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The natural progression of clinical symptoms in Parkinson’s disease may not be faster in the earlier stages: Results from the ADAGIO delayed-start study

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Abstract

Objectives: To evaluate the natural progression of symptoms in a large cohort of early PD patients with PD and to compare their progression rates in ADAGIO with those of previously published trials.

Background: ADAGIO was the largest clinical trial conducted in patients with early PD (n=1176). The main results demonstrated that the innovative delayed-start design to demonstrate that rasagiline 1 mg/day slows clinical progression of PD compared to placebo.

Methods: Patients were randomized to placebo groups; 588 patients had at least one follow-up visit. Baseline characteristics and patient disposition were recorded. The natural progression of clinical symptoms was evaluated using the change in Total-UPDRS score from baseline to last observed value (LOV) (for the placebo-controlled phase) were estimated using an ANCOVA model with treatment, country, and baseline Total-UPDRS score as covariates. Statistical analysis included all placebo-treated patients with evaluations at baseline and from week 12 or later. The annual rate of progression was determined by dividing the change from baseline to week 36 by 9 months and multiplying by 12.

Results: A total of 595 patients with early PD were randomized to placebo groups; 588 patients had at least one follow-up visit. Baseline characteristics and patient disposition were recorded. The natural progression of clinical symptoms was evaluated using the change in Total-UPDRS score from baseline to last observed value (LOV) (for the placebo-controlled phase) were estimated using an ANCOVA model with treatment, country, and baseline Total-UPDRS score as covariates. Statistical analysis included all placebo-treated patients with evaluations at baseline and from week 12 or later. The annual rate of progression was determined by dividing the change from baseline to week 36 by 9 months and multiplying by 12.

Conclusions: The annualized progression rate of clinical symptoms in early PD patients, as measured by deterioration in Total-UPDRS scores, was 4.3±0.3 units/year. The annual rate of progression in early PD was not significantly different between the subgroups. A recruitment bias related to the delayed-start design might account for this paradox.

Keywords: Parkinson’s disease, clinical trial, delayed-start design, disease progression, Total-UPDRS

Introduction

Parkinson disease (PD) is a chronic progressive disease with gradually deteriorating motor and non-motor symptoms. The progression of PD can vary widely from patient to patient. Understanding the natural progression of symptom development in ADAGIO would be of great help for the early stage PD patients who are not on any treatment at baseline. The progression of PD in ADAGIO is of interest because the ADAGIO cohort was the largest cohort of very early PD patients, allowing the assessment of the natural progression of clinical symptoms in early PD.

Methods

Patient population: ADAGIO included patients with early PD (n=1176). The main results demonstrated that the innovative delayed-start design to demonstrate that rasagiline 1 mg/day slows clinical progression of PD compared to placebo.

Statistical analysis: The annual rate of progression was determined by dividing the change from baseline to week 36 by 9 months and multiplying by 12.

Results

A total of 595 patients with early PD were randomized to placebo groups; 588 patients had at least one follow-up visit. Baseline characteristics and patient disposition were recorded. The natural progression of clinical symptoms was evaluated using the change in Total-UPDRS score from baseline to last observed value (LOV) (for the placebo-controlled phase) were estimated using an ANCOVA model with treatment, country, and baseline Total-UPDRS score as covariates. Statistical analysis included all placebo-treated patients with evaluations at baseline and from week 12 or later. The annual rate of progression was determined by dividing the change from baseline to week 36 by 9 months and multiplying by 12.

Conclusions

The annualized progression rate of clinical symptoms in early PD patients, as measured by deterioration in Total-UPDRS scores, was 4.3±0.3 units/year. The annual rate of progression in early PD was not significantly different between the subgroups. A recruitment bias related to the delayed-start design might account for this paradox.