A Controlled Trial of Rasagiline in Early Parkinson Disease

The TEMPO Study

Parkinson Study Group

Context: Monotherapy with rasagiline mesylate may be useful in early Parkinson disease (PD).

Objective: To evaluate the safety and efficacy of the selective monoamine oxidase type B inhibitor rasagiline.

Design: Multicenter, 26-week, parallel-group, randomized, double-blind, placebo-controlled clinical trial.

Setting: Academically based movement disorders clinics.

Patients: Patients with early PD not requiring dopaminergic therapy (n = 404).

Intervention: Research participants were randomized to rasagiline mesylate at dosages of 1 mg or 2 mg per day or matching placebo. A 1-week escalation period was followed by a 25-week maintenance period.

Main Outcome Measure: The primary prespecified measure of efficacy was the change in the total Unified Parkinson’s Disease Rating Scale score between baseline and 26 weeks of treatment, comparing each active treatment group with the placebo group.

Results: Monotherapy with rasagiline was effective in this 26-week study. The adjusted effect size for the total Unified Parkinson’s Disease Rating Scale was -4.20 units comparing 1 mg of rasagiline and placebo (95% confidence interval, -5.66 to -2.73 units; P < .001) and -3.56 units comparing a 2-mg dosage and placebo (95% confidence interval, -5.04 to -2.08 units; P < .001). There were no meaningful differences in the frequency of adverse events or premature withdrawals among the treatment groups.

Conclusions: Rasagiline is effective as monotherapy for patients with early PD. The 2 dosages in this trial were both effective relative to placebo. Further study is warranted to evaluate the longer-term effects of rasagiline in PD.

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ASAGILINE (N-propargyl-1 (R)-aminoindan; TVP-1012) mesylate is a selective irreversible inhibitor of monoamine oxidase type B (MAO-B).1 Dosages of 1 mg/d cause almost total inhibition of platelet MAO-B activity in humans.2 In experimental states of dopamine hypofunction, rasagiline, without concomitant levodopa, restored normal locomotor and cognitive function.3 In primates, rasagiline has been shown to increase striatal extracellular dopamine concentrations.4 Its major metabolite, aminoindan, has been shown to be active in rodent models relevant to Parkinson disease (PD).5

In a 10-week, randomized, placebo-controlled trial of rasagiline in patients with early, untreated PD,6 dosages of up to 4 mg/d were well tolerated. There were no occurrences of hypertension, bradycardia, or other cardiovascular adverse experiences. Based on these preliminary data, we conducted a randomized, multicenter, placebo-controlled, double-blind clinical trial over 6 months to determine the efficacy, safety, and tolerability of rasagiline on parkinsonian characteristics in untreated patients with early PD who had not developed sufficient disability to require dopaminergic therapy.

METHODS

ORGANIZATION

This multicenter study, organized by the Parkinson Study Group and sponsored by Teva Pharmaceutical Industries, Ltd (Netanya, Israel) and Teva Neuroscience, LLC (North Wales, Pa), was reviewed and approved by the institutional review board at each of the participating centers.
RECRUITMENT AND ENROLLMENT

Between November 1997 and June 1999, 404 eligible patients were enrolled in the trial at 32 sites in the United States and Canada. Eligible patients included those older than 35 years who had the presence of at least 2 of the cardinal signs of PD and whose disease severity was not greater than Hoehn and Yahr stage III. Subjects were excluded if they had (1) atypical or secondary parkinsonism, (2) unstable medical problems, including congestive heart failure of New York Heart Association class II or greater, (3) psychiatric problems that compromised the ability of the subject to give informed consent, (4) a Mini-Mental State Examination score of 23 or less, or (5) clinically significant depression. Subjects could be treated with anticholinergic medications, but other antiparkinsonian medications, including levodopa, dopamine agonists, selegiline, or amantadine, were not permitted. Antidepressants (with the exception of amitriptyline, paroxetine, sertraline, fluvoxamine, or trazodone) and sympathomimetics were not permitted.

STUDY DESIGN AND RANDOMIZATION

A randomized, double-blind, placebo-controlled, parallel-group design was employed. Eligible and consenting patients were randomly assigned at the baseline evaluation to 1 of 3 groups: rasagiline mesylate, 1 mg/d; rasagiline mesylate, 2 mg/d; or matching placebo. All patients, investigators, and coordinating staff were kept unaware of treatment assignments.

STUDY INTERVENTION

Patients received 1 mg or 2 mg of rasagiline or matching placebo (Teva Pharmaceutical Industries, Ltd) once daily. In a pilot study, these dosages were well tolerated, and there was preliminary evidence for efficacy at both dosages. Experimental treatment began with a 1-week titration period during which all subjects on active treatment received 1 mg/d of rasagiline. After 1 week, subjects assigned to 2 mg/d of rasagiline took the maintenance dosage for the remaining 25-week period. Subjects assigned to the 1 mg/d group continued to take that dosage for the remainder of the trial. Addition of or change in anticholinergic therapy was not allowed during the study.

PRIMARY OUTCOME VARIABLE

The prespecified primary measure of efficacy in the trial was the change in total Unified Parkinson’s Disease Rating Scale (UPDRS) score between baseline and the week 26 visit. Research participants who left the study prematurely or who were judged to require additional dopaminergic therapy before the week 26 visit had their last UPDRS scores carried forward.

PRESPECIFIED SECONDARY OUTCOME VARIABLES

Secondary measures of efficacy included changes in the mental, activities of daily living (ADL), and motor subscales of the UPDRS, as well as symptom-based subscores (tremor, rigidity, bradykinesia, and postural instability/gait disorder). Other secondary outcome variables included changes in the Hoehn and Yahr stage, the Schwab-England ADL scale, Beck Depression Inventory score, timed motor tests, and the Parkinson’s Disease Quality of Life (PDQUALIF) scale. All subjects who experienced a worsening of less than 3 units in their total UPDRS score from baseline to 26 weeks were classified as responders. In making the determination of the need for levodopa, the investigator was asked to consider the impact of PD symptoms on the ability of the research participant to remain employed, manage finances, carry out domestic responsibilities, and perform ADL. Measures of safety included frequency and severity of reported adverse effects.

STATISTICAL ANALYSIS

A statistical analysis plan was developed prior to unblinding. The primary statistical analyses were performed according to the intention-to-treat principle. For the analyses of the efficacy measures, if a subject was missing a response at a particular visit, the last available observation was carried forward and imputed for that visit. An overall significance level of 5% was used for formal significance testing and interval estimation.

The primary prespecified analysis of efficacy used analysis of covariance to compare the mean changes from baseline to last visit in each active treatment group with changes in the placebo group. All enrolled subjects with postrandomization data were included in the analysis. Baseline UPDRS score and rating investigator were included in the model as covariates. In the prespecified analysis plan, the treatment × investigator interaction term was to be included in the model if it was statistically significant at a level of P<.05. The Hochberg step-up Bonferroni method was used to control the overall type I error rate in the primary comparison. A primary comparison would be declared significant if it achieved P<.025 or if both comparisons (1-mg and 2-mg dosages vs placebo) satisfied P<.05.

Secondary outcome measures were analyzed in the same way as the primary response measure, except for time to levodopa therapy, which was analyzed using life-table techniques. Logistic regression was used to compare the proportion of responders in the 3 treatment groups. The total PDQUALIF score was calculated as the sum of the 32 individual items on the questionnaire. Analyses of safety measures were descriptive. Frequencies of adverse experiences and abnormal laboratory test results, vital signs, and electrocardiogram results were analyzed, with imbalances among treatment groups flagged at a nominal 5% level as judged by χ² tests.

POWER CALCULATIONS

Using data from prior studies conducted by the Parkinson Study Group, the pooled SD of the primary outcome measure was projected to be 7.4 units. Using the Hochberg step-up Bonferroni method, a sample size of 120 per group (total, 360 subjects) was estimated to give power between 81% and 93% to detect a significant effect of either or both dosages of rasagiline, when the true effect of 2 mg of rasagiline corresponds to a 3-unit improvement relative to placebo and the effect of 1 mg of rasagiline is between 0 and 3 units.

RESULTS

COMPARABILITY OF TREATMENT GROUPS AT BASELINE

Of the 473 subjects screened as potential study participants, 69 were found to be ineligible at screening. The most common specific reason for nonparticipation was failure to meet inclusion criteria (Figure 1). The 3 treatment groups were similar at baseline with regard to demographic variables. The baseline UPDRS ADL and mental scores were slightly higher (more impaired) in the 2-mg rasagiline group than in the other 2 groups. There were no significant differences between the groups with regard to total UPDRS or motor subscale scores at baseline (Table 1).
ANALYSIS OF EFFICACY MEASURES

The 26-week total UPDRS (last available observation carried forward) unadjusted mean (SD) scores were 24.8 (12.3), 26.6 (11.8), and 28.4 (14.3) for the 1-mg, 2-mg, and placebo groups, respectively. The unadjusted changes from baseline were 0.1 (6.8), 0.7 (5.8), and 3.9 (7.5), respectively. Figure 2 shows mean values and SEs of total UPDRS score by visit for all patients with data for that visit. Results restricted to the 328 patients who completed 6 months without additional therapy were similar (data not shown).

Adjusted total UPDRS score mean changes from baseline were calculated from the model that included baseline UPDRS scores and center-treatment interaction (Table 2). Both active treatment groups showed benefits relative to the placebo group (P < .001 for each comparison). The responders’ analysis of participants who experienced a less than 3-unit change in total UPDRS score also showed the effects of each active treatment (placebo, 49%; 1 mg, 66%; and 2 mg, 67%; P = .004 and P = .001 for the 1-mg and 2-mg groups, respectively, compared with the placebo group).

Of 138 subjects in the placebo group, 23 (16.7%) reached the secondary end point of needing levodopa therapy, compared with 15 (11.2%) of 134 subjects and 22 (16.7%) of 132 subjects in the 1-mg and 2-mg treatment groups, respectively. Kaplan-Meier analysis showed no statistically significant differences in the time to need for additional therapy among the 3 groups.

Both active treatment groups showed significant improvements in PDQUALIF scores compared with the placebo group. Exploratory analysis suggested that the benefit occurred primarily in the subscale measuring self-image/sexuality, with borderline effects on the social role subscale. Significant benefits were also noted in responses to the single question comparing present PD symptoms with those 3 months previously.

ANALYSIS OF SAFETY AND TOLERABILITY MEASURES

Adverse events were no more frequent in the active treatment groups than in the placebo group. The most commonly observed adverse experiences were infection (16%) and headache (12%). No other adverse event occurred with a frequency of more than 10%. All adverse events occurring with a frequency of more than 5% are shown in Table 3. There were no statistically signifi-

Table 1. Baseline Characteristics of the Study Cohort by Treatment Group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo Group (n = 138)</th>
<th>Rasagiline 1 mg/d Group (n = 134)</th>
<th>Rasagiline 2 mg/d Group (n = 132)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.5 (10.8)</td>
<td>61.6 (10.3)</td>
<td>60.4 (11.4)</td>
<td>.76</td>
</tr>
<tr>
<td>Disease duration, y</td>
<td>0.94 (1.10)</td>
<td>0.92 (1.24)</td>
<td>1.15 (1.32)</td>
<td>.35</td>
</tr>
<tr>
<td>Male sex, No. (%) of patients</td>
<td>93 (67.4)</td>
<td>90 (67.2)</td>
<td>74 (56.1)</td>
<td>.09</td>
</tr>
<tr>
<td>White race, No. (%) of patients</td>
<td>129 (93.5)</td>
<td>126 (94.0)</td>
<td>128 (97.0)</td>
<td>.39</td>
</tr>
<tr>
<td>Total UPDRS score</td>
<td>24.5 (11.6)</td>
<td>24.7 (11.3)</td>
<td>25.9 (9.5)</td>
<td>.19</td>
</tr>
<tr>
<td>Motor subscale</td>
<td>17.6 (8.8)</td>
<td>17.9 (8.9)</td>
<td>18.0 (7.5)</td>
<td>.71</td>
</tr>
<tr>
<td>ADL subscale</td>
<td>6.2 (3.5)</td>
<td>5.9 (3.4)</td>
<td>6.7 (3.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Mental subscale</td>
<td>0.8 (1.1)</td>
<td>0.9 (1.1)</td>
<td>1.2 (1.3)</td>
<td>.01</td>
</tr>
<tr>
<td>PIGD subscale</td>
<td>1.6 (1.4)</td>
<td>1.5 (1.2)</td>
<td>1.6 (1.1)</td>
<td>.38</td>
</tr>
<tr>
<td>Rigidity</td>
<td>4.0 (2.9)</td>
<td>3.9 (2.8)</td>
<td>3.8 (2.5)</td>
<td>.97</td>
</tr>
<tr>
<td>Tremor</td>
<td>3.3 (2.5)</td>
<td>3.1 (2.2)</td>
<td>3.6 (2.5)</td>
<td>.32</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>7.8 (4.7)</td>
<td>8.3 (4.9)</td>
<td>8.1 (4.3)</td>
<td>.65</td>
</tr>
<tr>
<td>Schwab &amp; England ADL scale</td>
<td>91.2 (6.3)</td>
<td>92.2 (5.7)</td>
<td>90.2 (6.2)</td>
<td>.06</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage</td>
<td>1.9 (0.5)</td>
<td>1.9 (0.5)</td>
<td>1.9 (0.5)</td>
<td>.93</td>
</tr>
<tr>
<td>PDQUALIF scale</td>
<td>26.9 (15.7)</td>
<td>28.3 (15.2)</td>
<td>30.2 (16.6)</td>
<td>.29</td>
</tr>
<tr>
<td>Beck Depression Inventory</td>
<td>2.5 (2.79)</td>
<td>2.39 (2.47)</td>
<td>2.05 (2.22)</td>
<td>.29</td>
</tr>
<tr>
<td>Timed motor score</td>
<td>13.5 (6.2)</td>
<td>12.8 (3.9)</td>
<td>13.0 (3.3)</td>
<td>.33</td>
</tr>
<tr>
<td>Receiving anticholinergics, No. (%) of patients</td>
<td>23 (17)</td>
<td>19 (14)</td>
<td>16 (12)</td>
<td>.47</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated. UPDRS indicates Unified Parkinson’s Disease Rating Scale; ADL, activities of daily living; PIGD, postural instability/gait disorder; and PDQUALIF, Parkinson’s Disease Quality of Life.
Twenty serious adverse events (defined as hospitalizations or new malignancies) occurred during the study. Four occurred in the placebo group (2 hospitalizations for elective operations, 1 for dizziness, and 1 for chest pain); 6 occurred in the 1 mg/d of rasagiline group (1 hospitalization for diverticulosis, 1 for surgical removal of benign ovarian masses, 1 for surgical repair of an aortic aneurysm, 1 for cardiac bypass surgery, 1 for atrial fibrillation, and 1 for angina); and 10 occurred in the 2 mg/d of rasagiline group (1 hospitalization for diverticulitis, 2 for chest pain, 1 for constipation, 1 for abdominal pain, and 3 participants with newly diagnosed malignancies [malignant melanoma, prostate carcinoma, and squamous cell carcinoma of the skin]). One subject in the 2 mg/d group experienced 2 serious adverse events (hospitalization for depression and delirium during that hospitalization).

There were no differences in laboratory test results, electrocardiogram abnormalities, standing or supine pulse, or standing blood pressure among the 3 groups. There was a small (4.04 mm Hg) but significant ($P = .05$) increase in supine systolic blood pressure in the 2-mg group relative to the placebo group, but not in the 1-mg group (2.37 mm Hg; $P = .16$). There were no differences in supine diastolic blood pressure or standing systolic or diastolic blood pressure.

This randomized, placebo-controlled clinical trial demonstrated that rasagiline at dosages of 1 mg and 2 mg per day results in better overall UPDRS performance compared with placebo over a 26-week period in patients with early PD. Significant differences between active treatment and placebo were also found in the motor and ADL subscales of the UPDRS and in the PDQUALIF scale. In addition, a higher proportion of patients in the active treatment groups responded to therapy, as judged by their

cant differences in the rates of early termination between the treatment groups and the placebo group. The percentages of subjects with at least 95% compliance in each group were comparable (placebo, 92.8%; 1 mg, 91.8%; and 2 mg, 89.4%).

## Table 3. Adverse Events by Treatment Group*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo Group (n = 138)</th>
<th>Rasagiline 1 mg/d Group (n = 134)</th>
<th>Rasagiline 2 mg/d Group (n = 132)</th>
<th>Combined Rasagiline Groups (n = 266)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>110 (79.7)</td>
<td>109 (81.3)</td>
<td>111 (84.1)</td>
<td>220 (82.7)</td>
</tr>
<tr>
<td>Any event (moderate or severe intensity)</td>
<td>63 (45.7)</td>
<td>58 (43.3)</td>
<td>60 (45.5)</td>
<td>118 (44.4)</td>
</tr>
<tr>
<td>Infection</td>
<td>22 (15.9)</td>
<td>20 (14.9)</td>
<td>21 (15.9)</td>
<td>41 (15.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>14 (10.1)</td>
<td>19 (14.2)</td>
<td>16 (12.1)</td>
<td>35 (13.2)</td>
</tr>
<tr>
<td>Accidental Injury</td>
<td>14 (10.1)</td>
<td>10 (7.5)</td>
<td>10 (7.6)</td>
<td>20 (7.5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (10.9)</td>
<td>9 (6.7)</td>
<td>10 (7.6)</td>
<td>19 (7.1)</td>
</tr>
<tr>
<td>Asthenia†</td>
<td>15 (10.9)</td>
<td>6 (4.5)</td>
<td>6 (4.5)</td>
<td>12 (4.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (7.2)</td>
<td>7 (5.2)</td>
<td>9 (6.8)</td>
<td>16 (6.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (4.3)</td>
<td>5 (3.7)</td>
<td>14 (10.6)</td>
<td>19 (7.1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (5.1)</td>
<td>7 (5.2)</td>
<td>8 (6.1)</td>
<td>15 (5.6)</td>
</tr>
<tr>
<td>Pain</td>
<td>8 (5.8)</td>
<td>8 (6.0)</td>
<td>6 (4.5)</td>
<td>14 (5.3)</td>
</tr>
</tbody>
</table>

*Data are presented as the number (percentage) of patients. Between-groups differences were not statistically significant, unless otherwise indicated.
†$P = .03$ for the difference between placebo and combined treatment groups; $P = .05$, difference between placebo and each of the individual treatment groups.
 change in total UPDRS score compared with the placebo group. There were no advantages in efficacy for 2 mg/d of rasagiline compared with the 1 mg/d dosage.

The magnitude of the symptomatic benefit of rasagiline seen in this study was comparable to that for selegiline over a comparable 6-month period in the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) study\(^{15,16}\) and studies of the MAO-B inhibitor lazabemide.\(^{17,18}\) In DATATOP, subjects treated with selegiline experienced a difference in total UPDRS scores after 3 months of approximately 3 units. When followed for up to 24 months, the difference between those receiving placebo and those receiving selegiline approached 7 units. A difference of approximately 2 units in total UPDRS score was seen after 6 months between lazabemide and placebo.\(^{19}\)

Studies of both lazabemide and selegiline have shown significant differences in the proportion of subjects who reached the end point of need for dopaminergic therapy. By contrast, no difference was seen in the current study, despite a comparable symptomatic effect as measured by UPDRS. (Explanations of the lack of difference in the need for levodopa in this trial are clearly speculative.) In contrast to the other trials, time to need for levodopa was
not the primary end point of this trial, and it was not pow-
ered to detect a difference in this secondary end point
over a 6-month period. It is possible that changes in in-
vestigator practices over time or the knowledge that all
subjects would receive active treatment after 6 months
may have influenced the decision to add or delay dopa-
mineergic therapy.

The symptomatic effect of rasagiline in this study is
more modest than the effects observed with dopa-
mine agonists as monotherapy for PD.20–22 However, the
difference between these effects is relatively small (less
than 4 UPDRS units), and a direct comparison would be
needed to determine if dopamine agonists do, indeed, pro-
vide superior symptomatic relief. The incidence of ad-
verse experiences, particularly somnolence, peripheral
edema, hallucinations, nausea, and constipation, is higher
with dopamine agonists than was observed in this trial.
As a result, initial therapy with rasagiline rather than a
dopamine agonist might be a way to provide effective
therapy for patients with mild disease while minimizing
some adverse effects.

Adverse experiences have been generally mild and
infrequent in trials involving MAO-B inhibitors as
monotherapy in early PD. This is true despite concern
about cardiovascular responses caused by nonspecific
MAO inhibition.18 In this trial, adverse events did not
occur with greater frequency in subjects receiving
rasagiline than in those receiving placebo. There were
no differences in vital signs, with the exception of
supine systolic blood pressure, which was slightly
higher in the 2 mg/d of rasagiline group than in either
the 1-mg or placebo group. Adverse experiences that
might be associated with vital sign changes such as
hypertension or orthostatic hypotension were reported
infrequently in all 3 groups.

The most likely mechanism of action of rasagiline
is through inhibition of MAO-B leading to slower
catabolism of endogenous dopamine. However, other
mechanisms are also possible. In addition to the effect
of MAO-B on dopamine catabolism, rasagiline possesses
an aminoidan metabolite with antiparkinsonian prop-
erties.3 Rasagiline has been shown to protect neurons
against a range of experimentally induced neuronal
injuries23–24 in animal models and exert an antiapoptotic
effect in cell culture.25 Therefore, another possible
mechanism of action of rasagiline is through slowing
the rate of loss of dopaminergic neurons. A longer-
duration study with a different design would be needed
to examine the potential disease-modifying effects of
rasagiline.

This 26-week controlled study indicates that rasagi-
line is an effective therapy for patients with early PD
and may be a reasonable treatment option for these patients.
Further studies over longer periods of time are needed
to determine the effect of rasagiline on patients receiv-
ing treatment with levodopa and dopamine agonists and
on the potential of this selective MAO-B inhibitor to
modify the progression of PD.

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Belden, Klimek, B. Shannon, Hunter, Allen, Berry,
Gardiner, Del Rizzo, Gray, Betcher, Brown, Ewanishin,
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