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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

Objective: Describe the natural progression of symptoms in a large cohort of early patients with Parkinson's disease (PD).

Background: ADAGIO was the largest clinical trial conducted in patients with early PD (n=1176). Half of ADAGIO patients received placebo for up to 36 weeks, providing an opportunity to study clinical progression in early stage PD.

Analysis: Changes in Total-UPDRS scores from baseline to last observed value were estimated using an ANCOVA model in 588 untreated patients who received placebo for 36-weeks. Subgroup analyses were conducted in subjects with high (>25.5) and low (≤14) baseline Total-UPDRS scores.

Results: Overall, placebo-treated patients deteriorated with a mean change from baseline to 36 weeks of 4.3 ± 0.3 units. Extrapolation gives an estimated natural disease progression of 6.2 units/year. Placebo patients with higher baseline scores (n=145) showed faster progression (change from baseline 6.2 ± 0.8 units; extrapolation to 9.0 units/year)*. By contrast, patients with lower baseline scores (n=160) deteriorated by 2.8 ± 0.7 units at 36 weeks (4.0 units/year)*.

Conclusions: The rate of progression on placebo in ADAGIO was slower than anticipated (6.2 *vs.* 8–12 Total-UPDRS/year in previous studies) in contrast with the fact that (i) patients were recruited at an earlier stage than in other trials (mean time from diagnosis 4.5 months; mean baseline Total-UPDRS 20.4) and (ii) dopaminergic cell loss is believed to progress faster in early stages. A recruitment bias related to the delayed-start design might account for this paradox, but the observation that patients with lower baseline Total-UPDRS scores showed even slower symptom progression does not support this hypothesis. It is likely that the rate of cell loss does not directly correlate with symptom progression. Furthermore, the faster progression of patients with higher baseline scores (upper quartile) may explain the previously reported ability to detect a larger magnitude of disease-modifying effect in this sub-population of ADAGIO.

*Data revised from submitted abstract; new analyses were performed for the quartiles using the model to allow comparison

Introduction

- Parkinson's disease (PD) is a chronic progressive disease with gradually deteriorating motor and non-motor function and increasing disability. However, there is little prospective data on clinical progression of PD and controversy exists on the rate of clinical disease progression through the course of the disease.
- Retrospective neuropathological data and prospective neuroimaging observations have suggested a non-linear progression of dopaminergic cell loss in PD. Based on these findings, it is generally speculated that the neurodegenerative process is faster in the early stages as compared with the later ones.[1-3] Moreover, in a population-based survey looking at treated patients with more advanced PD, Schrag *et al.*[4] reached the conclusion that progression of motor scores in PD decreases with advancing disease.
- Measuring the rate of disease progression in clinical cohorts is mainly limited by the remarkable symptomatic efficacy of the currently available antiparkinsonian medications. These drugs are usually given as soon as the patients' features become noticeable or disabling and their symptomatic benefit then masks the subsequent progression of the symptoms. However, it has been estimated that the rate of clinical deterioration in drug-naïve patients with early PD is rapid (decline of about 8 to 12 Total-UPDRS points within the first year).[5]
- The recent ADAGIO (**A**ttenuation of **D**isease progression with **A**zilect **Gi**ven **O**nce-daily) study used an innovative delayed-start design to demonstrate that rasagiline 1 mg/day slows clinical progression of symptoms as measured by deterioration in Total-UPDRS scores.[6]
- In addition to its novel design, the ADAGIO study stands out from other PD trials as it is the largest clinical trial (n=1176) conducted in patients who were still in the very early stages of their disease course (average time from PD diagnosis of 4.5 months, mean baseline Total-UPDRS 20.4 points).[6,7]
- Importantly, about half of these patients received treatment with placebo for up to 9 months. ADAGIO therefore provides an unprecedented opportunity to study the clinical characteristics of disease progression in its very early motor stages.

- The aim of this analysis is to better describe and understand the progression of disease in the earliest cohort of symptomatic PD patients ever followed. We had anticipated that the rate of progression in ADAGIO would be fast; since this study was conducted in such an early PD population.

Methods[2]

Patients

- The ADAGIO study recruited patients with early, previously untreated PD.
- Diagnosis of PD was based on having 2 cardinal signs (resting tremor, bradykinesia, rigidity).
- Hoehn and Yahr <3.
- Other entry criteria included disease duration of less than 18 months from time of diagnosis and a determination in the best judgment of the investigator that the patient would not require anti-parkinsonian treatment in the subsequent 9 months.
- Patients with >3 weeks of treatment with any anti-parkinsonian medication prior to baseline were not eligible for the study. Prior use of rasagiline, selegiline, or coenzyme Q10 (in daily doses >300 mg) within the previous 120 days was also prohibited.

Study design

- ADAGIO was a delayed-start study with novel hierarchical endpoints, designed to assess if rasagiline has disease-modifying properties in early PD.
  - Phase I of the study (relevant for this analysis) was a 36-week double-blind, placebo-controlled phase. UPDRS assessments were made at baseline and at Weeks 12, 24, 36.
  - Phase II of the study (not relevant for this analysis) was a 36-week double-blind, active-treatment phase in which all patients were on active study intervention.
- After obtaining IRB-approved informed consent, subjects were randomized in a 1:1:1:1 ratio into one of four treatment groups (rasagiline 1 mg/day, rasagiline 2 mg/day, placebo control for rasagiline 1 mg/day and placebo control for rasagiline 2 mg/day) based on a randomization scheme with blocks stratified by center.
- If subjects in any treatment group required additional anti-parkinsonian medication during Phase I of the trial, they could proceed directly to Phase II.

Statistical analysis

- As in the primary analysis of ADAGIO, data for the placebo groups during Phase I were combined. The analysis included all placebo-treated patients with evaluations at baseline and from week 12 or later.
- Changes in Total-UPDRS scores 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 explanatory variables.
- In addition, subgroup analyses were conducted in placebo subjects in the highest (>25.5; 'Upper Quartile') and lowest (≤14; 'Lower Quartile') quartiles of baseline Total-UPDRS scores.
- For slope estimates from 12 to 36 weeks, statistical analysis was performed using a mixed-model repeated-measures analysis of covariance (MMRM) that included the following fixed effects: treatment group, week in trial, week-by-treatment interaction, center, and Total-UPDRS score at baseline.
- In order to compare the rate of progression with other studies (see Table 2 for annualised rates from other major studies in early PD), the 36 weeks data was annualised by dividing the change from baseline in Total-UPDRS score at LOV (as estimated using the ANCOVA model described above) by 36 and multiplying by 52.

Results

Baseline characteristics and patient disposition

- A total of 595 patients with early PD were randomized to placebo groups; 588 patients had at least one UPDRS measurement from week 12 and were included in this analysis.
- Of these, 160 patients had baseline Total-UPDRS scores ≤14 ('Lower Quartile') and 145 patients had baseline Total-UPDRS scores >25.5 ('Upper Quartile').

Table 1: Placebo group baseline demographics

	All (n=588)	Lower Quartile (≤14) (n=160)	Upper Quartile (>25.5) (n=145)	P value (Lower *vs.* Upper Quartile)
Age (years), mean ± SD	62.13 ± 9.61	59.95 ± 9.88	64.41 ± 9.48	<0.0001
Time from PD diagnosis (months), mean ± SD	4.47 ± 4.59	4.16 ± 4.51	4.70 ± 4.52	0.30
UPDRS Total (range: 0–176), mean ± SD	20.10 ± 8.43	10.80 ± 1.45	31.65 ± 8.43	<0.0001
Modified Hoehn and Yahr, mean ± SD	1.49 ± 0.48	1.21 ± 0.37	1.77 ± 0.45	<0.0001

- Patients in the 'Upper Quartile' were older and had more advanced symptomology (as evidenced by higher Total-UPDRS and Hoehn and Yahr scores) than patients in the 'Lower Quartile'. There was no significant difference in the time from PD diagnosis between the subgroups.

Rates of progression in placebo patients (Change in Total-UPDRS scores, ANCOVA)

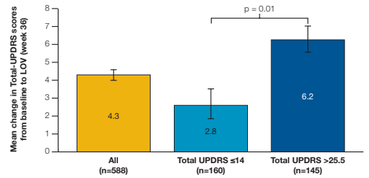
Full placebo group

- Overall, placebo-treated patients deteriorated with a mean ± SE change from baseline to 36 weeks of 4.3 ± 0.3 units (Figure 1). This equates to an annualised rate of 6.2 Total-UPDRS units/year.

Quartile analyses

- Compared with the full placebo group, patients in the 'Upper Quartile' (>25.5 baseline Total-UPDRS) showed greater progression with a mean ± SE change from baseline to week 36 of 6.2 ± 0.8 units (Figure 1). This equates to an annualised rate of 9.0 Total-UPDRS units/year.
- By contrast, patients in the 'Lower Quartile' (≤14 baseline Total-UPDRS) deteriorated from baseline by only 2.8 ± 0.7 units at 36. This equates to an annualised rate of 4.0 Total-UPDRS units/year.
- The difference in the progression to week 36 between the two subgroups was statistically significant (mean difference -3.42 ± 1.36 units; p = 0.01).

Figure 1: Progression over 36 weeks in the placebo arm of the ADAGIO study



Rates of progression in placebo patients (Slope estimates weeks 12–36, MMRM)

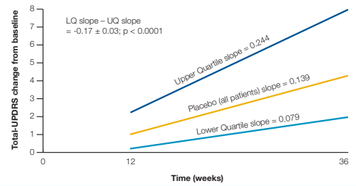
Full placebo group

- Overall, the slope estimate for placebo-treated patients was 0.14 ± 0.01 Total-UPDRS units/week (Figure 2).[6]

Quartile analyses

- Similar to the ANCOVA analysis, the slope estimates demonstrated a slower rate of Total-UPDRS deterioration for the 'Lower Quartile' (0.08 ± 0.02 Total-UPDRS units/week) *versus* the 'Upper Quartile' (0.24 ± 0.02 Total-UPDRS units/week) resulting in a statically significant difference of –0.17 ± 0.03 Total-UPDRS units/week; p < 0.0001 (Figure 2).

Figure 2: Rates of progression (Total-UPDRS units/week) for the placebo cohort



Conclusions

- ADAGIO enrolled the largest cohort of very early PD patients, allowing the assessment of UPDRS progression in the very early stage of the disease.
- Based on the hypothesis that dopaminergic cell loss in PD decreases exponentially with advancing duration of disease, we anticipated that the ADAGIO cohort, composed of PD patients at an early symptomatic motor stage (time from diagnosis: 4.5 months) and lower Total-UPDRS baseline score than those of previous trials (Table 2)[8-12] would show a relatively rapid clinical deterioration.
- Contrary to this idea, the annualised mean change in Total-UPDRS scores from baseline to endpoint on placebo in ADAGIO was only 6.2 Total-UPDRS/year, which is noticeably lower than that observed in other studies of early untreated PD (Table 2).
- Interestingly, within the ADAGIO cohort, patients in the 'Upper Quartile' (>25.5 Total-UPDRS at baseline) had a greater deterioration in Total-UPDRS scores at endpoint than those in the 'Lower Quartile' (≤14 Total-UPDRS at baseline). Moreover, using slope analysis, 'Upper Quartile' patients progressed faster than patients in the 'Lower Quartile', further supporting the results of the ANCOVA differences.
- One could speculate that the slower UPDRS progression in ADAGIO might be due to some recruitment bias. Indeed, in order to minimize the risk of premature drop-out in a delayed-start design, investigators are encouraged not to include patients who are expected to require symptomatic medications during the first phase of the trial, and this design feature might have enriched the population with slower progressors. However, most placebo-controlled studies in early PD also use such criteria, and if it were the case, it would have been even more difficult to detect a disease modification effect in ADAGIO.
- Additional factors could have also contributed to this observation
  - For example, age has been reported as a significant factor in the natural history of PD and there is some evidence that patients with younger age at onset have a slower disease progression, at least regarding motor impairment.[13] The mean age of the ADAGIO cohort was not different from that of previously published trials (Table 2). However, in agreement with this observation, the patients of the upper quartile who progressed fast were older (64 years) than those of the lower quartile (60 years) who progressed slowly.
  - Although this analysis focused on Total-UPDRS scores at baseline, other relevant factors may exist such as patient phenotype, presence of tremor, and co-morbidities.
- It should be stressed that the present findings are not necessarily irreconcilable with the fact that post-mortem and *in vivo* neuroimaging studies suggest that the pathological process may progress faster at earlier stages. It is conceivable that no direct correlation exists between the degree of dopamine denervation and the severity of the clinical symptoms. For example, compensatory mechanisms involving receptor sensitivity and neuronal plasticity may account for such discrepancies.

- Finally, the results of the present analysis have important implications for the overall interpretation of the results of the ADAGIO study.[6]
  - The faster progression of patients with higher baseline scores (Upper Quartile) may explain why it was easier to detect a larger magnitude of disease-modifying effect in the Upper Quartile population of ADAGIO.[6] As opposed to primary analysis of the entire ADAGIO population (effect size for 1 mg dose -1.68 ± 0.75 and 0.36 ± 0.68 for the 2 mg dose), in the post-hoc analysis of the Upper Quartile, statistically significant and numerically larger results were achieved when comparing the early and delayed start arms of both the 1 and 2 mg doses (-3.4 ± 1.66 and -3.63 ± 1.72 Total-UPDRS points respectively).
  - The slower than initially anticipated rate of progression observed in the ADAGIO study should be taken into account when considering the clinical importance of the rasagiline 1 mg disease-modifying effect (1.7 Total-UPDRS units) observed between the early- and delayed-start groups. Considering a rate of deterioration in Total-UPDRS score of 4.3 units/9 months on placebo, the observed 1.7 unit reduction over 9 months on rasagiline early-start corresponds on average to a 40% reduction in the rate of progression.

Table 2: Rate of progression in placebo arm of clinical trials in early, untreated PD

Study	Drug	Baseline Total-UPDRS score	Age at baseline	Total-UPDRS/ trial duration	Total-UPDRS/ year
DATATOP[8,14]	Deprenyl/ tocopherol	25.4	61.1	12/year	12/year
ROADS[9]	Lazabemide	19.7	62.5	8/year	8/year
QE2[10]	Coenzyme Q10	24.1	63.1	12/16 months	9/year
TEMPO[11]	Rasagiline	24.5	60.5	4.1/6 months	8.2/year
ELLDOPA[12]	Levodopa	26.3	63.9	8.4/9.5 months	10.6/year
ADAGIO[6]	Rasagiline	20.1	62.1	4.3/36 weeks	6.2/year*

Table adapted from Fahn 2005[15]. *When annualised by months (dividing by 9 months and multiplying by 12 months – according to a method used for the above published trials) the annual rate of progression is 5.7 Total-UPDRS units/year

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