



Levodopa treatment in Parkinson's disease: earlier or later?

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More than 50 years after its introduction, levodopa is still considered the mainstay of treatment of Parkinson's disease (PD) and remains the gold standard against which new therapies must be measured (1). As the most effective drug for PD, a single oral dose of levodopa is able to ameliorate dramatically motor signs providing benefits on deftness, gait and speech for a limited period of time known as on time (2). However, when levodopa should be started is still a matter of debate. The idea of adopting an initial levodopa-sparing strategy derived from concerns about motor complications. After the so-called "honey-moon" period of levodopa effectiveness, motor fluctuations and dyskinesia appear. The prospective STRIDE-PD study revealed that more than 50% of PD patients develop motor complications, fluctuations and/or dyskinesia, after 4 years of treatment with levodopa at an average dosage of 400 mg daily (3). Long-term studies suggested that all patients eventually have to face up to levodopa-related motor complications (4,5). Initial treatment with dopamine agonists, such as pramipexole, seems to lead to lower incidence of dyskinesia and wearing off (6). However, this approach can be considered appropriate only for younger patients and when clinical manifestations are mild and tolerable. Dopamine agonists and other levodopa-sparing medications including monoamine oxidase B inhibitors and catechol-O-methyl transferase inhibitors are efficacious but not sufficient to control severe motor disturbances compared to levodopa treatment (7). Further concerns are about the possible neurotoxic effects of levodopa due to the increased production of reactive oxygen species. However, no conclusive results about neurotoxicity of

levodopa have been provided so far (8). Rather, it seems that levodopa promotes dopaminergic neurons recovery, also increasing sprouting of striatal dopaminergic terminals in rodents treated with 6-hydroxydopamine (9), suggesting a potential modifying effect on disease progression. The concept of "disease modifying drug" refers to the impact on disease pathogenesis able to slow down the disease progression and hopefully to prevent further neuronal cell death. It encompasses different types of strategy including (I) neuroprotection, (II) compensation, bolstering or supporting failing compensatory mechanisms, (III) neurorescue, salvaging dying neurons either by reversing metabolic abnormalities or providing trophic support, and (IV) neurorestoration, which provides cell-based therapies designed to replace degenerating neurons (10). Theoretically, levodopa could act at (II) and (III) level. With the aim of resolving the conundrum about the possible disease-modifying effects of levodopa, the LEAP-study [see Verschuur *et al.*, (11)] was carried out having the ELLDOPA trial as a reference (12). In the double-blind, placebo-controlled ELLDOPA ("Earlier versus Later Levodopa Therapy in Parkinson's disease") trial, 361 early PD patients were randomly assigned to receive either low (150 mg daily), medium (300 mg daily), or high (600 mg daily) levodopa doses versus placebo. Treatment period was 40 weeks, followed by a 2-week washout period. The change in the Unified Parkinson's Disease Rating Scale (UPDRS) scores from baseline to week 42 was the primary outcome. At week 42 the UPDRS scores were lower than at baseline (-1.4 units) only in the highest levodopa dose group. At week 42 UPDRS scores slightly increased in the other two

levodopa groups (+1.9 units) and the increase was even more evident in the placebo group (+7.0 units), suggesting that levodopa either slows down disease progression or has a “carry-over effect”. Of interest, at baseline and after 42-week treatment, a subset of patients underwent single-photon emission computed tomography (SPECT) to assess striatal dopamine transporter density. A more marked decline in the transporter density was demonstrated in the levodopa groups compared to placebo, suggesting that levodopa causes either loss of nigro-striatal dopaminergic neurons or down regulation of dopamine transporter activity.

In order to overcome the ambiguous results obtained from the ELLDOPA trial, a delayed-start technique in the double-blind placebo-controlled multicenter LEAP (“Levodopa in Early Parkinson’s Disease”) study was designed (13). Early PD patients were randomly assigned to receive levodopa/carbidopa 100/25 mg tid for 80 weeks (early-start group) or placebo for 40 weeks followed by levodopa/carbidopa 100/25 mg tid for 40 weeks (delayed-start group). Similar to ELLDOPA trial, the primary outcome was the change in the UPDRS score from baseline to week 80. Secondary outcomes were the progression rates between weeks 4 and 40 and between weeks 44 and 80, calculated as the mean change in the UPDRS score per week. The strategy of a delayed-start trial was aimed at exploring the disease-modifying effect of levodopa and separating it from a mere symptomatic effect. Accordingly, in levodopa treated patients, a slower disease progression at week 40 would indicate either a symptomatic effect, a disease-modifying effect, or both; conversely, at week 80, this result would be interpreted as levodopa disease-modifying effect. Verschuur and Colleagues found that the difference between groups in the mean change of UPDRS score from baseline to week 80 was not significant. The progression rate of symptoms between weeks 44 and 80 did not differ between the two groups, as well. Furthermore, the long-term follow-up study also provided an opportunity to investigate the effect of motor complications in levodopa treated patients. So, the onset of motor complications did not show differences between the two groups. These results suggest that levodopa has not a disease-modifying effect.

The main limitation of the LEAP trial is represented by the high percentage (39%) of patients on placebo needing levodopa and the number (11%) of patients on levodopa who were shifted to the open-label treatment with the same levodopa dose during the phase I, making the results less powerful and more difficult to interpret.

The trial provides valuable data to be considered in clinical practice. Early introduction of levodopa is not mandatory, since it does not result in a slower progression of disease. A strict initial sparing strategy with long-lasting delay in levodopa initiation is not indicated as well, if levodopa treatment is necessary for guaranteeing satisfactory performance in daily life functional activities. Further trials including larger samples of PD patients, higher levodopa doses and longer periods of levodopa administration would be welcome in order to definitely confirm the LEAP results. Also, availability of novel routes able to optimize levodopa pharmacokinetic profile, as well as more stable formulations (14), might either add arguments to, or modify, the conclusions from the LEAP trial. So far, effective disease-modifying drugs are not available. Reasons for this failure may be the unsatisfactory knowledge of disease pathogenesis, and the clinical-biological heterogeneity of the enrolled patients. We should also consider that even patients at early stage already have extensive neurodegeneration (15). Pathophysiological, prognostic or theranostic biomarkers are actually missing. Hence, selection of patients for future trials should move from a simple clinical definition towards a PD “molecular” subtyping.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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