

Role of rasagiline in treating Parkinson's disease: Effect on disease progression

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Abstract: Rasagiline is a second generation, selective, irreversible monoamine oxidase type B (MAO-B) inhibitor. It has demonstrated efficacy in monotherapy for early Parkinson's disease (PD) patients in one large randomized, placebo-controlled trial (TVP-1012 in Early Monotherapy for Parkinson's Disease Outpatients), and has shown ability to reduce off time in more advanced PD patients with motor fluctuations in two large placebo-controlled trials (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of "Off", and Lasting Effect in Adjunct Therapy With Rasagiline Given Once Daily). Preclinical data abound to suggest potential for neuroprotection by this compound against a variety of neurotoxic insults in cell cultures and in animals. The lack of amphetamine metabolites provides an advantage over the first generation MAO-B inhibitor selegiline. One large trial has investigated the potential for disease modification in PD patients (Attenuation of Disease progression with Azilect Given Once-daily) and preliminary results maintain some possible advantage to earlier initiation of the 1 mg/day dose. The clinical significance of the difference detected remains a consideration.

Keywords: rasagiline, Parkinson's disease, neuroprotection, selegiline

Introduction

Parkinson's disease (PD) is a progressive, neurodegenerative disorder characterized pathologically by the loss of dopamine-producing neurons in the substantia nigra pars compacta and Lewy body deposition in multiple brain areas.¹ The depletion of nigrostriatal dopamine results in dysfunction of communication between the striatum and the cortex, leading to motor deficits that include tremor, rigidity, and bradykinesia, and to cognitive and behavioral sequelae in many patients. By the time symptoms occur, approximately 80% of striatal dopaminergic neurons, and 50% of nigral neurons are lost.¹ Multiple pharmacologic strategies are employed to overcome the relative dopamine deficiency. These include supplying levodopa, which serves as a substrate for creating more dopamine, administering dopamine agonists, which stimulate dopamine receptors, anticholinergic drugs, and drugs which inhibit the metabolism of endogenous (and exogenous) dopamine to increase the available supply. The latter category includes inhibitors of the two major enzymes responsible for dopamine metabolism, catechol-O-methyltransferase, and monoamine oxidase. In the US, the first generation monoamine oxidase type B (MAO-B) inhibitor, selegiline, and the second generation drug, rasagiline, are available for this purpose. Rasagiline offers the advantages of increased tolerability, lack of amphetamine metabolites, and approval for monotherapy in early PD. Data in cell cultures and animal studies highlight a neuroprotective effect

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of rasagiline and clinical trials offer suggestive evidence of a possible disease-modifying effect in humans. This review will discuss the role of rasagiline in the treatment of PD and its potential role in modifying disease progression.

Therapeutic rationale

As PD symptoms are thought to originate from dysfunction of nigrostriatal dopamine circuits and their connections, various strategies are employed for enhancing dopaminergic function. These include providing an exogenous substrate for dopamine production (levodopa), stimulating endogenous dopamine receptors with dopamine agonists, using anticholinergic medications which work by not fully understood mechanisms, and inhibition of dopamine metabolism to increase the amount of available endogenous (and exogenous) dopamine at nerve terminals.²

Dopamine is metabolized primarily by two enzymatic pathways; by catechol-O-methyl transferase (COMT) into 3-methoxytyramine (3-MT), and by monoamine oxidase (MAO) into dihydroxyphenylacetic acid (DOPAC). DOPAC is further metabolized by COMT into HVA, and 3-MT is metabolized by MAO into HVA. Monoamine oxidase (MAO) is embedded in the outer mitochondrial membrane³ and appears to be the primary enzyme responsible for dopamine metabolism, as 70%–80% of striatal HVA originates from DOPAC, and 20%–30% from 3-MT.⁴ There are two distinct isoenzymes, MAO-A and MAO-B. Type A is primarily located in the gut and metabolizes catecholamines as well as dietary tyramine. It contributes to the oxidative deamination of dopamine, serotonin, and norepinephrine.² Inhibition of this isoform has been associated with the “cheese reaction” which derives its name from the potential of aged cheeses and other tyramine-rich foods to cause a hypertensive crisis. Brain MAO, however, is primarily type B.⁵ MAO-B is the largely predominant isoform, comprising over 80% of MAO activity, and contributes to most of the metabolic breakdown of dopamine. It also has a role in deaminating beta-phenylethylamine, which stimulates release of dopamine and inhibits its reuptake.⁵ Therefore, inhibition of MAO-B increases available dopamine.

Older monoamine oxidase inhibitors nonselectively inhibited both types A and B, whereas newer selective drugs specifically target MAO type B. Efficacy of selective MAO-B inhibition in treating early PD was initially established for selegiline (deprenyl) in DATATOP (Deprenyl and Tocopherol Antioxidative therapy of Parkinsonism).^{6,7} In this multicenter placebo-controlled study, 800 patients with early, untreated PD were randomized to receive deprenyl

10 mg/day, tocopherol (vitamin E) 2,000 IU/day, both, or placebo. The primary endpoint was time to progression of disability sufficient to require levodopa therapy. Secondary endpoints were Unified Parkinson's Disease Rating Score (UPDRS) motor scores, and activities of daily living scores.⁶ The study concluded that deprenyl, but not tocopherol, had a significant impact on delaying progression of disability. The hazard ratio for probability of reaching the primary endpoint in selegiline vs placebo patients was 0.5 (95% CI: 0.41–0.62). Deprenyl patients required levodopa at a median of approximately nine months later. Benefit in motor scores was detected early, within the first three months, highlighting the symptomatic effect of the drug. The difference was sustained at the (14 ± 6-month) follow-up,⁷ but an extension of the study (maintaining the blinding of the initial phase) involving 310 of the original 800 patients who had not reached the primary endpoint determined that after another 18 months (12 ± 5), the superiority was not sustained.⁸ This emphasizes that a major challenge in drawing conclusions regarding disease modification from deprenyl is the inability to separate symptomatic benefit from disease modification. The measures for assessing course of disease rely on quantifying symptoms. Therefore, the early therapeutic benefit is not clearly differentiated from a delay in progression of disability.

Nonetheless, based on the results of DATATOP, the US Food and Drug Administration (FDA) approved selegiline for adjunctive symptomatic therapy in early PD.⁹ The Zydis formulation was subsequently developed, which dissolves in the mouth and is buccally absorbed, avoiding effects of first-pass metabolism and increasing bioavailability, while decreasing amphetamine metabolites.^{10,11}

The second generation MAO-B inhibitor rasagiline was subsequently developed and proved to be clinically effective, as discussed below. In 2006, rasagiline was the first MAO-B inhibitor to receive FDA approval for monotherapy in early PD, and was also approved for adjunctive therapy in moderate to advanced PD with motor fluctuations.¹²

Pharmacokinetics and dosing

Rasagiline is a second generation, irreversible MAO-B inhibitor which, unlike selegiline, is not a methamphetamine derivative. Rather, rasagiline is a secondary cyclic benzylamine and indane derivative⁵ with the chemical structure (N-propargyl-1[R]-aminoindan). It is rapidly absorbed and undergoes metabolism by the cytochrome P450 (CYP) hepatic enzymes, primarily CYP1A2.⁵ Therefore, it should be avoided in patients with moderate to severe hepatic insufficiency.¹³

Co-administration with potent CYP1A2 inducers (such as omeprazole) or inhibitors (such as cimetidine) can decrease or increase the area under the concentration-time curve (AUC). In contrast, selegiline is metabolized by multiple CYP enzymes, leading to much greater potential for drug interactions. Rasagiline is five times as potent as selegiline with regard to dose required to inhibit MAO-B by 50%.¹⁴ Both drugs readily cross the blood-brain barrier.¹⁴

The primary metabolite of rasagiline is 1-R-aminoindan, whereas selegiline is metabolized primarily to desmethylselegiline, L-methamphetamine, and L-amphetamine. Both aminoindan and desmethylselegiline have shown evidence of antiapoptotic properties *in vitro*, but the amphetamine metabolites may block the neuroprotective effects of the latter.^{15–17} Less than 1% of rasagiline is excreted unchanged in the urine.¹³

Inhibition of MAO-B by rasagiline is irreversible. Platelet MAO-B inhibition correlates well with brain MAO-B, and serves as a marker of MAO-B activity. This has revealed that 35% of MAO-B activity was inhibited within one hour of administration of 1 mg rasagiline in healthy volunteers.^{18,19} (11) C-I-deprenyl PET was able to detect decrease MAO-B activity in the thalamus and basal ganglia immediately after a 10-day period of administering rasagiline to healthy volunteers. Activity returned to normal over six weeks, consistent with the half-life for *de novo* enzyme synthesis. Duration of effect as assessed by platelet MAO-B activity appears to be approximately two weeks after discontinuation.^{12,20}

Selectivity for MAO-B over MAO-A is lost in a dose-dependent manner, as determined in a rat study of escalating doses.¹⁴ The specific dose at which selectivity is lost in humans is not fully known.

Evidence for therapeutic efficacy

Monotherapy: TEMPO

The TEMPO trial ([TVP-1012] in Early Monotherapy for Parkinson's disease Outpatients) was a (multicenter) two-phased, parallel-group, delayed start, randomized, double-blinded placebo-controlled trial evaluating the symptomatic and potentially disease modifying properties of rasagiline. In the first phase, 404 early, untreated PD patients were randomized to rasagiline 1 mg, 2 mg, or placebo for 26 weeks. The primary endpoint was change in total UPDRS score from baseline, and secondary outcomes included UPDRS motor score, activities of daily living (ADL) score, quality of life (QOL) measure, among others.²¹ At 26 weeks, both dosages of rasagiline were superior to placebo. The total change in UPDRS was –4.2 units for the 1 mg dose (95% CI:

–5.66 to –2.73; $p < 0.001$), and –3.56 for the 2 mg dose relative to placebo (95% CI: –5.04 to –2.08; $p < 0.001$). Motor subscales were improved over placebo as well: –2.71 and –1.68 for the 1 mg and 2 mg doses, respectively. Both treatment groups were superior to placebo with regard to ADL and QOL scores as well.^{21,22} This provided evidence of therapeutic efficacy in monotherapy in early PD.

In the second phase of the study, all patients received the 2 mg dose. This delayed start phase was incorporated to determine if there was a therapeutic advantage to early treatment. If so, the delayed start group would not “catch up” with regard to symptomatic improvement. At 52 weeks, a statistically significant advantage was maintained in UPDRS scores of the early treatment groups, with mean adjusted difference of –1.82 ($p = 0.05$) for 1 mg early dosing over placebo, and –2.29 ($p = 0.01$) for 2 mg early dosing over the early placebo group.²³ (PSG 04) (Negative numbers indicate improved UPDRS scores.) These results seemed to suggest less functional decline in the early treatment groups relative to early placebo groups.

Open label extension study of the TEMPO study followed 306 patients on rasagiline for up to 6.5 years. All patients took 2 mg/day until May 2000, when the dose was uniformly changed to 1 mg/day. Average decline in UPDRS was 2–3 points per year, which reflected an improvement over historical reports of 8–11 UPDRS points/year in placebo groups with similar baseline characteristics. After two years of treatment, approximately half of the patients were maintained without dopaminergic therapy. The beneficial effect of early vs delayed start was maintained for the 6.5-year period, offering further support for the persistent symptomatic benefit of rasagiline, and the potential role in slowing symptom progression.^{19,24,25}

At the same time, critics have questioned whether the delayed start design is able to distinguish symptomatic improvement from disease progression.

Adjunctive therapy: PRESTO, LARGO

Two large placebo-controlled trials have evaluated the role of rasagiline as adjunctive therapy to levodopa in PD.

The PRESTO study (Parkinson's Rasagiline: Efficacy and Safety in the Treatment of “Off”) was a 26-week trial of 472 patients, with an average disease duration of nine years, with motor fluctuations on optimized levodopa treatment. Each had at least 2.5 hours of “off” time daily (average six hours), and was randomized to rasagiline 0.5 mg, 1 mg, or placebo. Levodopa dose was sustained (through the course of the study) after titration to the assigned dose. Both groups

had significantly greater improvement (reduction) in off time, which was the primary endpoint, over placebo: -1.4 hour (-23%) in the 0.5 mg group, and -1.8 hour (-29%) in the 1 mg group, vs -0.9 hour (-15%) for placebo. Furthermore, improvements in secondary endpoints of “on” motor scores and “off” ADL scores were seen in both rasagiline groups. Dyskinesias were more commonly seen, likely attributable to restrictions on levodopa reduction, but tolerability was good and there was no significant difference in patients discontinuing the study between treatment and placebo groups.²⁶

The LARGO study (Lasting Effect in Adjunct Therapy with Rasagiline Given Once Daily) was an 18-week, double-blind, randomized, active comparator study which compared rasagiline 1 mg daily, entacapone 200 mg with each levodopa dose, and matching placebos for their ability to reduce “off” time in 687 levodopa-treated patients with motor fluctuations. At the end of 18 weeks, the primary endpoint was mean change in daily “off” time from baseline. Rasagiline significantly reduced “off” time by (-1.18 hours; $p = 0.0001$) relative to placebo, and entacapone had a similar effect (-1.2 hours; $p < 0.0001$). Secondary endpoints reaching significance included “on” time without dyskinesia (0.85 hours vs 0.03 hours for placebo; $p = 0.0005$ for both), clinical global impression scores, “off” ADL scores, and “on” motor scores.²⁷

Evidence for potential neuroprotection

Rasagiline has shown evidence of neuroprotective properties in multiple *in vitro* and *in vivo* models with various mechanisms of neurotoxicity. The mechanism cannot be solely accounted for by MAO-B inhibition.

Rasagiline has shown protection against various neuronal insults in cell cultures. These include protection against glutamate-induced toxicity in rat hippocampal neuronal cultures¹⁷ and against apoptotic cell death from deprivation of oxygen and glucose, or from serum and nerve growth factor in pheochromocytoma (PC12) cells.^{15,16} Rasagiline also demonstrated antiapoptotic activity against peroxynitrite from SIN-1-induced DNA damage in human dopaminergic neuroblastoma SH-SY5Y cells.²⁸

In vivo evidence of neuroprotection also exists. Rat models of PD using 6-OHDA striatal lesioning revealed increased survival of dopaminergic neurons subsequently treated with rasagiline relative to controls.²⁹ Rodent models have also demonstrated improvements in motor function after drug-induced dopaminergic dysfunction, and in motor and cognitive function post-hypoxia.³⁰ Furthermore, rasagiline-treated mice had faster recovery of motor function

and spatial memory, and less cerebral edema, after closed head injury. Stroke models in the rat demonstrated decreased infarct sized after MCA occlusion and improved neurological severity scores in multiple models.^{2,31,32}

The mechanism for rasagiline’s neuroprotection may in part relate to MAO-B inhibition. In primate models of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) dopaminergic neurotoxicity, pretreatment with rasagiline, via MAO-B inhibition, is able to interfere with enzymatic conversion of MPTP to a potent neurotoxin, also decreasing free radical generation which would disrupt mitochondrial respiration and lead to cell death.^{33,34} This has previously been demonstrated in a rat model as well.³⁵

At the same time, there is evidence that the S-enantiomer (TV1022) of rasagiline is neuroprotective to the same extent, despite having 1000 times less potency for MAO-B. These include studies in animals exposed to head injury and global ischemia, and in cell cultures exposed to neurotoxins.³⁶ Further, the human neuroblastoma SH-SY5Y cell cultures, which do not contain MAO-B, also are protected from peroxynitrite and 6-OHDA induced apoptosis by rasagiline pretreatment.^{28,37} The mechanism appears to be stabilization of mitochondrial membrane potential and prevention of the mitochondrial permeability transition pore from opening. Activation of proapoptotic substances such as caspase 3 was also inhibited by rasagiline.^{28,37}

The propargylamine moiety of rasagiline has also been identified as a direct source of neuroprotection³⁶ by protecting mitochondrial viability and preventing the apoptotic cascade. Various cellular insults lead to change in the permeability of the mitochondrial membrane potential, causing opening of the mitochondrial permeability transition pore and decline in the membrane potential. This normally causes inhibition of the ubiquitin-proteasome complex and release of proapoptotic factors.³⁶ Direct binding of the propargylamine moiety, however, prevents downstream activation of proapoptotic factors,^{37–40} partially via activation of antiapoptotic factors including Bcl-2 and protein kinase C, and also by downregulation of proapoptotic catalysts including FAS and Bax protein families.³⁶

Rasagiline offers an advantage over the first-generation MAO-B inhibitor selegiline in its lack of amphetamine metabolites, which may interfere with neuroprotection.

In a model of oxygen/glucose deprivation of rat PC12 cells, rasagiline reduced cell death by 45%–55%, whereas selegiline reduced cell death by 30%. Addition of 1-R-aminoindan (the major rasagiline metabolite) did not deter from its benefit, but addition of L-methamphetamine (major selegiline

metabolite) actually enhanced cell death in cultures. Neither metabolite was independently neurotoxic in nondeprived cells.¹⁶ Another study of apoptotic cell death in PC12 cells deprived of serum and nerve growth factors found similar results of attenuation of the neuroprotection by selegiline by its metabolite, whereas interestingly 1-R-aminoindan actually had independent protective effects.¹⁵

Furthermore, rasagiline was able to protect rat and human fetal me encephalic cells from cell death 15%–20% more effectively than selegiline, and also to selectively increase dopaminergic cell survival.^{41,42}

Results of the *in vitro* and animal studies above may or may not have direct clinical relevance to humans. Even if rasagiline can be protective against the various neurological insults studied, the ability to protect to human patients from PD progression has not been confirmed. The accumulation of preclinical data to suggest potential neuroprotective properties has been ultimately challenged clinically in the ADAGIO study (Attenuation of Disease progression with Azilect Given Once-daily), a randomized, double-blinded, multicenter, placebo-controlled trial with a delayed start design to assess rasagiline as a possible disease-modifying therapy in PD.⁴³ For this study, 1,176 untreated PD patients at 129 international sites, with disease duration less than 18 months were enrolled. In phase I, subjects were randomized equally to one of four groups: 1 mg daily for the duration of the study, 2 mg/day for the duration of the study (early start groups), placebo for phase I followed by 1 mg/day, or placebo for phase I followed by 2 mg/day (delayed start groups). Phase I and II were 36 weeks each, and if additional anti-parkinsonian medications were required, a subject would proceed to phase II. No further adjustments were allowed in phase II without exiting the study. The rationale of the study was that if a true disease-modifying, and not solely symptomatic, effect existed, the separation between early start and placebo groups would be maintained at 72 weeks. If the effect was purely symptomatic, the slopes of the curves would be expected to converge.⁴³ The three primary efficacy hypotheses would assess 1) rate of UPDRS progression in phase I (slope), between weeks 12–36, for treated vs placebo groups, 2) change from baseline total UPDRS score at 72 weeks for each group, and 3) noninferiority of the slope of early start groups (1 or 2 mg rasagiline) vs delayed start groups in phase II, weeks 48–72. Secondary outcomes included total change in UPDRS during phase I, percentage of subjects requiring additional antiparkinsonian medication, and time until additional therapy is required.

Although the results of ADAGIO have not yet been published, they were presented at both the 12th Congress of the European Federation of Neurological Societies, in Madrid, Spain in August 2008 and at American Neurological Association meeting in December 2008.⁴⁴ Early treatment with 1 mg/day rasagiline reached all three primary endpoints: superiority of slope in weeks 12–36 (-0.05 ; $p = 0.013$, 95% CI: -0.08 , -0.01), change from baseline UPDRS to week 72 (-1.7 units; $p = 0.025$, 95% CI: -3.15 , -0.21), and noninferiority of slope in weeks 48–72 for the early start group (0.0 ; 90% CI: -0.04 , 0.04). Interestingly, the 2 mg/day dose did not meet the endpoint for change in UPDRS from baseline to week 72. The clinical significance of the 1.7 unit difference in the total UPDRS score (ie, combined score of all UPDRS subscores) is somewhat controversial. Furthermore, the inferior performance of the higher 2 mg dose relative to the 1 mg dose is difficult to account for. These results await peer review, but the study seems to have demonstrated that 1 mg was safe, and possibly disease-modifying.

Tolerability

Rasagiline was very well tolerated in clinical trials. Adverse events (AEs) were no more frequent than in the placebo group in the TEMPO trial.²¹ The most common AEs observed in the first six months (during which placebo was available for comparison) were infection (16%) and headache (12%). Serious AEs (malignancy or hospitalizations) occurred in four placebo patients, six taking 1 mg/day, and 10 on 2 mg/day. In the second six months, when everyone received 2 mg/day, the most common AEs were infection (10.8), headache (5.4%), unintentional injury (4.9%), and dizziness (4.6%).^{2,21} Early withdrawal rates were not statistically different between placebo and treatment groups. In the open-label extension phase up to 6.5 years after initiation, tolerability remained good even when administered along with dopaminergic therapies. Most common AEs reported were infection, accidental injury, nausea, and arthralgia. By the end of the extension phase, 43 of the original 398 patients had withdrawn due to AE.²⁴ In the LARGO study, adverse events were similar to placebo, and in PRESTO, rasagiline patients had greater gastrointestinal side effects, anorexia and weight loss, balance trouble, and dyskinesias. Serious adverse effects were rare, and included accidental injury (six), arthritis, worsening PD, melanoma, stroke, infection (three each). Depression was less common with rasagiline therapy than in the placebo group.²⁶ Treatment discontinuation rates in PRESTO and LARGO combined were 4.2% for rasagiline and 4.9% for placebo.²⁶

Tyramine

Nonselective MAO inhibitors are known to have risk for tyramine reactions (“cheese reaction”) or hypertensive crises when the drugs inhibit the peripheral metabolism of tyramine, which is found in certain aged cheeses, sausages, and wines. Rasagiline, a selective MAO-B inhibitor, when used in the therapeutic dosing range, does not seem to carry this risk. No tyramine reactions were reported in any of the three phase III clinical trials of rasagiline in PD, despite the fact that no dietary restrictions were imposed in any of them.¹⁹ Tyramine challenges have been studied in doses that exceed those practically achieved by dietary exposure (50–75 mg challenges), and no clinically significant hypertension (“pressor response”) could be elicited.⁴⁵ Still, because the exact dose where selectivity for MAO type B is lost is not yet characterized, the FDA maintained the requirement for a warning in package labeling.

Serotonin

Serious reactions have been reported when nonselective MAO inhibitors, or selegiline were used together with a selective serotonin/norepinephrine reuptake inhibitors (SSRI or SNRI). These have included mental status changes, motor and autonomic symptoms. In PRESTO, 77 patients took SSRIs concomitantly with rasagiline, and no adverse interactions were reported.²⁶ The Parkinson Study Group was surveyed to determine frequency of serotonin syndrome and found that 11 cases were seen in 4,568 patients treated with the combination of eldepryl and an antidepressant, suggesting a frequency of 0.24%. Of these, only two patients (0.04%) experienced serious side effects, and no deaths were reported.⁴⁶ It should be mentioned that these studies may not have included all SSRIs, nor the full range of doses encountered in practice. Because the possibility of serotonin syndrome has not been adequately ruled out with rasagiline, avoidance of combination with tricyclic or tetracyclic antidepressants, SSRIs, or SNRIs is advised.

Conclusion

Clinical trials support the use of once daily rasagiline for symptomatic improvement in patients with early PD. Data suggests that delaying the use of rasagiline by six months may lead to poorer outcomes. More long-term data is needed to clarify the duration of this separation in symptom benefit. Rasagiline improves “on” time in patients with advanced PD and motor fluctuations on levodopa, similar to the benefit observed with entacapone. Both are recommended by the American Academy of Neurology to reduce off time in

patients with motor fluctuations and dyskinesias.⁴⁷ Preclinical data demonstrates neuroprotection in multiple neuronal populations subjected to various mechanisms of toxicity or injury, and the mechanism is not fully accounted for by MAO inhibition. The propargyl moiety of rasagiline may have neuroprotective properties, and the lack of amphetamine metabolites may preserve neuroprotection, in contrast to the first generation MAO-B inhibitor selegiline. The ADAGIO study seems to have suggested a disease-modifying effect with 1 mg/day of rasagiline, but the relevance of the 1.7 unit difference in total UPDRS score, and the reason that the higher 2 mg dose did not meet all the primary endpoints are debatable. Further studies may be necessary to help elucidate the degree of clinically meaningful disease modification that rasagiline has to offer.

Disclosure

The authors report no conflicts of interest in this work.

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