

The role of rasagiline in the treatment of Parkinson's disease

Julie Leegwater-Kim¹
Elena Bortan²

¹Tufts University School of Medicine
and Department of Neurology,
Lahey Clinic, Burlington, MA, USA;

²Department of Neurology, Lahey
Clinic, Burlington, MA, USA

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1% to 2% of people older than 60 years. Treatment of PD consists of symptomatic therapies while neuroprotective strategies have remained elusive. Rasagiline is a novel, potent, and irreversible monoamine oxidase type B (MAO-B) inhibitor which has been approved for treatment of PD. Rasagiline inhibits MAO-B more potently than selegiline and has the advantage of once-daily dosing. In several large, randomized, placebo-controlled trials, rasagiline has demonstrated efficacy as monotherapy in early PD and as adjunctive therapy in advanced PD. In addition, rasagiline has been shown to have neuroprotective effects in in vitro and in vivo studies. The recently completed delayed-start ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) trial suggests a potential disease-modifying effect for rasagiline 1 mg/day, though the clinical import of this finding has yet to be established.

Keywords: rasagiline, monoamine oxidase inhibitor, Parkinson's disease

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder manifested by the cardinal features of tremor at rest, rigidity, bradykinesia, and loss of postural reflexes. In addition to motor symptoms, PD is associated with a host of non-motor symptoms including autonomic disturbance, sleep disorders, depression, psychosis, and dementia. The mean age of onset of PD is 60 years and both the prevalence and incidence increase with age, with 1% to 2% of the population over age 60 years affected by the disease.¹ The primary pathology of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNpc) with subsequent depletion of nigrostriatal dopamine, and the development of Lewy bodies, proteinaceous intracytoplasmic inclusions. Recent studies have shown that PD is also associated with extensive non-dopaminergic pathology involving noradrenergic neurons in the locus coeruleus, cholinergic neurons in the nucleus basalis of Meynert, serotonergic neurons in the midline raphe, and neurons of the autonomic nervous system.² The seminal work of Braak et al has demonstrated that the pathological changes in PD occur in a relatively predictable, topographically distinct sequence of events beginning with the olfactory structures and medulla oblongata, spreading to the substantia nigra, and eventually affecting neocortical structures.³

Though the exact pathogenetic mechanisms leading to cell death in PD are not fully understood, a number of factors including mitochondrial dysfunction, oxidative stress, excitotoxicity, dysfunction of the ubiquitin-proteasome pathway, and apoptosis have been implicated.⁴⁻⁶ In 5% to 10% of patients with PD, there is a familial pattern

Correspondence: Julie Leegwater-Kim
Lahey Clinic, 41 Mall Rd., Burlington, MA
01805, USA
Tel +1 781-744-5127
Fax +1 781-744-5243
Email leegwa00@lahey.org

of inheritance and, to date, linkage to 11 different genes has been reported.^{7,8} However, most gene mutations observed in PD kindreds do not appear to account for the vast majority of PD patients who develop PD sporadically.⁹ One exception is LRRK2 mutations which appear to occur in 41% of North African Arabs with sporadic PD and 13.3% of Ashkenazi Jews with sporadic PD.^{10,11} Epidemiologic studies have found associations between a variety of environmental agents (pesticides, herbicides, rural living) and risk of PD but none of these agents has been shown to definitively cause PD.¹² Thus, the cause of the large majority of cases of sporadic PD is unknown and likely a result of a complex interplay between genetic susceptibility and environmental factors.

Current treatment of PD is symptomatic and the primary pharmacologic therapies include dopamine replacement with levodopa, synthetic dopamine agonists, and drugs which increase dopamine supply by inhibiting its metabolism (catechol-O-methyltransferase inhibitors and monoamine oxidase B [MAO-B] inhibitors).

The treatment of PD is symptom-driven and highly individualized, depending on each patient's specific needs. Future objectives for the development of new anti-parkinsonian medications should include: the prevention of disease progression, the mitigation or prevention of medication-related motor complications, the simplification of treatment regimens, and restorative treatments to provide new neurons or stimulate the growth of surviving cells. Recently, novel clinical trial designs have provided a new approach in evaluating PD drugs for possible neuroprotective, or disease-modifying, effects. The aim of this paper is to review the data on the efficacy, safety, and possible disease-modifying effects of rasagiline in PD.

MAO-B inhibitors in PD

The interest in MAO-B inhibitors to treat PD stems from their ability to slow the breakdown of striatal dopamine. Monoamine oxidase (MAO) is an enzyme embedded in the outer mitochondrial membrane that is involved in the oxidative deamination of monoamine neurotransmitters (dopamine, serotonin, norepinephrine) and biogenic amines (tyramine).^{13,14} Two isoforms of the enzyme, MAO-A and MAO-B, have been described. MAO-A is located primarily in peripheral organs where it contributes ~80% of total MAO activity in the gastrointestinal tract. MAO-B is the major isoform in the brain and abundant in the basal ganglia.^{15,16} In the human brain the distribution of MAO-A and MAO-B differs in various regions. MAO-A is localized to the noradrenergic neurons of the locus coeruleus while MAO-B is

present in the serotonergic neurons of the raphe nuclei and in glial cells.

The propargylamines are selective MAO-B inhibitors which have been approved for the treatment of PD. These compounds incorporate a propargyl chain which appears to confer neuroprotective effects in a variety of in vitro and in vivo model systems.^{17–21} Selegiline (deprenyl, Eldepryl®) is a methylamphetamine with a propargyl residue which selectively and irreversibly inhibits MAO. It was approved for treatment of PD in the US in 1979. In the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study, selegiline was found to be safe and efficacious in early PD and delayed the introduction of levodopa therapy when compared with placebo.^{22,23} However, the mild symptomatic effects of selegiline confounded the interpretation of a possible neuroprotective effect.²⁴ Selegiline is metabolized to L-methamphetamine and L-amphetamine, and there has been speculation about possible toxic effects of these derivatives.^{25,26}

Rasagiline

Rasagiline (Azilect®; Teva Neuroscience, Inc.) is a second-generation propargylamine that is a highly selective, irreversible MAO-B inhibitor. Rasagiline is a secondary cyclic benzylamine and indane derivative. Because it does not have an amphetamine-like scaffolding it does not generate amphetamine or methamphetamine metabolites. Rasagiline is metabolized by cytochrome P-450 to form its chief metabolite, 1-(R)aminoindan, which has been shown to have neuroprotective effects in vitro.²⁷ Rasagiline is available in 0.5 mg and 1 mg tablets and is taken once daily.

Rasagiline pharmacology

A number of in vitro and in vivo studies have shown that rasagiline has high specificity for the MAO-B isoform. In animal models, based on the dose required to inhibit enzyme activity by 50% (ED₅₀), rasagiline inhibited MAO-B 60 to 65 times more potently than MAO-A.^{28–30} The specificity of rasagiline for MAO-B inhibition was similar to that of selegiline. In a small study of 3 healthy individuals administered rasagiline 1 mg per day for 10 days, positron emission tomography using ¹¹C-L-deprenyl tracer showed complete blockade of MAO-B binding sites by rasagiline.³¹

Measurement of the potency of MAO-B of rasagiline using ED₅₀ values found it to be ~5 times more potent than selegiline in rats given chronic daily doses. The clinically relevant degree of inhibition of MAO-B has been estimated to be 80%, and when ED₈₀ values were examined, rasagiline exhibited ~10 times greater potency than selegiline.³⁰

In pharmacokinetic studies in healthy volunteers and PD patients, rasagiline inhibits MAO-B rapidly and exhibits a dose-dependent effect. In a study of single-dose rasagiline in healthy subjects, 1, 2, 5, and 10 mg were administered and within 1 hour post dose, 33%, 55%, 79%, and 99% platelet MAO-B inhibition was achieved, respectively.³² In a study of patients with PD, rasagiline had a half-life of 1.34 hours, median time to C_{max} of 0.5 hours, and volume of distribution of 182 L.³⁴

Rasagiline is metabolized via CYP1A2-mediated dealkylation to 1-R-aminoindan. Mean oral clearance of rasagiline is 994.3 L/hour. In subjects with mild hepatic impairment (Child–Pugh score of 5–6), caution should be exercised when administering rasagiline as the mean peak plasma concentration and mean area under the curve are increased. Rasagiline administration should be avoided in subjects with moderate to severe hepatic impairment (Child–Pugh score > 7).³⁴

Neuroprotective effects of rasagiline

Though the etiopathogenesis of PD is not fully understood, current data suggest a role for signal-mediated apoptosis in neuronal cell death in PD and have sparked interest in anti-apoptotic agents as possible neuroprotective therapies in PD.^{35–37} The propargylamines have been demonstrated to have anti-apoptotic effects in cell culture and animal studies. The anti-apoptotic effect appears to be conferred by the propargyl chain and is independent of MAO-B inhibition.^{20,23,38} At the cellular level, propargylamines have been shown to exert their neuroprotective effects by preventing nuclear translocation of GADPH, preserving mitochondrial potential, upregulating anti-apoptotic molecules, and downregulating pro-apoptotic factors.³⁹

Rasagiline has demonstrated neuroprotective properties in a host of in vitro and in vivo studies. In vitro, rasagiline protects against an array of toxins, including MPTP, 6-hydroxydopamine (6-OHDA) and serum and growth factor deprivation (reviewed in³⁸). Rasagiline increased the survival of fetal mesencephalic dopaminergic neurons in culture.⁴⁰ In a study using the dopaminergic cell line SH-SY5Y, rasagiline protected against N-methyl(R)salsolinol – induced apoptosis and was found to stabilize mitochondrial membrane potential and induce anti-apoptotic Bcl-2.⁴¹ In a rodent PD model in which rats were injected with 6-OHDA to produce an ipsilateral lesion of the substantia nigra, treatment with rasagiline protected dopaminergic neurons and reduced motor stereotypies.⁴² In a rat model of PD which used microinjections of lactacystin (a ubiquitin-proteasome system inhibitor) into the median forebrain bundle, rasagiline was found to

have neuroprotective effects.⁴³ A recent study of a transgenic mouse model of multiple system atrophy, a neurodegenerative Parkinson-plus disease, showed that treatment with rasagiline led to significant reduction of 3-NP-induced neuronal loss in striatum, substantia nigra pars compacta, cerebellar cortex, pontine nuclei and inferior olives.⁴⁴

The neuroprotective effects of rasagiline appear to extend to non-dopaminergic motor neurons as well. Rasagiline administration was protective against immediate sequelae of closed head injury in the mouse.⁴⁵ Treatment with rasagiline in rats with middle cerebral artery occlusion reduced infarct size volume, improved cognitive performance and reduced necrotic brain area.⁴⁶ In a familial mouse model of amyotrophic lateral sclerosis rasagiline, in combination with riluzole, increased survival time by approximately 20%.⁴⁷

In comparative studies of rasagiline and selegiline, rasagiline demonstrated greater potency as a neuroprotective agent.^{43,48} In addition, a recent study of an animal model of PD found that while both rasagiline and selegiline had neuroprotective effects, rasagiline also exerted a restorative effect on nigrostriatal degeneration.⁴³

Clinical efficacy of rasagiline in PD Rasagiline as monotherapy in early PD

The pivotal TEMPO trial (Rasagiline Mesylate [TVP-1-12] in Early Monotherapy for Parkinson's Disease Outpatients) was a 6-month, randomized, placebo-controlled, double-blind study to determine the efficacy, safety and tolerability of rasagiline in treatment-naïve patients with early PD.⁴⁹ A total of 404 subjects with early PD were randomized to receive placebo, rasagiline 1 mg/day, or rasagiline 2 mg/day. Subjects had to be over age 35 with at least 2 cardinal signs of PD and disease severity of Hoehn and Yahr score of III or less. Subjects were excluded if they had atypical or secondary parkinsonism, a Mini-Mental Status Exam score of 23 or less, clinically significant depression or unstable medical problems. The primary outcome measure was change in the total United Parkinson's Disease Rating Scale (UPDRS) score. Secondary outcome measures included change in the UPDRS motor subscore, activities of daily living (ADL) subscore, and the Beck Depression Inventory score.

At 26 weeks, both the rasagiline 1 mg and 2 mg treatment groups had significantly improved motor and total UPDRS scores compared with the placebo group ($P < 0.00001$). Adjusted total UPDRS score mean change from baseline were 4.20 units for the rasagiline 1 mg group and 3.56 units for the rasagiline 2 mg group. There were a greater percentage of responders (subjects with worsening in UPDRS of

less than 3 units) in the treatment groups compared with the placebo group (placebo: 49%; rasagiline 1 mg: 66%; rasagiline 2 mg: 67%).⁴⁹

Following the initial 6-month efficacy trial, TEMPO was extended to a total period of one year.⁵⁰ During the second phase of the trial, subjects who had been randomized to placebo were switched to rasagiline 2 mg/day while subjects originally taking rasagiline were continued on their active medication. The treatment design was an “add-on” delayed-start trial which posited that if treatment with rasagiline had a disease-modifying effect rather than a purely symptomatic one, the delayed treatment group should not achieve the same degree of improvement than the early treatment group (see below). The primary measure of efficacy was the change in total UPDRS from baseline to week 52.

Three hundred seventy-one subjects from the original study entered the second phase. At the end of 52 weeks, the mean change in total UPDRS score for the three different treatment groups were: 3.01 (rasagiline 1 mg/day); 1.97 (rasagiline 2 mg/day); 4.17 (delayed rasagiline 2 mg/day). Compared with the delayed treatment group, the subjects who had been maintained on rasagiline from the outset had smaller increases in the total UPDRS score (−0.82 units for rasagiline 1 mg; −0.29 units for rasagiline 2 mg).⁵⁰ The results from the TEMPO trial suggested a possible disease-modifying effect of rasagiline which has been studied further in the ADAGIO trial (see below).

Rasagiline as adjunctive treatment in PD

The efficacy of rasagiline as adjunctive therapy in advanced PD patients with motor fluctuations was studied in 2 large, placebo-controlled trials, LARGO and PRESTO.^{54,55} The PRESTO study (Parkinson’s Rasagiline: Efficacy and Safety in the Treatment of “Off”) was a randomized, placebo-controlled, double-blind trial of subjects with advanced PD with motor fluctuations. The efficacy, tolerability and safety of rasagiline as adjunctive therapy were determined in 472 PD patients at sites in the US and Canada. Eligible patients had to have a Hoehn and Yahr score of less than 5 in the “off” state, experience at least 2½ hours in the “off” state daily, and be maintained on an optimal and stable dose of levodopa therapy for at least 2 weeks prior to screening visit. Subjects were randomized to receive rasagiline 0.5 mg/day, rasagiline 1 mg/day, or matching placebo. The primary measure of efficacy was change from baseline in mean total daily “off” time; secondary endpoints included changes from baseline in the UPDRS-ADL subscale during “off” periods, changes in UPDRS-motor subscale during

“on” times, and the investigators’ clinical global impression (CGI-I) of patient improvement. Both rasagiline treatment groups demonstrated statistically significant reductions in “off” time compared to placebo. The rasagiline 1 mg/day group experienced 0.94 hour less “off” time than placebo and rasagiline 0.5 mg/day had 0.49 hour less “off” time. The rasagiline treated groups also demonstrated significant improvement on UPDRS-ADL during “off” time, UPDRS-motor subscore during “on” time, and CGI-I. Daily on-time increased during treatment with both doses of rasagiline. In patients treated with 1 mg/day of rasagiline, the increase in on-time was greater compared with those patients who received 0.5 mg/day rasagiline and most of the increase was without a secondary increase of dyskinesia. The dyskinesia was reported as an adverse event in ~18% of patients receiving rasagiline compared with 10% of the placebo group.⁵¹

The second study, LARGO (Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily), was an 18-week, randomized, placebo-controlled, double-blind, double-dummy study carried out at 74 sites in Europe, Israel and Argentina. The study was designed to test the efficacy and safety of rasagiline as an adjunct to levodopa compared with placebo and to compare effects of entacapone with placebo. Subjects had to have moderate to advanced PD with motor fluctuations, have at least 1 hour per day in the “off” state, and be clinically stable for at least 14 days prior to baseline. 687 subjects were randomized to receive rasagiline 1 mg/day, entacapone 200 mg with every levodopa dose, or matching placebo. The primary endpoint was mean change in daily “off” time from baseline. When compared to placebo, rasagiline significantly reduced “off” time (−1.18 hours; $P = 0.0001$) as did entacapone (−1.2 hours; $P < 0.0001$). There was a corresponding increase in daily “on” time for both treatment groups, most of which was without troublesome dyskinesia. There was also a small but significant reduction in levodopa dose with rasagiline (~24 mg/day) or entacapone (~19 mg/day), compared with an increase of 5 mg/day with placebo ($P = 0.0003$, and $P = 0.0024$ vs placebo, respectively). A number of secondary endpoints including CGI-score, UPDRS-motor score (“on” state), and UPDRS-ADL (“off” state) were significantly improved in the rasagiline and entacapone groups.⁵²

Safety and tolerability

In the three phase III clinical trials presented above (TEMPO, PRESTO, and LARGO), rasagiline was well tolerated.^{49–52} In the first 6 months of the TEMPO study, the frequency of adverse events in the treatment and placebo groups was

similar. The most commonly reported adverse events were infection (18%) and headache (12%). Twenty serious adverse events (defined as hospitalizations or new malignancy) occurred during the study: 4 in the placebo group, 6 in the rasagiline 1 mg group, and 10 in the rasagiline 2 mg group. Two subjects in the rasagiline 2 mg group developed skin cancer (melanoma and squamous cell carcinoma).⁴⁹ During the second phase of the TEMPO study (when all participants were receiving rasagiline), the most commonly reported side effects were: infection (10.8%), headache (5.4%), unintentional injury (4.9%), and dizziness (4.6%). Serious adverse events included 17 hospitalizations and 5 newly diagnosed neoplasms including melanoma (1), basal cell carcinoma (1), and squamous cell carcinoma (2).⁵⁰ In the long-term extension of the TEMPO study, the most common adverse events (AEs) reported were infection, accidental injury, dizziness, sleep disorder, and nausea.⁵³ In the PRESTO trial, subjects taking rasagiline reported more weight loss, vomiting, anorexia, dyskinesia and balance difficulty when compared with the placebo group. The gastrointestinal adverse reactions appeared to be dose-dependent. Rasagiline did not have any adverse effects on blood pressure or pulse. Three cases of melanoma developed in the rasagiline group during the study.⁵¹ In the LARGO study, the active treatment and placebo groups had similar frequency of adverse events. The occurrence of dopaminergic adverse events was similar in all three groups. Postural hypotension occurred in 2% of subjects in the rasagiline and entacapone groups.⁵²

Treatment discontinuation rates were low in all three studies. In the TEMPO trial, there was no statistically significant difference between early discontinuation in the rasagiline and placebo groups.⁴⁹ Termination due to AE observed in the open-label extension of the TEMPO trial was similar in the delayed-start and early start groups (11.4% vs 10.5%).⁵³ In the LARGO study, there were fewer early discontinuation rates and fewer discontinuations due to adverse events in the rasagiline group compared with entacapone and placebo.⁵²

Serotonergic drugs

The development of serotonin syndrome, characterized by acute changes in mental status, autonomic dysfunction, myoclonus and hyperreflexia, has been described when nonselective MAOIs and selective serotonin reuptake inhibitors (SSRIs) are taken together. The possibility of serotonin syndrome occurring with concomitant use of MAO-B inhibitors and SSRIs has been suggested⁵⁴ though reported cases appear to be rare. In a survey of investigators in the Parkinson Study Group, a possible serotonin syndrome was reported in

11 of 4568 patients (0.24%) taking both selegiline and SSRI. Only 2 patients experienced serious symptoms (0.04%) and no deaths were reported.⁵⁵

In both the TEMPO and LARGO studies, a limited number of antidepressants including SSRIs were permitted: sertraline, paroxetine, citalopram, trazodone and amitriptyline. No adverse interactions were reported.^{49,52} In the Azilect post-marketing period, non-fatal cases of serotonin syndrome have been reported in subjects taking antidepressants and rasagiline concomitantly. Current Azilect labeling advises the avoidance of coadministration of rasagiline and antidepressants.³⁴ In practice, this may be difficult given the high prevalence of depression in PD. Therefore, clinical judgment and vigilance should be used when treating PD patients with both rasagiline and an antidepressant, and patients should be educated about possible drug interactions and the symptoms associated with serotonin syndrome.

Tyramine and rasagiline

Tyramine, an indirectly acting sympathomimetic found in aged cheeses and cured meats, is metabolized by MAO in the gastrointestinal system. A “cheese effect”, tyramine pressor response, can occur in patients taking non-selective MAOIs (ie, tranylcypromine, phenelzine) who ingest foods high in tyramine.⁵⁶ Because the vast majority of MAO in the intestine is the MAO-A isoform, a selective MAO-B inhibitor such as rasagiline is not likely to cause this effect. However, such selectivity diminishes with increasing dose and because of this concern, the US Food and Drug Administration initially required a warning to restrict dietary tyramine in patients taking rasagiline. In the three phase III studies of rasagiline in PD (TEMPO, PRESTO, LARGO), there were no specified dietary restrictions and rasagiline was well-tolerated with no reported tyramine pressor reactions.^{49–55}

In a study of PD patients enrolled in the TEMPO or PRESTO trials, tyramine challenges of 50 to 75 mg were performed on 72 rasagiline-treated patients and 38 placebo-treated patients immediately following the completion of each study, within 24 hours after the last rasagiline dose. None of the 55 subjects from the TEMPO study (38 rasagiline, 17 placebo) met the prespecified endpoint (three consecutive measurements of SBP with increases of more or equal with 30 mm Hg or heart rate reduction less than 40 bpm over 10 min). In the PRESTO study, 3/34 patients taking rasagiline and 1/21 patients taking placebo developed asymptomatic, self-limiting elevation in SBP > 30 mm Hg for 3 consecutive measurements after tyramine challenge, but without bradycardia or ECG changes.⁵⁷

A recent study conducted in healthy subjects assessed tyramine sensitivity when administered with rasagiline. There were seven treatment groups and within each group subjects were randomly assigned to receive MAO-I or placebo. MAO-Is tested were: phenelzine 45 mg/day, selegiline 10 mg/day, and increasing doses of rasagiline ranging from 1 mg/day to 6 mg/day. The primary outcome measure was the ratio of the amount of tyramine needed to drive a specific elevation of blood pressure off drug vs on drug. The ratio was highest for phenelzine. Difference in outcome for rasagiline vs placebo and selegiline was not significant, indicating that rasagiline at recommended doses was a selective MAO-B inhibitor and as selective as selegiline.⁵⁸ The results of this study were recently reviewed by the FDA and the bolded warning for tyramine was removed.³⁴

Other drug interactions

Rasagiline is a substrate for CYP1A2 enzyme and therefore patients who are taking CYP1A2 inhibiting drugs should receive a maximum dose of rasagiline 0.5 mg daily.

Concomitant use of meperidine, tramadol, methadone, propoxyphene, dextromethorphan and St. John's wort is contraindicated. There is no contraindication for use of rasagiline with sympathomimetic agents or general or local anesthetics.

Potential disease-modifying effects of rasagiline in PD

A current goal of PD research is the identification of neuroprotective, or disease-modifying, agents. A number of promising candidate drugs have been tested but results have been limited or confounded by lack of reliable biomarkers of disease progression and potential symptomatic drug effects.⁵⁹ As discussed earlier, rasagiline has been shown to provide neuroprotective effects in in vitro and in vivo studies. The TEMPO results suggested a potential disease-modifying effect of rasagiline and an open-label extension study of the TEMPO trial demonstrated that the beneficial effect of early rasagiline treatment persisted for up to 6.5 years.⁵³ The ADAGIO (Attenuation of Disease Progression with Azilect Given Once-daily) study was designed to further study the potential of rasagiline as a neuroprotective, or disease-modifying, agent. ADAGIO was the first prospectively designed, multicenter, placebo-controlled, double-blind trial utilizing a delayed-start method to study rasagiline in early untreated PD patients. The delayed-start design was employed to attempt to avoid confounding symptomatic medication effects seen in previous trial designs. In this paradigm, there are two

phases. In the first phase, drug-naïve patients are randomized to receive active treatment or placebo for a fixed time interval. In the second phase, patients taking the placebo drug are switched to the study drug so that patients in all study groups are receiving active treatment. If the study drug has symptomatic effects only, it would be expected that any differences between the two groups that developed in the first phase would not persist in the second phase. However, if there were disease-modifying as well as symptomatic effects of the active treatment, differences between the two groups should persist at the end of the second phase, ie, the delayed-start group would not "catch up" to the early-start group.⁶⁰

ADAGIO was an 18-month long study performed in 2 phases, each lasting 36 weeks. 1176 subjects were randomized to 4 different treatment groups: 1) placebo during phase I followed by 1 mg/day rasagiline in phase II; 2) placebo during phase I followed by 2 mg/day rasagiline in phase II; 3) 1 mg/day rasagiline during phases I and II; 4) 1 mg/day rasagiline during phases I and II. There were three primary efficacy endpoints: 1) rate of UPDRS progression during the placebo-controlled phase from week 12 to week 36 for the placebo and rasagiline treated groups, 2) estimate of change from baseline to week 72 in total UPDRS score in both groups, and 3) non-inferiority of the slope estimates of the early-start and delayed-start rasagiline groups during the active phase (weeks 48–72). Rasagiline at a dose of 1 mg/day met all three hierarchical primary endpoints: slower rate of worsening as measured by change in the slopes in the first phase (0.09 ± 0.02 vs 0.14 ± 0.01 points per week; $P = 0.01$); less worsening in mean total UPDRS between baseline and week 72 (2.82 ± 0.53 vs 4.50 ± 0.56 points; $P = 0.02$); noninferiority of the slopes in the active phase (0.85 ± 0.02 vs 0.85 ± 0.02 points per week; $P < 0.0001$). Rasagiline 2 mg dose, however, did not reach all three endpoints of the primary analysis. A subgroup analysis of the 2 mg group showed that for those subjects with the highest quartile of UPDRS scores at baseline (patients more affected by the disease), early-start rasagiline provided significant benefit over delayed-start rasagiline. These results suggest that the higher dose of rasagiline may have masked a possible disease-modifying effect in PD subjects with milder disease.⁶¹

The different results for the two doses of rasagiline are difficult to explain. In addition, the clinical significance of a 1.7 unit difference on the UPDRS is not clear. Future studies are needed to confirm the positive findings for rasagiline 1 mg, and studies of rasagiline PD patients with more advanced disease should be considered to untangle symptomatic from potential disease-modifying effects of higher

dose rasagiline. Moreover, long-term data will be needed to determine whether the benefits seen with early-start rasagiline 1 mg persist with disease progression.

Conclusions

Rasagiline is a potent, selective and irreversible MAO-B inhibitor that has demonstrated efficacy in early and advanced stages of PD. Rasagiline possesses a number of advantages over selegiline including its once daily dosing, milder side effect profile, more potent MAO-B inhibition, and non-amphetamine metabolites. Rasagiline has also been shown to have neuroprotective properties in cell culture and animal models of PD. The ADAGIO trial has suggested that rasagiline 1 mg/day may have a disease-modifying effect in early PD. However, these findings were not borne out with the 2 mg dose. Further studies are needed to confirm these results and to determine whether initial benefits with rasagiline are sustained and have long-term effects on disease progression in PD.

Disclosures

Dr Leegwater-Kim has received honoraria from Teva Pharmaceutical Industries. Dr Bortan has no disclosures.

References

- De Lau LM, Breteler MM. Epidemiology of Parkinson's disease. *Lancet Neurol*. 2006;5:525–35.
- Forno LS. Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol*. 1996;55:259–272.
- Braak H, Del Tredici K, Rub U, et al. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*. 2003;24:197–211.
- Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. *Neuron*. 2003;39:889–909.
- Olanow CW. Pathogenesis of cell death in Parkinson's disease. *Mov Disord*. 2007;22:S335–S342.
- Dawson TM, Dawson VL. Molecular pathways of neurodegeneration in Parkinson's disease. *Science*. 2003;302:819–622.
- Hardy J, Cai H, Cookson MR, Gwinn-Hardy K, Singleton A. Genetics of Parkinson's disease and parkinsonism. *Ann Neurol*. 2006;60:389–398.
- Klein C, Lohmann-Hedrich K. Impact of recent genetic findings in Parkinson's disease. *Curr Opin Neurol*. 2007;20:453–464.
- Tanner CM, Ottman R, Goldman SM, et al. Parkinson disease in twins: an etiologic study. *JAMA*. 1999;281:341–346.
- Lesage S, Durr A, Tazir M, et al. LRRK2 G2019S as a cause of Parkinson's disease in Ashkenazi Jews. *N Engl J Med*. 2006;354:424–425.
- Ozelius LJ, Senthil G, Saunders-Pullman R, et al. LRRK2 G2019S as a cause of Parkinson's disease in North African Arabs. *N Engl J Med*. 2006;354:422–423.
- Lai BC, Marion SA, Teschke K, Tsui JK. Occupational and environmental risk factors for Parkinson's disease. *Parkinsonism Relat Disord*. 2002;8:297–309.
- Vogel WH, Orfei V, Century B. Activities of enzymes involved in the formation and destruction of biogenic amines in various areas of human brain. *J Pharmacol Exp Ther*. 1969;165:196–203.
- Tallman JF, Saavedra JM, Axelrod J. Biosynthesis and metabolism of endogenous tyramine and its normal presence in sympathetic nerves. *J Pharmacol Exp Ther*. 1976;199:216–221.
- Collins GG, Sandler M, Williams ED, Youdim MB. Multiple forms of human brain monoamine oxidase. *Nature*. 1970;225:817–820.
- Youdim MB, Collins GG, Sandler M, et al. Human brain monoamine oxidase, multiple forms and selective inhibitors. *Nature*. 1972;236:225–228.
- Tatton WG, Greenwood CE. Rescue of dying neurons: a new action for deprenyl in MPTP parkinsonism. *J Neurosci Res*. 1991;30:666–672.
- Mytilineou C, Radcliffe P, Leonardi EK, Werner P, Olanow CW. L-deprenyl protects mesencephalic dopamine neurons from glutamate receptor-mediated toxicity in vitro. *J Neurochem*. 1997;68:33–39.
- Tatton W, Chalmers-Redman R, Tatton N. Neuroprotection by deprenyl and other propargylamines: glyceraldehyde-3-phosphate dehydrogenase rather than monoamine oxidase B. *J Neural Transm*. 2003;110:509–515.
- Finberg JP, Lamensdorf I, Commissiong JW, Youdim MB. Pharmacology and neuroprotective properties of rasagiline. *J Neural Transm Suppl*. 1996;48:95–101.
- Weinreb O, Amit T, Bar-Am O, Chillag-Talmor O, Youdim MB. Novel neuroprotective mechanism of action of rasagiline is associated with its propargyl moiety: interaction of Bcl-2 family members with PKC pathway. *Ann NY Acad Sci*. 2005;1053:348–355.
- The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989;321:1364–1371.
- The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1993;328:176–183.
- Olanow CW, Calne D. Does selegiline monotherapy in Parkinson's disease act by symptomatic or protective mechanisms? *Neurology*. 1992;42(4 Suppl 4):13–26.
- Ricaurte GA, Seiden LS, Schuster CR. Further evidence that amphetamines produce long-lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. *Brain Res*. 1984;303:359–364.
- Churchyard A, Mathias CJ, Boonkongchuen P, Lees AJ. Autonomic effects of selegiline: possible cardiovascular toxicity in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 1997;63:228–234.
- Bar-Am O, Amit T, Youdim MB. Aminoindan and hydroxyaminoindan, metabolites of rasagiline and l-dopamine, respectively, exert neuroprotective properties in vitro. *J Neurochem*. 2007;103:500–508.
- Finberg JP, Youdim MB. Modification of blood pressure and nictating membrane response to sympathetic amines by selective monoamine oxidase inhibitors, types A and B, in the cat. *Br J Pharmacol*. 1985;85:541–546.
- Sterling J, Veinberg A, Lerner D, et al. (R)(+)-N-propargyl-1-aminoindan (rasagiline) and derivatives: highly selective and potent inhibitors of monoamine oxidase B. *J Neural Transm Suppl*. 1998;52:301–305.
- Youdim MB, Gross A, Finberg JP. Rasagiline [N-propargyl-1R(+)-aminoindan], a selective and potent inhibitor of mitochondrial monoamine oxidase B. *Br J Pharmacol*. 2001;132:500–506.
- Freedman NM, Mishani E, Krausz Y, et al. In vivo measurement of brain monoamine oxidase B occupancy by rasagiline, using (11)C-l-deprenyl and PET. *J Nucl Med*. 2005;46:1618–1624.
- Thébault JJ, Guillaume M, Levy R. Tolerability, safety, pharmacodynamics, and pharmacokinetics of rasagiline: a potent, selective, and irreversible monoamine oxidase type B inhibitor. *Pharmacotherapy*. 2004;24:1295–1305.
- Stern MB, Marek KL, Friedman J. Double-blind, randomized, controlled trial of rasagiline as monotherapy in early Parkinson's disease patients. *Mov Disord*. 2004;19:916–923.
- Azilect (rasagiline mesylate) [package insert]. Kansas City, MO: Teva Neuroscience; 2006.
- Hirsch EC, Hunot S, Faucheux B, et al. Dopaminergic neurons degenerate by apoptosis in Parkinson's disease. *Mov Disord*. 1999;14:383–385.

36. Mochizuki H, Goto K, Mori H, Mizuno Y. Histochemical detection of apoptosis in Parkinson's disease. *J Neurol Sci.* 1996;137:120–123.
37. Olanow CW. Rationale for considering that propargylamines might be neuroprotective in Parkinson's disease. *Neurology.* 2006;66:S69–S79.
38. Tatton WG, Chalmers-Redman RM. Modulation of gene expression rather than monoamine oxidase inhibition: (–)-deprenyl-related compounds in controlling neurodegeneration. *Neurology.* 1996;47:S171–S183.
39. Naoi M, Maruyama W, Yi H, Akao Y, Yamaoka Y, Shamoto-Nagai M. Neuroprotection by propargylamines in Parkinson's disease: intracellular mechanism underlying the anti-apoptotic function and search for clinical markers. *J Neural Transm Suppl.* 2007;(72):121–131.
40. Goggi J, Theofilopoulos S, Riaz SS, Jauniaux E, Stern GM, Bradford HF. The neuronal survival effects of rasagiline and deprenyl on fetal human and rat ventral mesencephalic neurones in culture. *Neuroreport.* 2000;11:3937–3941.
41. Yi H, Maruyama W, Akao Y, et al. N-Propargylamine protects SH-SY5Y cells from apoptosis induced by an endogenous neurotoxin, N-methyl(R)salsolinol, through stabilization of mitochondrial membrane and induction of anti-apoptotic Bcl-2. *J Neural Transm.* 2006;113:21–32.
42. Blandini F, Armentero MT, Fancellu R, Blaugrund E, Nappi G. Neuroprotective effect of rasagiline in a rodent model of Parkinson's disease. *Exp Neurol.* 2004;187:455–459.
43. Zhu W, Xie W, Pan T, et al. Comparison of neuroprotective and neurorestorative capabilities of rasagiline and selegiline against lactacystin-induced nigrostriatal dopaminergic degeneration. *J Neurochem.* 2008;105:1970–1978.
44. Stefanova N, Poewe W, Wenning GK. Rasagiline is neuroprotective in a transgenic model of multiple system atrophy. *Exp Neurol.* 2007;210:421–427.
45. Huang W, Chen Y, Shohami E, Weinstock M. Neuroprotective effect of rasagiline, a selective monoamine oxidase-B inhibitor, against closed head injury in the mouse. *Eur J Pharmacol.* 1999;366:127–135.
46. Speiser Z, Mayk A, Litinetsky L, et al. Rasagiline is neuroprotective in an experimental model of brain ischemia in the rat. *J Neural Transm.* 2007;114:595–605.
47. Waibel S, Reuter A, Malessa S, Blaugrund E, Ludolph AC. Rasagiline alone and in combination with riluzole prolongs survival in an ALS mouse model. *J Neurol.* 2004;251:1080–1084.
48. Maruyama W, Takahashi T, Youdim M, Naoi M. The anti-Parkinson drug, rasagiline, prevents apoptotic DNA damage induced by peroxynitrite in human dopaminergic neuroblastoma SH-SY5Y cells. *J Neural Transm.* 2002;109:467–481.
49. Parkinson Study Group. A controlled trial of rasagiline in early Parkinson disease: the TEMPO Study. *Arch Neurol.* 2002;59:1937–1943.
50. Parkinson Study Group. A controlled, randomized delayed-start study of rasagiline in early Parkinson disease. *Arch Neurol.* 2004;61:561–566.
51. Parkinson Study Group. A randomized placebo-controlled trial with rasagiline in levodopa-treated patients with Parkinson Disease and motor fluctuations. The PRESTO study. *Arch Neurol.* 2005;62:241–248.
52. Rascol O, Brooks DJ, Melamed E, et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomized, double blind, parallel-group trial. *Lancet.* 2005;365:947–954.
53. Hauser RA, Lew MF, Hurtig HI, et al. Long-term outcome of early versus delayed rasagiline treatment in early Parkinson's disease. *Mov Disord.* 2009;24:564–573.
54. Suchowersky O, DeVries JD. Interaction of fluoxetine and selegiline. *Can J Psychiatry.* 1990;35:571–572.
55. Richard IH, Kurlan R, Tanner C, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. *Neurology.* 1997;48:1070–1076.
56. Blackwell B, Marley E, Price J, Taylor D. Hypertensive interactions between monoamine oxidase inhibitors and foodstuffs. *Br J Psychiatry.* 1967;113:349–365.
57. DeMarcaida JA, Schwid SR, White WB, et al. Effects of tyramine administration in Parkinson's disease patients treated with selective MAO-B inhibitor rasagiline. *Mov Disord.* 2006;21:1716–1721.
58. Goren T, Adar L, Sasson N. A clinical pharmacology study to determine the selective and non-selective doses of the monoamine oxidase type B inhibitor, rasagiline. *Neurology.* 2009;72(Suppl 3):A320–A321.
59. Schapira AH, Olanow CW. Neuroprotection in Parkinson disease: mysteries, myths, and misconceptions. *JAMA.* 2004;291:358–364.
60. Olanow CW, Hauser RA, Jankovic J, et al. A randomized, double-blind, placebo-controlled, delayed start study to assess rasagiline as a disease modifying therapy in Parkinson's disease (the ADAGIO study): rationale, design, and baseline characteristics. *Mov Disord.* 2008;23:2194–2201.
61. Olanow C, Rascol O, Hauser R; for the ADAGIO Study Investigators. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. *N Engl J Med.* 2009;361:1268–1278.

Clinical Interventions in Aging

Publish your work in this journal

Clinical Interventions in Aging is an international, peer-reviewed journal focusing on evidence-based reports on the value or lack thereof of treatments intended to prevent or delay the onset of maladaptive correlates of aging in human beings. This journal is indexed on PubMed Central, MedLine, the American Chemical Society's 'Chemical Abstracts Ser-

Submit your manuscript here: <http://www.dovepress.com/clinical-interventions-in-aging-journal>

Dovepress

vice' (CAS), Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.