EDITORIAL

WHAT'S NEW IN THE MANAGEMENT OF PARKINSON'S DISEASE ? – A SHORT COMMENT ON ADAGIO TRIAL

An open label, multicentric, non-comparativ study – Romania 2007

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The phase III ADAGIO study **is the first clinical trial designed to distinguish symptomatic versus disease-modifying effects of a drug in Parkinson's disease. Its results have been first presented during the 12th Congress of European Federation of Neurological Societies (EFNS) in Madrid, Spain as part of a "Late Breaking News" session.**

The ADAGIO study showed that Parkinson's disease (PD) patients who took rasagiline 1mg tablets once-daily upon entry into the trial, demonstrated a significant improvement compared to those who initiated the drug treatment 9 months later. The 1mg dose met all three primary endpoints, as well as the secondary endpoint, with statistical significance.

In order to better understand the clinical significance of these results we have to define the „disease – modifying drug" **concept related to PD; it refers to the capacity of a therapy to interfere with the neuronal pathogenesis of the disease and slow functional decline (in patients with prodromal or manifest illness) or, ideally, forestall the onset of ilness (in presymptomatic subjects),** *clinically reflected in preventing, slowing or reversing clinical progression.*

Although till now a number of trial designs have been used in studies to evaluate disease modification for PD, all have limitations related to: time to endpoint trials (e.g., DATATOP, TCH346), washout (e.g., ELLDOPA), neuroimaging (e.g., CALM-PD, REAL-PET), futility – evaluation of clinical symptoms (e.g., CoQ10). Taking into account the observations and suggestions from the trials related to antidementia drug development (also reffering to a relatively slow neurodegenerative disease), a delayed-start design has been proposed also for detecting the suggested disease-modifying capacity of an anti-parkinsonian drug.

The main hypothesis is that if a drug has only pure symptomatic effects, the evolution of the symptom improvement is the same no matter if the treatment is initiated early or later, but if the drug has disease-modifying capacity, the clinical improvement obtained through the early initiation of treatment is better than that obtained if the same drug therapy is initiated latter, and this difference of improved symptomatology is maintained during long-term evolution.

The previous data from the TEMPO trial, using rasagiline in two different dosage (1mg and respectively 2mg daily versus placebo) suggested that rasagiline could have such a disease modifying effect, as patients randomised to receive rasagiline early had (at 12 months) better clinical scores than those with a 6-month delayed-start; these results cannot be explained entirely by a symptomatic effect and this signal warranted investigation in a large *study specifically designed* **to address the** *potential disease-modifying effects* **of rasagiline – the** ADAGIO (*A*ttenuation of *D*isease progression with *A*zilect Given *O*nce-daily) **trial. This was a multicentre, double-blind, placebo-controlled, parallel-groups on early untreated PD patients who did not used any anti-parkinsonian medications; the trial included 1,176 subjects in 129 centres from 14 countries (including Romania, with 5 centres). After randomization, the subjects included have been grouped initially in 4 arms (in a 1:1:1:1 ratio) for the first phase of the trial, which lasted 36 weeks (9 months) designed as double-blind placebo-controlled phase: 1 arm received**

rasagiline 1 mg/ day, 1 arm received rasagiline 2 mg/ day and 2 arms received placebo. After these 36 weeks, for the next 36 weeks (the following 9 months) the 1 mg/ day and 2mg/ day respectively, rasagiline arms continued to receive the same doses also in double blind, but 1 initially placebo arm received rasagiline 1 mg/ day and the other initially placebo arm received 2 mg/ day rasagiline (this was the second phase of the study, the double-blind active-treatment phase).

The primary analysis included three hierarchical endpoints based on Total-UPDRS (Unified Parkinson's Disease Rating Scale) scores and linked to the early start arm:

A) superiority of slopes showing the evolution of UPDRS scores in weeks 12-36 (–0.05; p=0.013, 95%CI –0.08, –0.01)
B) change from baseline to week 72 (–1.7 units; p = 0.025, 95%CI –3.15, –0.21)
C) non-inferiority of slopes (0.15 margin) in weeks 48-72 (0.0 difference between early start slope and the delayed start slope; 90%CI –0.04, 0.04) confirming that separation between the groups is consistent.

At the end of the trial, the principal statistical analyses on the change of UPDRS score from the baseline have shown: significant better evolution of the patients treated in the active arms during the first phase of the trial (placebo-controlled) and superiority of early-start versus delayed-start active treatment during the active-treatment controlled phase for the 1 mg/day dose, but not also for 2 mg/ day dose (both phases being in double-blind).

In summary: ADAGIO is one of the largest studies conducted in PD with one of the earliest populations studied; it is the *first prospective delayed-start study in PD* **that uses** *novel endpoints* **to determine** *disease-modifying effects; a disease modifying effect was demonstrated for the 1 mg/ day dose of rasagiline* **but the same effect was not demonstrated for the 2 mg/day dose; the symptomatic effect observed in TEMPO was replicated in ADAGIO PC phase for both rasagiline doses versus placebo, as long as TEMPO trial has been primarly designed to assess the efficacy and safety of rasagiline in patients with early PD disease, while ADAGIO trial was prospectively designed to investigate the effect of rasagiline on disease progression.**

In both trials rasagiline was well tolerated with no specific concerns.

The successful outcome of the study provides further rationale for the early use of rasagiline among Parkinson's disease patients and we expect in the near future changes of the guideliness of the most important scientific societies in the world concerning the management of early Parkinson's disease.

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REFERENCES

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