease.To study the dosing patterns and characteristics of advanced Parkinson's disease (PD) patients who completed and discontinued conversion to IPX066 from other levodopa formulations.In another study author evaluated the effect of levodopa-carbidopa intestinal gel (LCIG, also carbidopa-levodopa enteral suspension/CLES) treatment on resting tremor in patients with advanced Parkinson's disease (PD).

Keywords: Carbidopa, Levodopa, Parkinson's Disease

Introduction:

Parkinson's disease (PD) is a progressively disabling neurodegenerative disorder that is manifested clinically by bradykinesia, tremor, rigidity, flexed posture, postural instability, and freezing of gait. It is characterized pathologically by the loss of pigmented dopaminergic neurons in the substantia nigra. The course of the clinical decline parallels that of the progressive degeneration of the remaining dopaminergic neurons.[1] The use of levodopa as dopamine-replacement therapy is highly effective in ameliorating the symptoms of the disease and remains the standard drug with which other therapies are compared.[2,3] Parkinson's disease (PD) is a neurodegenerative disease that presents several challenges for the treating physicians. Treatment strategies depend on the patient's age, disease stage, most troublesome symptoms, the balance between efficacy and risk for each treatment option, and other factors. However, it is important to base treatment decisions on the best available data for each intervention. EFNS and Movement Disorder Society–European Section (MDS-ES) have collaborated to produce evidence- based recommendations for the treatment of PD.[4,5] IPX066 is an extended-release formulation of carbidopa-levodopa (CD-LD). Following an initial peak at about one hour, plasma

concentrations are maintained for about 4-5 hours.[6] IPX066 improved motor symptoms and activities of daily living in advanced PD patients. Infusion of levodopa/carbidopa intestinal gel (Duodopa®; Abbott) was introduced in Sweden in 1991 as an experimental treatment in advanced Parkinson's disease and obtained EU approval in 2004. There is compelling evidence for short-term use of this treatment; however, long-term data are scarce.[7] Levodopa/carbidopa intestinal gel (LCIG) infusion is nowadays becoming an established therapeutic option for advanced Parkinson's disease (PD) patients with fluctuating symptoms unresponsive to conventional oral treatment. As the implementation of LCIG therapy is increasing, there is a need for safety and efficacy data from current clinical practice.[8]

IPX066, Extended-Release Carbidopa-Levodopa, from Other Carbidopa-Levodopa Formulations- Dosing Patterns in Advanced Parkinson's Disease Patients

Objective of this study was to describe the dosing patterns and characteristics of advanced Parkinson's disease (PD) patients who completed conversion to IPX066 from other levodopa formulations**.**

In this study ADVANCE-PD and ASCEND-PD examined the efficacy and safety of IPX066 vs. immediate-release (IR) CD-LD and CD-LD+entacapone (CLE), respectively. Advanced PD patients underwent a 6-week open-label conversion to IPX066 prior to treatment randomization. The initial IPX066 dose was guided by a conversion chart based on ranges of daily LD dose (e.g., 400-550 mg/day). The final dose ratio (IPX066:previous LD formulation) at the end of conversion, as well as the difference from the initial suggested IPX066 dose, were examined overall and within high and low halves of each range on the conversion chart.

Results of this study shows that In ADVANCE-PD, 393 (87.3%) patients completed conversion; 60% ended higher (median: 435 mg) and 16% ended lower (median: 245 mg) than the recommended initial IPX066 dose. In ASCEND-PD, 91 (82.7%) completed conversion; 56% ended higher (median: 380 mg) and 13% ended lower (median: 245 mg) than the recommended dose. At the end of conversion, mean LD dose ratios were 2.1 (IPX066:IR) and 2.8 (IPX066:CLE). Dose ratios tended to be higher for patients with either less frequent LD dosing (4x/day) or taking lower LD doses (400-550 mg/day) at study entry. Patients in the high end of each dose range of the conversion chart required a greater mean change in IPX066 dose compared to the initial recommended dose. Final dose ratios were generally not affected by position within each dose range.[6]

IPX066, Extended-Release Carbidopa-Levodopa – Discontinued characteristics of Advanced Parkinson's Disease Patients

The aim of this study was to describe the characteristics of advanced Parkinson's disease (PD) patients who discontinued treatment during conversion to IPX066.

In this authors examined ADVANCE-PD the efficacy and safety of IPX066 compared to immediate-release (IR) CD-LD in advanced PD patients with motor fluctuations. Prior to randomization, patients underwent a 6-week conversion from IR to IPX066.

Results evaluated that Out of 450 patients who started conversion to IPX066, 57 (12.7%) discontinued during the conversion period. Patients who discontinued had a longer duration of PD compared to those who completed conversion (mean±SD: 9.1±6.2 vs. 7.4±4.5 yrs, respectively) and a higher proportion of patients with more advanced disease (Hoehn & Yahr Stage III-IV, 56.1% vs. 43.0%, respectively). Patients who discontinued had a higher IR dose (874.6±356.9 mg/day) and dose frequency (5.7±2.2 doses/day) at study entry than those who completed conversion (775.8±353.3 mg/day, 5.0±1.6 doses/day, respectively). Less than 10% of patients taking 400-799 mg/day of IR at study entry discontinued, while 19.1% on ≥1000 mg/day discontinued. Similarly, 10.9% of patients taking IR 4-6 times/day at study entry discontinued vs. 25.0% taking IR >6 times/day. A higher proportion of patients who discontinued were taking IPX066 ≥5 times/day (21.1%) than those who completed dose conversion (8.1%). Of the discontinuations, 23 (40.4%) were due to adverse events (AE) and 13 (22.8%) were due to lack of efficacy. The most common AEs leading to discontinuation were dyskinesia (n=5), anxiety (n=4), and dizziness, nausea, and somnolence (n=3 each).[9]

Levodopa-Carbidopa Intestinal Gel –Efficacy on Resting Tremor in Patients with Advanced Parkinson's Disease

Objective of this study was to evaluate the effect of levodopa-carbidopa intestinal gel (LCIG, also carbidopa-levodopa enteral suspension/CLES) treatment on resting tremor in patients with advanced Parkinson's disease (PD).

In this authors enrolled 286/354 patients in a 54-week, open-label study with baseline and post-PEG-J assessment of Unified Parkinson's Disease Rating Scale (UPDRS), UPDRS Part III Q#20 (resting tremor) total score (5 categories: arms, legs, and face), safety and diary data were analyzed post-hoc in 3 subgroups defined by max baseline tremor score: No Tremor (n=196,

69%), Mild Tremor (max score =1 in any category, n=38, 13%), and Significant (SIG) Tremor (max score ≥2 in any category, n=52, 18%).

Result of this study shows that Reductions in mean[SD] change from baseline to final of Q#20 total score in the Mild Tremor (-1.29[1.0]) and SIG Tremor (-4.17[3.6]) groups were substantial (No Tremor, 0.21[0.7]). At final, 79% of the Mild Tremor patients had no tremor and 2(5%) had a max score increase to 2; 88% of the SIG Tremor patients had a max tremor score reduction and none had an increase. Amantadine use (No Tremor, Mild Tremor and SIG Tremor, respectively: baseline= 31%, 32%, 27%; during study= 10%, 8%, 12%) and levodopa dose (mg mean[SD] change from baseline to final= 423[647], 336[585], 441[546]) were consistent across subgroups. Improvements in "off" time were comparable between subgroups (mean[SD] change from baseline to final= -4.2[2.7] $p<0.001$, -4.6[2.9] $p<0.001$, -5.4[2.8] $p<0.001$). Adverse events (AE) were reported in 91% of enrollers; serious AEs reported in 31%. The tremor AE was reported in 4/196 (2.0%) No Tremor, 1/38 (2.6%) Mild Tremor, and 1/52 (1.9%) SIG Tremor patients.[10]

Conclusions: Lower LD dose and lower dosing frequency at study entry led to higher final dose ratios. The position within each dose range had little effect on the final dose ratios. Patients with higher IR CD-LD dose and dose frequency and with later stage disease tended to have higher rates of discontinuation during conversion to IPX066. Tremor remains prevalent in advanced PD patients; however LCIG appears to alleviate resting tremor not well controlled by optimized oral treatment in these patients. Levodopa/carbidopa intestinal gel infusion is a long-term treatment alternative in patients with advanced Parkinson's disease. LCIG infusion is effective for the long-term treatment of advanced PD patients and exerts a positive and clinically significant effect on motor complications with a relatively low dropout rate.

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