Randomized Delayed-Start Trial of Levodopa in Parkinson's Disease

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In treating Parkinson's disease (PD), physicians may delay the initiation of levodopa therapy for various reasons (i.e., concern for dyskinesias). However, the ELLDOPA trial (NEJM 2004) showed a significant benefit to early levodopa therapy in patients with early and mild PD. Specifically, levodopa-treated patients (vs. placebo) had less, PD-related symptom progression at the end of the trial (i.e., 40wks of treatment). However, the study results from the ELLDOPA trial suggested that either 1) early levodopa treatment slowed disease progression, or 2) 40wks of levodopa treatment had a prolonged effect on PD-related symptom control. The trial was not designed to differentiate between the two possibilities. As such, the goal of the current study was to determine if early levodopa therapy indeed leads to a substantial, disease-modifying effect in patients with early PD.

Experimental design and statistics: This was a multi-center, randomized, double-blind, placebo-controlled, delay-start trial conducted across 7 academic hospitals in the Netherlands. Eligibility criteria included 1) $\geq$ 30yrs of age, 2) no current anti-PD medications, 3) a diagnosis of PD in the last 2 yrs, and 4) life expectancy of > 2yrs. Exclusion criteria is noted below.[1] Eligible patients were randomized (1:1) to one of two groups: the "early-start" group, which received 80wks of carbidopa-levodopa (25-100mg) 3x/d, or the "delay-start" group, which received placebo for the first 40wks (phase 1), then carbidopa-levodopa (25-100mg) 3x/d for the second 40wks (phase 2)[2]. Using this study design, the primary outcome was the change in the UPDRS scores from baseline to week 80, and the main secondary outcome was the rate of progression of UPDRS scores from 4-40wks (Phase 1) and from 44-80wks (Phase 2). Other secondary analyses (conducted at week 80) included measures of overall disability, MMSE scores, depression, and disease-related quality of life, as well as treatment-related complications (dyskinesias, motor fluctuations). Statistically, an analysis of covariance model was used to compare the primary outcome between the two treatment groups. For the main secondary outcome, the rates of PD-related symptom progression were assessed in the two treatment groups during both study phases (at specified follow up assessments). Non-inferiority analyses were used to compare these progression rates between the treatment groups during phase 2 of the study, to assess for any effect (detrimental or beneficial) of early vs. delayed-start levodopa. Finally, remaining secondary outcomes were analyzed via parametric or non-parametric statistics, when appropriate.

Results: A total of 445 eligible patients underwent randomization (222 to early-start, 223 to delay-start). Baseline patient characteristics were similar between the two study groups (Table 1). In terms of the primary outcome, changes in UPDRS scores from baseline to week 80 did NOT differ significantly between the two treatment groups (-1.0pt in early-start vs. -2.0pts in delay-start, $p = 0.44$; Table 2 and Figure 2). For the secondary outcome analyses, the change in UPDRS scores from baseline to week 40 favored the early start group (-3.1pts in early-start, 2.0pts in delay-start), reflecting an immediate effect of levodopa on PD-related symptoms, though the rate of symptom progression did not differ significantly between the two groups. Similarly, in phase 2, the rates of progression for each treatment group did not meet criterion for non-inferiority of early vs. late receipt of levodopa. Specifically, as shown in Figure 3, UPDRS scores of the delay-start group "caught up" to those of the early-start group.

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[1] Exclusion criteria: previous treatment with anti-PD meds, tremor as predominant symptom (w/associated disability), dementia, atypical or secondary parkinsonism

[2] If a patient in the delay-start group developed symptoms warranting of treatment during phase 1, they were given open-label levodopa for the remainder of phase 1. Their data was included in their original group assignment.

Finally, there were no group differences in disability scores, MMSE scores, depression, or quality of life at week 80 (Table 2), nor were there differences in the rates of treatment-related complications at week 80 (Table 3).

Conclusions: Overall, early vs. delayed initiation of levodopa had no significant effect on PD-related symptom severity at trial completion. Although PD-related symptom severity differed between the treatment groups in phase 1 (lower in the early-start vs. the delay-start group), there were no differences in the progression of PD-related symptoms across phase 2, leading to the ultimate lack of group differences by the end of the study period. As such, these data suggest that although levodopa certainly had a strong, immediate effect on PD-related symptoms, there was no disease-modifying effect of levodopa over the trial period. Namely, a disease-modifying effect of levodopa would have shown "parallelism" of the UPDRS score curves from the two treatment groups during phase 2 of the study. Finally, data from this study also confirmed that early initiation of levodopa can be considered safe and non-detrimental in patients with a relatively new diagnosis of PD. Future studies using either higher doses of levodopa or a longer duration of levodopa therapy may be considered to determine if levodopa alters the overall course of PD.

Summary completed by Elaine Sinclair, DO/PhD