Selegilene Is Ineffective in a Collaborative Double-blind, Placebo-Controlled Trial for Treatment of Amyotrophic Lateral Sclerosis

Dale J. Lange, MD; Peregrine L. Murphy, MS, MDiv; Beverly Diamond, PhD; Vicki Appel, RN; Eugene C. Lai, MD, PhD; David S. Younger, MD; Stanley H. Appel, MD

Background: The cause of amyotrophic lateral sclerosis (ALS) is not known, and there is no effective treatment. Cell death may be caused by oxidative damage. Selegilene hydrochloride (Eldepryl) is a monoamine oxidase-B inhibitor with antioxidant properties.

Objective: To determine if selegilene affects the clinical course of patients with ALS.

Design: Six-month, double-blind, placebo-controlled study of 133 patients with classical ALS and symptoms for less than 3 years. The primary end point to indicate effectiveness was the rate of change of the Appel ALS total score, an index of disease severity that incorporates strength and function in limbs, respiratory function, and bulbar function.

Results: Of the 133 patients, 67 were randomized to receive selegilene and 66 to receive placebo. One hundred four patients (53 in the selegilene group and 51 in the placebo group) completed the 6-month trial. Both groups were comparable for baseline characteristics and mean Appel ALS total score (70.5 points for the selegilene group and 70.6 for the placebo group). There was no difference in the rate of progression as measured by the Appel ALS total score, showing an average increase of 22 points in 6 months. The monthly rate of change was 3.4 for the selegilene group and 3.5 for the placebo group. There was 1 adverse reaction: worsening depression. Seven patients died during the study (4 in the selegilene group and 3 in the placebo group).

Conclusion: Selegilene treatment had no significant effect on the rate of clinical progression or outcome of ALS.

Arch Neurol. 1998;55:93-96

MYOTROPHIC lateral sclerosis (ALS) is a progressive neuromuscular disease manifested as weakness and wasting of all skeletal muscles of the body, ending in death due to respiratory failure. The cause is unknown, but possibilities include oxidative damage, toxic effects of glutamate, deficiency of neurotrophic factors, chronic viral infection, and immunological attack against motor neurons. Another neurodegenerative disease, Parkinson disease, seems to progress slower when patients are treated with the monoamine oxidase-B (MAO-B) inhibitor selegilene hydrochloride (Eldepryl). To determine if similar effects could be seen in ALS, we performed a randomized, double-blind, placebo-controlled trial.

RESULTS

Of the 133 patients enrolled in the study, 67 were randomized to the selegilene group and 66 to the placebo group. One hundred four patients (53 in the selegilene group and 51 in the placebo group) completed the 6-month trial. Both groups were comparable for baseline characteristics and mean Appel ALS total score (70.5 points for the selegilene group and 70.6 for the placebo group). There was no difference in the rate of progression as measured by the Appel ALS total score, showing an average increase of 22 points in 6 months. The monthly rate of change was 3.4 for the selegilene group and 3.5 for the placebo group. There was 1 adverse reaction: worsening depression. Seven patients died during the study (4 in the selegilene group and 3 in the placebo group).

Conclusion: Selegilene treatment had no significant effect on the rate of clinical progression or outcome of ALS.

Arch Neurol. 1998;55:93-96

©1998 American Medical Association. All rights reserved.
PATIENTS AND METHODS

The study was performed at The Neurological Institute, Columbia-Presbyterian Medical Center, New York, NY, and Baylor College of Medicine, Houston, Tex. One hundred thirty-three patients were randomized after meeting criteria for classical ALS (weakness, wasting, and fasciculations in ≥2 levels of the central nervous system, with pathological reflexes or overactive reflexes in weak, wasted limbs). Patients were excluded if there was evidence of any of the following conditions: multifocal neuropathy with conduction block, paraproteinemia, elevated serum levels of GM1 antibodies, sensorimotor peripheral neuropathy, previous infection with poliovirus, lower motor neuron disease only, primary lateral sclerosis, previous allergy to selegiline, or abnormal results of endocrinologic studies. Patients with serious medical problems or poor family support were deemed to have possible sources of interference with completion of the study, and they were also excluded. The research team at each site consisted of 2 investigators and a study coordinator unaware of randomization status and another investigator who reviewed laboratory data. Informed consent was obtained from each patient after the nature of the study was explained.

Entry criteria included ages from 25 to 65 years, symptom duration of less than 3 years, mild to moderate disease with an Appel ALS (AALS) total score from 30 to 80, and no immunosuppressant therapy or other drug therapy for at least 3 months before enrollment.

The oral selegiline hydrochloride dose was 5 mg twice daily. Patients were randomized to the selegiline or placebo group. Patients were examined at baseline and at 4, 8, 16, and 24 weeks using the AALS score. According to this assessment, a normal person has a total AALS score of 30 points, and a person with a maximal muscle dysfunction has a score of 164 points. People with mild disease who function independently average 52 points; those who can no longer work average 99 points; and patients who are completely bed-bound average 133 points. Patients with scores above 115 points or who had forced vital capacities below 39% of predicted values were considered to have treatment failure and entered an open-label phase. All patients admitted to the trial had an AALS total score of less than 65.

Descriptive statistics were computed for selected demographic and clinical characteristics. To assess differences between the treated and untreated groups on these measures, chi-squared and unpaired, 2-tailed t tests were computed. The natural logarithms were used in all t test calculations.

Using an intent-to-treat model, 2 separate analyses were computed to assess the effects of treatment on the progression of the disease. First, the Friedman analysis of variance (ANOVA) using a rate of change was calculated. A rate of change for each patient randomized in the study was calculated using a regression slope. A rate of change was calculated for the overall AALS score and each of its subscales in this manner.

Second, Kaplan-Meier survival curves, using an overall change of 22 points on the overall AALS score as the end point, were calculated. This end point was selected because it represents a major change in a patient’s lifestyle and a shift in clinical categories as previously identified. Also, it has been used in other trials. The power of the study was 80% at a level of .05 (n=180).

RATE OF CHANGE

The mean (±SD) rate of change for the AALS total score was 3.4±0.4 for the selegiline group and 3.5±0.5 for the placebo group. Using the rate of change as the dependent measure, a Friedman ANOVA found no significant difference between groups (Figure 1). The same analysis was conducted for each of the component AALS scores, ie, bulbar, respiratory, manual muscle, lower extremity function, and upper extremity function. No statistically significant differences were found between groups for any of these analyses (Table 3).

We conducted an analysis excluding those patients with a rapid rate of change (ie, a change of ≥48 points during the study) and another including only patients with prominent lower motor neuron involvement (ie, relatively low bulbar and respiratory scores compared with manual muscle scores). Other analyses using age at first symptom as a covariate and comparing men and women were considered. The comparisons for all of these models were based on the Friedman ANOVA using rates of change as the dependent measure. No statistically significant difference was found for any of the models.

SURVIVAL ANALYSIS

For this analysis, the end point was calculated based on disease progression. An increase in AALS total score of 22 points was selected based on the clinical implications of a change of this magnitude and because it has been used in other studies. A patient was censored when a progression of 22 points was first seen. As a result, patients could be censored at any evaluation point if they met this requirement. Using this end point, no significant difference was found between groups (Wilcoxon χ²=0.01; P=.98) (Figure 2). At the end of the 6-month study, an equal number of patients from both groups had experienced an increase of 22 points or more in their AALS total score. At month 4, slightly more patients in the placebo group (n=13 [20%]) than in the selegiline group (n=9 [13%]) experienced the increase. This difference was lost in month 6, when the failure rate for both groups was equal. The same analysis was conducted using a progression to 11 points on the AALS total score. Again, the difference was not significant.

ADVERSE REACTIONS

One patient required dose adjustment downward and eventual withdrawal because of worsening depression. No clinically significant hepatotoxic effects were found.

TREATMENT FAILURES AND DEATH

Of the 29 patients not completing the 24-week study, 12 withdrew voluntarily (6 from each group); 9 withdrew...
because they reached early termination criteria (AALS total score, >115, or forced vital capacity, <39% of that predicted) (5 in the selegiline group and 4 in the placebo group); and 7 died during the study (4 in the selegiline group and 3 in the placebo group). One patient withdrew because of adverse reactions.

In this randomized, double-blind, placebo-controlled trial, selegiline had no significant effect on the course of sporadic ALS. Selegiline is a monoamine oxidase-B inhibitor with antioxidant properties. After our study was completed, experimental evidence suggested that the loss of motor neurons in familial ALS is due to impaired regulation of free radicals formed by excessive oxidative processes. Superoxide dismutase is 1 of 2 principal intracellular enzymes responsible for degrading intracellular free radicals. Results of animal experiments suggest that selegiline hydrochloride increases superoxide dismutase activity in the striatum of rats receiving 1 mg/kg per day for 3 weeks. The dose given in this study, 10 mg/d, effectively inhibits 90% of monoamine oxidase-B within minutes of administration.
and subjective information. The following 5 areas are tested: bulbar, respiratory, muscle strength, and arm and leg function. Recognizing that ALS affects individual patients in different areas of the body with variable severity, the AALS score assigns a weight to each region, giving the respective scores equal weight in the total score. Patients with pure bulbar disease can have a score showing a degree of clinical affliction similar to that seen in limb or respiratory involvement. Therefore, the total AALS score is an index of clinical severity, irrespective of the principal sites of involvement. The rate of symptom progression of 3.5 points per month was found in both centers, making reproducibility between centers high. Therefore, the scale is not only clinically useful but is also reproducible. Recent studies of a larger population of more than 800 patients confirmed the linearity of rate of progression.17

If oxidative abnormalities are important in the pathogenesis of ALS, there are several reasons why selegiline might not have been effective in our study. First, our entry criteria allowed patients with symptoms for as long as 3 years to enter. The disease might have been too far advanced to rescue the affected neurons. Second, the active agent, selegiline, may not have entered the central nervous system in sufficiently high quantities to affect spinal motor neurons. Third, the primary action may not be on the oxidative system, and the effect might be too weak to cause clinically evident change. Last, we failed to recruit the necessary 180 patients to reach a power of 80%, and a small clinical effect might have been detected if more patients had been recruited.

Accepted for publication May 21, 1997.

Supported by the Muscular Dystrophy Association of America, Tucson, Ariz.

Reprints: Dale J. Lange, MD, The Neurological Institute, Columbia-Presbyterian Medical Center, 710 W 168th St, New York, NY 10032.

REFERENCES