Efficacy of rasagiline in patients with the parkinsonian variant of multiple system atrophy: a randomised, placebo-controlled trial

*Werner Poewe, Klaus Seppi, Cheryl J Fitzer-Attas, Gregor K Wenning, Sid Gilman, Phillip A Low, Nir Giladi, Paolo Barone, Cristina Sampaio, Eli Eyal, Olivier Rascol, for the Rasagiline-for-MSA investigators**

Summary

Background **Multiple system atrophy is a complex neurodegenerative disorder for which no effective treatment exists. We aimed to assess the effect of rasagiline on symptoms and progression of the parkinsonian variant of multiple system atrophy.**

Methods **We did this randomised, double-blind, placebo-controlled trial between Dec 15, 2009, and Oct 20, 2011, at 40 academic sites specialised in the care of patients with multiple systemic atrophy across 12 countries. Eligible participants aged 30 years or older with possible or probable parkinsonian variant multiple system atrophy were randomly assigned (1:1), via computer-generated block randomisation (block size of four), to receive either rasagiline 1 mg per day or placebo. Randomisation was stratified by study centre. The investigators, study funder, and personnel involved in patient assessment, monitoring, analysis and data management were masked to group assignment. The primary endpoint was change from baseline to study end in total Unified Multiple System Atrophy Rating Scale (UMSARS) score (parts I and II). Analysis was by modified intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00977665.**

Findings **We randomly assigned 174 participants to the rasagiline group (n=84) or the placebo group (n=90); 21 (25%) patients in the rasagiline group and 15 (17%) in the placebo group withdrew from the study early. At week 48, patients in the rasagiline group had progressed by an adjusted mean of 7·2 (SE 1·2) total UMSARS units versus 7·8 (1·1) units in those in the placebo group. This treatment difference of –0·60 (95% CI –3·68 to 2·47; p=0·70) was not significant. 68 (81%) patients in the rasagiline group and 67 (74%) patients in the placebo group reported adverse events, and we recorded serious adverse events in 29 (35%) versus 23 (26%) patients. The most common adverse events in the rasagiline group were dizziness (n=10 [12%]), peripheral oedema (n=9 [11%]), urinary tract infections (n=9 [11%]), and orthostatic hypotension (n=8 [10%]).**

Interpretation **In this population of patients with the parkinsonian variant of multiple system atrophy, treatment with rasagiline 1 mg per day did not show a significant benefit as assessed by UMSARS. The study confirms the sensitivity of clinical outcomes for multiple system atrophy to detect clinically significant decline, even in individuals with early disease.**

Funding **Teva Pharmaceutical Industries and H Lundbeck A/S.**

Lancet Neurol 2015; 14: 145–52

Published Online December 8, 2014 http://dx.doi.org/10.1016/S1474-4422(14)70288-1

See Comment page 126

*See appendix for full list of study investigators

Department of Neurology (Prof W Poewe MD, Prof K Seppi MD), **Division of Neurobiology** (Prof G K Wenning MD), **Innsbruck Medical University, Innsbruck, Austria; Teva Pharmaceutical Industries, Petach Tikva, Israel** (C J Fitzer-Attas PhD, E Eyal MSc); **CHDI Foundation, Princeton, NJ, USA** (C J Fitzer-Attas, Prof C Sampaio MD); **Geddes Road, Ann Arbor, MI, USA** (S Gilman MD); **Mayo Clinic, Department of Neurology, Rochester, MN, USA** (Prof P A Low MD); **Sackler School of Medicine, Sagol School of Neuroscience, Tel-Aviv University Department of Neurology, Tel-Aviv Sourasky Medical Center, Tel Aviv, Israel** (Prof N Giladi MD); **Università degli Studi di Salerno, Dipartimento di Medicina e Chirurgia, Via Giovanni Paolo II, Salerno, Italy** (Prof Paolo Barone MD); **Clinical Investigation Center CIC1436, Departments of Clinical Pharmacology and Neurosciences, INSERM and University Hospital of Toulouse, Faculty of Medicine, Toulouse, France** (Prof Olivier Rascol MD)

Correspondence to: Professor Werner Poewe, Department of Neurology, Innsbruck Medical University, Innsbruck A-6020, Austria **werner.poewe@i-med.ac.at**

See Online for appendix

Introduction

Multiple system atrophy is a progressive neurodegenerative disease characterised by varying combinations of parkinsonian features, autonomic failure, cerebellar ataxia, and pyramidal signs.[1–4] Parkinsonism is the predominant syndrome in about 60–80% of patients with multiple system atrophy, and disease progression is rapid, with loss of independent ambulation or intelligible speech happening within 5–6 years and death within 7–10 years of diagnosis.[2,3,5] Present symptomatic treatments for multiple system atrophy have little effect and disease-modifying therapies are a key unmet need. However, very few trials have addressed this issue and no drug trial has had sufficient statistical power to show disease-modifying effects.[6–9]

Rasagiline is a monoamine oxidase B inhibitor indicated for the symptomatic treatment of Parkinson's disease. Case reports have documented the off-label use of rasagiline in patients with the parkinsonian variant of multiple system atrophy;[10] evidence to support such use is otherwise scarce. Nevertheless, preclinical studies have shown the neuroprotective efficacy of rasagiline in different disease models and against various injuries.[11] In particular, a study using a transgenic mouse model of multiple system atrophy showed that treatment with rasagiline at a dose of 2·5 mg/kg prevented cell loss in the substantia nigra, striatum, and cerebellum, and was associated with behavioural improvement.[12] Furthermore, when we started our study, substantial efforts were being made to assess whether treatment with rasagiline had any effect on the rate of clinical progression in patients with Parkinson's disease.[13,14] We therefore assessed the clinical effect of rasagiline on symptom progression in patients with the parkinsonian variant of multiple system atrophy.

Methods

Study design and patients

We did this multicentre, randomised, double-blind, placebo-controlled study between Dec 15, 2009, and Oct 20, 2011, at 40 academic sites specialised in the care of patients with multiple systemic atrophy across 12 countries (Austria, Canada, France, Germany, Hungary, Israel, Italy, Netherlands, Portugal, Spain, UK, and USA).

We enrolled participants aged 30 years or older if they had a diagnosis of possible or probable parkinsonian variant multiple system atrophy, according to published clinical criteria.[15] Presence of supporting MRI features was not required for inclusion because these features have not been validated in patients with the parkinsonian variant of multiple system atrophy and are not mandatory for the clinical definition of the disorder. Eligible patients had early disease (ie, <3 years from the time of documented diagnosis of multiple system atrophy to enrolment) and, on the basis of investigators' clinical judgment, an anticipated survival of at least 3 years. Exclusion criteria were severe orthostatic symptoms (score of ≥3 on Unified MSA Rating Scale [UMSARS] question 9); speech impairment (score of ≥3 on UMSARS question 1); swallowing impairment (score of ≥3 on UMSARS question 2); impairment in ambulation (score of ≥3 on UMSARS question 7); or falling more frequently than once per week (score of ≥3 on UMSARS question 8). We also excluded patients taking disallowed drugs according to the local rasagiline label, monoamine oxidase inhibitors within 3 months before baseline visit, midodrine or other sympathomimetics within 4 weeks before baseline visit, or any investigational products within 60 days before baseline assessment, and those with poorly controlled hypertension or any clinically significant or unstable medical or surgical disorder that in the investigators' judgment precluded safe and complete study participation. We allowed use of antidepressants as specified in the local rasagiline label. All anti-parkinsonian drugs and allowed treatments of orthostatic hypotension (fludrocortisone, pyridostigmine, or vasopressin) were kept unchanged from the baseline visit until at least the week 24 visit.

We enrolled a subset of patients from ten of the 40 participating study sites to undergo MRI, with structural MRI using routine sequences and diffusion tensor imaging. Sites were chosen dependent on their ability to meet the technical requirements of the substudy; all patients recruited at the MRI sites were invited to participate.

Institutional review boards at the participating sites approved the study protocol and the trial was done in accordance with the Declaration of Helsinki. Patients provided written informed consent before randomisation.

Randomisation and masking

Patients were randomly assigned by the study funder in a 1:1 ratio, via computer-generated block randomisation (block size of four), to receive either rasagiline 1 mg per day or matching placebo for 48 weeks. Randomisation was stratified by study centre. Rasagiline and placebo tablets were identical in appearance and taste, and were packaged in bottles containing 110 tablets. The investigators and personnel involved in patient assessment, monitoring, analysis, and data management were masked to group assignment. Patients were assigned to a treatment group within 4 weeks of screening and were allocated their randomisation number at the day of initiation of study drug. Patients were instructed to take their first tablet after all baseline assessments had been done.

Procedures

We assessed patients at the screening visit and at study weeks 0 (baseline), 12, 24, 36, and 48 (termination visit for study completers). The UMSARS assessment was done by the same investigator at every study visit. We assessed the Composite Autonomic Symptom Scale (COMPASS)-Select score at baseline and at weeks 24 and 48; the Clinical Global Impression of Improvement (CGI-I) scale at week 48; and the MSA Health-Related Quality-of-Life (MSA-QoL) scale,[16] the Montreal Cognitive Assessment Scale (MoCA),[17] and the Beck Depression Inventory (BDI) at baseline and week 48. An independent data and safety monitoring board periodically received masked safety data. We recorded adverse events and vital signs at each visit and patients kept a weekly falls diary.

Patients enrolled in the imaging study were imaged at baseline and at the end of the study (ie, at week 48 or other termination visit for those who left the study before week 48) with identical MRI scanners at all participating sites (1·5T Siemens Avanto) in line with the common standard protocol described by Scherfler and colleagues.[18] Centralised image analysis was done at Medical University Innsbruck by two independent investigators who were masked to treatment allocation and scan order.

Outcomes

The primary efficacy endpoint was change from baseline to week 48 in the total UMSARS score (sum of parts I and II).[19] Key secondary efficacy endpoints were change from baseline to end of study in the CGI-I scale;[20] change from baseline to week 24 in UMSARS total score; proportion of patients with loss of independent ambulation by end of study, defined by a score of 3 or more in UMSARS-I item 7 (walking); change from baseline to end of study in scores of the COMPASS-Select;[21] and change from baseline to end of study in the MSA-QoL scale. Exploratory variables were change from baseline to week 48 in the MoCA and BDI; change from baseline to week 48 in UMSARS parts I, II, and IV; change from baseline to week 12 in UMSARS total score; change in anti-parkinsonian or anti-orthostatic hypotension drugs; number of falls; and the proportion of patients reaching a score of 3 or more on UMSARS-I items 1 (speech), 2 (swallowing), and 8 (falling).