The New England
Journal of Medicine

Volume 330 MARCH 3, 1994 Number 9

A CONTROLLED TRIAL OF RILUZOLE IN AMYOTROPHIC LATERAL SCLEROSIS

G. BENSIMON, L. LACOMBLEZ, V. MEININGER, AND THE ALS/RILUZOLE STUDY GROUP*

Abstract *Background.* Amyotrophic lateral sclerosis is a progressive motor neuron disease for which there is no adequate treatment. Some research suggests that the excitatory amino acid neurotransmitter glutamate may be involved in the pathogenesis.

Methods. To evaluate the efficacy and safety of the antiglutamate agent riluzole, we conducted a prospective, double-blind, placebo-controlled trial in 155 outpatients with amyotrophic lateral sclerosis. The dose of riluzole was 100 mg per day. Randomization was stratified according to the site of disease onset (the bulbar region or the limbs). The primary end points were survival and rates of change in functional status. The main secondary end point was change in muscle strength. Analyses were undertaken after 12 months of treatment and at the end of the placebo-controlled period (median follow-up, 573 days).

Results. After 12 months, 45 of 78 patients (58 percent) in the placebo group were still alive, as compared with 57 of 77 patients (74 percent) in the riluzole group ($P = 0.014$). For patients with bulbar-onset disease, one-year survival rates were 35 percent (6 of 17) with placebo and 73 percent (11 of 15) with riluzole ($P = 0.014$), whereas for those with limb-onset disease one-year survival was 64 percent and 74 percent, respectively ($P = 0.17$). The survival advantage with riluzole was smaller (37 percent [29 of 78] with placebo vs. 49 percent [38 of 77] with riluzole) at the end of the placebo-controlled period, but it remained significant in the overall population ($P = 0.046$) as well as in the patients with bulbar-onset disease (18 percent [3 of 17] vs. 53 percent [8 of 15], $P = 0.013$). The deterioration of muscle strength was significantly slower in the riluzole group than in the placebo group ($P = 0.028$). Adverse reactions to riluzole included asthenia, spasticity, and mild elevations in aminotransferase levels. Twenty-seven patients in the riluzole group withdrew from the study, as compared with 17 in the placebo group.

Conclusions. The antiglutamate agent riluzole appears to slow the progression of amyotrophic lateral sclerosis, and it may improve survival in patients with disease of bulbar onset. (N Engl J Med 1994;330:585-91.)

AMYOTROPHIC lateral sclerosis is a progressive and fatal neurodegenerative disorder[1] associated with survival ranging from a few months to decades (median, 37 to 49 months).[2-5] Known prognostic factors include age at onset, site of onset, duration of weakness, and degree of clinical disability or respiratory function.[2-6] The cause of the disease is unknown, and no treatment is known that influences survival.

There are many hypotheses about the cause of the disease.[7] One holds that glutamate, the primary excitatory neurotransmitter in the central nervous system, accumulates to toxic concentrations at synapses and causes neurons to die, probably through a calcium-dependent pathway. Supporting this hypothesis are observations of abnormal glutamate metabolism,[8,9] altered leukocyte glutamate dehydrogenase,[10] and decreased high-affinity glutamate uptake by synaptosomes from the spinal cord and motor cortex.[11] Drugs that modulate the glutamatergic system have been proposed as possible treatment in amyotrophic lateral sclerosis.[12,13]

In preclinical studies, riluzole (2-amino-6-(trifluoromethoxy)benzothiazole, RP 54274) was found to modulate the glutamatergic transmission.[14,15] In phase 1 trials in healthy human volunteers, single doses of riluzole of up to 200 mg were well tolerated and safe.

We conducted a prospective, randomized, double-blind, placebo-controlled, stratified trial to determine whether riluzole is beneficial to patients with amyotrophic lateral sclerosis. The principal end points were survival and the rate of change in functional status. Secondary assessments were based on changes in muscle strength, respiratory function, the patient's subjective assessment of symptoms, global clinical impressions, and the patient's ability to tolerate treatment.

METHODS

This trial was conducted according to the European guidelines for good clinical practice.[16]

Eligibility of Patients

Outpatients 20 to 75 years of age were eligible for inclusion in the study. To ensure the accuracy of the diagnosis, the patient's clinical status at entry had to be consistent with probable or definite amyotrophic lateral sclerosis.[17,18] Patients were excluded if they had signs

From the Department of Clinical Pharmacology, Hôpital de la Pitié-Salpêtrière (G.B., L.L.); and the Centre SLA, Hôtel-Dieu de Paris (V.M.) — both in Paris. Address reprint requests to Dr. Meininger at the Centre SLA, Hôtel-Dieu de Paris, 1, rue de la Cité, 75004 Paris, France.

Supported by Rhône-Poulenc Rorer.

*The participants in the ALS/Riluzole Study Group are listed in the Appendix.

of conduction blocks of motor nerves, sensory nerves, or both on electromyography, paraproteinemia on immunoelectrophoresis, substantial lesions accounting for the clinical signs on imaging studies (computed tomography or magnetic resonance imaging), or signs of dementia. To improve the detection of outcomes, patients were excluded if more than five years had elapsed since the onset of their first symptoms, if they had other incapacitating or life-threatening diseases, if they had a forced vital capacity of 60 percent of the expected value or less, if they had undergone tracheostomy, if they had hepatic or renal dysfunction, or if they were pregnant.

All eligible patients gave written informed consent (with the assistance of a spouse when necessary) to participation in the study. Recruitment began after the formal approval of the protocol by the ethics committee of the Pitié-Salpêtrière Hospital (Paris).

Randomization and Treatment

Randomization was stratified according to the center where the patient was treated (one of seven centers) and the site of the onset of disease (a limb or the bulbar region). Patients with bulbar-onset disease were defined as having initial signs and symptoms in the bulbar region, but they had clinically definite or probable amyotrophic lateral sclerosis at the time of enrollment. Patients with limb-onset disease had initial signs and symptoms in the limbs, even if they had bulbar involvement at the time of enrollment. Treatment assignments were made separately in each center and were based on randomization codes established by blocking. Patients were given either 100 mg of riluzole per day in 50-mg tablets or tablets of identical-appearing placebo to be taken orally twice a day, morning and evening, before meals. The tablets of riluzole and placebo were provided by Rhône-Poulenc Rorer (Antony, France).

Determination of Outcome Measures and Follow-up

After entry into the study, each patient was scheduled for examination every two months. All the investigators were trained before the trial, in order to improve the reliability of the evaluations of functional status and muscle function.

Primary Efficacy Outcomes

The primary efficacy outcomes were prospectively defined as survival and changes in functional status after 12 months of treatment. The principal events included in the determination of the survival rate were death (from any cause) and tracheostomy, since in the terminal stage of the disease respiratory failure leads to either event.[4]

Functional status was assessed with a four-point rating that included scores for limb function, bulbar function, the results of clinical examination, and symptoms reported by the patient. The interrater reliability of this scale has been demonstrated elsewhere.[19] Limb function and bulbar function were evaluated with modified Norris scales (maximal score for limb function, 63; for bulbar function, 39).[20] Each score was evaluated at entry and every two months thereafter.

Secondary Efficacy Outcomes

The secondary efficacy outcomes included muscle-testing scores, measures of respiratory function, scores on the Clinical Global Impression of Change scale, and the patient's subjective evaluations of fasciculations, cramps, stiffness, and tiredness, expressed on four 100-mm visual-analogue scales. Twenty-two muscle functions were assessed with the patient in the sitting position according to the five-grade scale of the Medical Research Council (maximal score, 110).[20] Respiratory function was monitored with tests of forced vital capacity and expressed as a percentage of the expected value. Scores for muscle strength, clinical global impressions, and the visual-analogue scales were obtained at study entry and every two months thereafter; respiratory function was assessed at entry and every six months thereafter.

Safety, Intercurrent Events, Withdrawal from Treatment, and Loss to Follow-up

Information on adverse effects of medication and on intercurrent events was sought at each visit by direct questioning of the patient, through clinical examination, and from the laboratory findings. Hepatic function and muscle enzymes were monitored every two weeks from study entry to month 7, and every two months beginning with month 8. Biochemical and hematologic evaluations were performed at study entry and every two months thereafter. All determinations of laboratory values were performed in the same laboratory (CERBA, Saint Ouen l'Aumone, France).

For the determination of plasma concentrations of the study drug, blood samples (10 ml collected in tubes containing heparin) were obtained monthly from month 1 to month 4, and every two months thereafter. Samples were drawn before the morning administration of the drug and sent to one central laboratory. After centrifugation at $1300 \times g$ for 10 minutes, the plasma was frozen at $-18^{\circ}C$ until it was processed at the end of the study. Reasons for withdrawal from treatment included the occurrence of a serious adverse event, an increase in alanine aminotransferase (to more than three times the upper limit of the normal range), and the withdrawal of the patient's consent. Withdrawal from treatment was not a reason for termination of the study, and follow-up of patients every two months continued in the intention-to-treat analysis.

In the event of a loss to follow-up, the administrators of the trial sought information about the patient from the family or the family physician and requested a death certificate from the city hall in the patient's place of birth.

Sample Size and Power

Extrapolation from previous studies[2-5] and our own data[6,20] suggested 12-month survival rates of 35 percent for patients with bulbar-onset disease and 65 percent for patients with limb-onset disease, yielding an overall estimated survival rate of 55 percent in the placebo group, given the expected ratio of one patient with bulbar-onset disease to every two patients with limb-onset disease. A minimal number of 110 patients in the sample was prospectively fixed so that an improvement from 55 percent to 85 percent in the one-year survival rate could be detected, with an alpha level of 5 percent and a beta level of 90 percent, by one-tailed test.[21]

Statistical Analysis

Statistical analyses were performed on an intention-to-treat basis and included all randomized patients. Continuous variables for demographic data and clinical values at entry were compared by a two-way analysis of variance that included the assigned treatment, the site of onset, and interactions between these two factors. Qualitative variables were compared by Pearson's chi-square tests. Survival curves for the study groups were compared by the Mantel–Cox (log-rank)[22] statistic, stratified according to the site of onset of disease.

Prognostic factors were determined by a Cox proportional-hazards analysis,[23] stratified according to the site of onset of disease, with a stepwise procedure. The effect of treatment on survival was also assessed with control for selected prognostic factors (by Wald's test). The slopes of the clinical scores over time were estimated with the unweighted least-squares method.[24] The factors included in the model were treatment (riluzole vs. placebo), site of disease onset (bulbar region vs. limb), and interactions of both factors.

Although a one-tailed hypothesis was used in planning the analysis, the results of the statistical comparisons of the variables related to efficacy are conservatively presented with two-tailed P values.

Results

Demographic Data

From June 1990 through November 1990, 155 patients were enrolled (32 with bulbar-onset disease and 123 with limb-onset disease). The primary date on which data were censored (November 30, 1991) was set as 12 months after the enrollment of the final patient. After this date, the trial continued under double-blind conditions until the analysis of efficacy at 12 months (in March 1992), at which time the patients receiving placebo were switched to riluzole.

In the analysis of demographic data, limb and bulbar functional scores, and scores for muscle strength, data are presented for the first 12 months of treatment. In the analysis of survival, data are reported for the first 12-month period and continuing to the end of the placebo-controlled period (March 12, 1992). The interval between randomization and March 12, 1992, ranged from 483 to 632 days (median, 573). In the analysis of safety, results are presented as of the end of the placebo-controlled period.

Seventy-seven patients were randomly assigned to riluzole (62 patients with limb-onset disease and 15 with bulbar-onset disease), and 78 patients to placebo (61 and 17 patients, respectively). All the patients satisfied the criteria for probable or definite amyotrophic lateral sclerosis. Twenty-four patients did not entirely meet the criteria chosen to prevent the inclusion of patients with conditions or characteristics that might interfere with the main outcome or safety measures. Since these factors were chosen for reasons of statistical power and since these patients all had amyotrophic lateral sclerosis, it was decided under completely blinded conditions to keep them in the trial and to pool them with the remaining patients in the intention-to-treat analysis without knowledge of their outcomes. Post hoc analysis showed that these patients were evenly distributed between groups: there were 11 in the riluzole group and 13 in the placebo group. Analysis of these patients according to risk factors further showed that the number of extreme values for factors positively or negatively predictive of survival was balanced in the placebo group (7 and 7, respectively), whereas in the riluzole group these values were unfavorably distributed (3 and 8, respectively). Thus, the extreme values for risk factors were not dramatically unbalanced in any one group. The two study groups were similar at entry (both as a whole and when stratified according to site of onset). The differences between the patients with bulbar-onset disease and those with limb-onset disease were as expected[4,6] (Table 1). Five patients had the familial form of the disease (one in the placebo group and four in the riluzole group).

Survival

In the analysis of survival, there was no loss to follow-up. There was a statistically significant difference in survival between the two study groups (Fig. 1). At 12 months, 45 of the 78 patients in the placebo group (58 percent) remained alive, as compared with 57 of the 77 in the riluzole group (74 percent) ($P = 0.014$). A post hoc analysis that excluded the 24 patients who did not meet all the entry criteria changed the percentages of surviving patients very little (12-month survival, 60 percent in the placebo group vs. 71 percent in the riluzole group). However, survival was no longer significant ($P = 0.11$), since the exclusion of the 24 patients reduced the statistical power considerably.

In the overall population, by the end of the placebo-controlled period 29 of the 78 patients in the placebo group (37 percent) remained alive, as compared with 38 of the 77 patients in the riluzole group (49 percent) ($P = 0.046$). The median survival was 449 days and 532 days in the placebo and riluzole groups, respectively. Overall, riluzole therapy reduced mortality by 38.6 percent at 12 months and by 19.4 percent at 21 months (the end of the placebo-controlled period), an effect that is both clinically important and statistically significant.

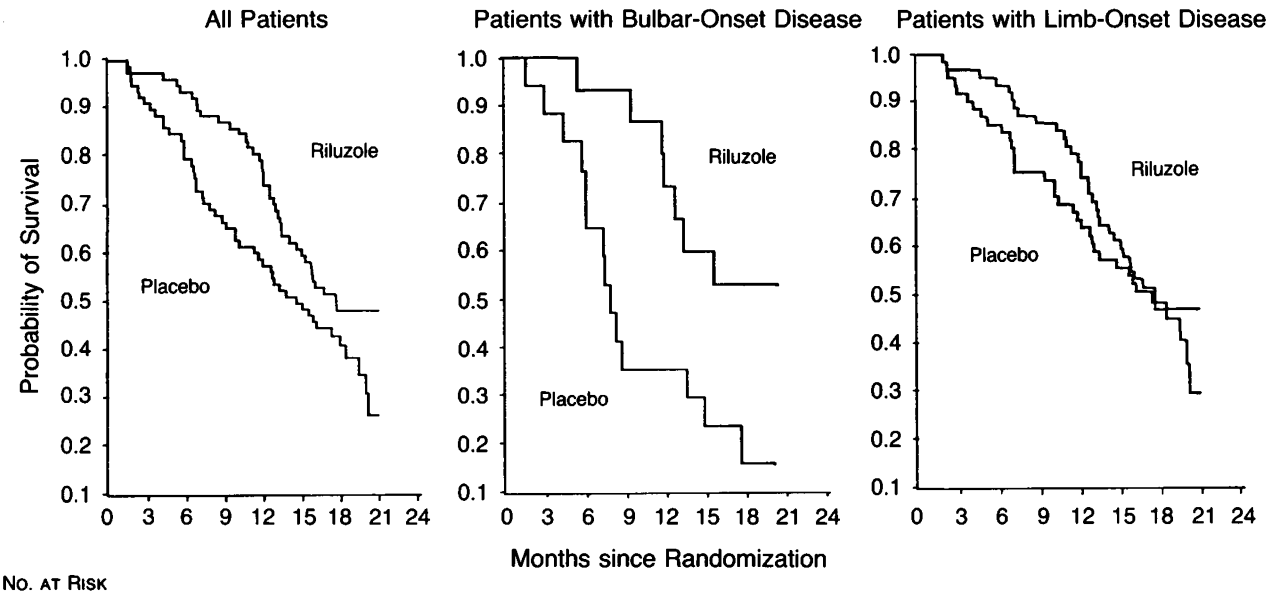
Unexpectedly, the treatment effect was greater in patients with bulbar-onset disease than in those with limb-onset disease (Fig. 1). Among the patients with bulbar-onset disease, 6 of the 17 patients in the placebo group (35 percent) remained alive at 12 months, as compared with 11 of the 15 patients in the riluzole group (73 percent) ($P = 0.014$). At the end of the placebo-controlled period, there was still a significant difference between treatments: 3 of 17 patients in the placebo group (18 percent) remained alive, as compared with 8 of 15 patients

Table 1. Base-Line Characteristics of Patients with Amyotrophic Lateral Sclerosis, According to Treatment Assignment and Site of Onset of the Disease.*

Characteristic	Limb-Onset Disease		Bulbar-Onset Disease		Any Treatment		Any Site of Onset	
	Placebo (N = 61)	Riluzole (N = 62)	Placebo (N = 17)	Riluzole (N = 15)	Limb-onset disease (N = 123)	Bulbar-onset disease (N = 32)	Placebo (N = 78)	Riluzole (N = 77)
Sex (M/F)	40/21	39/23	6/11	6/9	79†/44	12/20	46/32	45/32
Age (yr)	56.6±12	56.5±10	63.3±7	57.9±10	56.6±11	60.7±9	58.1±11	56.8±11
Weight (kg)	65.7±11	67.0±13	63.1±12	61.9±13	66.3±12	62.5±12	65.1±12	66.0±12
Duration of disease (yr)	2.4±1.6	2.2±1.6	1.6±0.8	1.8±1.5	2.3±1.4†	1.71±1.1	2.3±1.8	2.2±1.7
FVC (fraction of normal)	0.87±0.23	0.95±0.16	0.82±0.21	0.76±0.27	0.9±0.2†	0.79±0.23	0.86±0.18	0.92±0.17
Limb-function score	36.5±16	39.0±17	55.9±7	53.0±10	37.8±16†	54.6±9	40.8±16	41.7±16
Bulbar-function score	34.6±6	33.9±7	14.1±7	17.7±10	34.2±7†	15.8±8	30.1±11	30.7±10
Muscle-testing score	75.5±20	79.5±17	92.3±13	95.9±11	77.5±18†	94±12	79.1±19	82.7±17
Stiffness scale (mm)	34±32	33±34	26±35	37±32	34±32	31±32	32±33	34±33
Tiredness scale (mm)	57±29	59±28	43±31	48±27	58±28†	45±28	54±29	57±28
CGI severity scale	4.4±0.8	4.3±0.8	4.0±0.8	3.9±1.2	4.3±0.8†	3.9±0.9	4.3±0.9	4.2±0.9

*Plus–minus values are means ±SD. Statistical significance was calculated by an analysis of variance that included treatment group, site of disease onset, and the interaction of these two factors. No statistically significant differences were observed between treatment groups, and no interaction of treatment with site of disease onset was found. The comparison of sites of disease onset was as expected. FVC denotes forced vital capacity, and CGI clinical global impression.

†$P<0.05$ for the comparison with the values for patients with bulbar-onset disease receiving any treatment, by two-tailed test.



	All Patients								Patients with Bulbar-Onset Disease								Patients with Limb-Onset Disease							
No. at Risk																								
Placebo	78	71	62	52	45	38	19	0	17	15	11	6	6	4	2	0	61	56	51	46	39	34	17	0
Riluzole	77	75	72	67	57	45	23	0	15	15	14	14	11	9	5	0	62	60	58	53	46	36	18	0
No. Who Died																								
Placebo	0	7	16	26	33	40	45	49	0	2	6	11	11	13	14	14	0	5	10	15	21	27	31	35
Riluzole	0	2	5	10	20	32	39	39	0	0	1	1	4	6	7	7	0	2	4	9	16	26	32	32

Figure 1. Kaplan–Meier Plots of Survival in Patients with Amyotrophic Lateral Sclerosis Who Were Given Placebo or Riluzole.

The numbers of patients still at risk in each group at the beginning of each three-month period are shown below the figure, as well as the cumulative numbers of deaths. Curves were compared by the Mantel log-rank test. In the overall population (left-hand panel), the curves for the two groups differed significantly at 12 months ($P = 0.014$) and 21 months ($P = 0.046$), when the placebo-controlled period ended (median follow-up, 573 days). In the patients with bulbar-onset disease (middle panel), the curves differed significantly at 12 months ($P = 0.014$) and 21 months ($P = 0.013$). In the patients with limb-onset disease (right-hand panel), the curves did not differ significantly at either 12 or 21 months.

in the riluzole group (53 percent) ($P = 0.013$). The median survival was 239 days in the placebo group, whereas the median survival had not been reached after 476 days in the riluzole group.

Among the patients with limb-onset disease, there was a trend toward improved survival at 12 months in the riluzole group, with 46 of 62 patients (74 percent) still alive, as compared with 39 of 61 patients alive in the placebo group (64 percent). In this subgroup, the results were not statistically significant ($P = 0.17$). At the end of the placebo-controlled period, 26 of 61 patients in the placebo group (43 percent) remained alive, as compared with 30 of 62 patients in the riluzole group (48 percent) ($P = 0.355$). There was no apparent gain in median survival (523 vs. 531 days for placebo and riluzole, respectively).

The stepwise analysis of risk factors (by the Cox proportional-hazards method) selected age, duration of disease, forced vital capacity, bulbar-function score, the tiredness score, and the stiffness score as significant prognostic variables at entry. After adjustment for these variables, the difference in survival between treatments was significant only at 12 months

Table 2. Relative Risk of Death or Tracheostomy during the Study Period, According to Treatment Assignment and Prognostic Variables Measured at Entry.*

Variables	At 12 mo		At End of Study	
	Relative risk (95% CI)	P value	Relative risk (95% CI)	P value
Riluzole group (relative to placebo group)	0.43 (0.24–0.77)	0.005	0.66 (0.42–1.02)	0.058
Forced vital capacity (per 10% of normal value)	0.77 (0.66–0.90)	0.001	0.76 (0.67–0.86)	<0.001
Age (per 10 years)	1.44 (1.06–1.95)	0.02	1.54 (1.23–1.91)	<0.001
Duration of disease (per year)	0.82 (0.65–1.03)	0.09	0.82 (0.68–0.98)	0.03
Bulbar-function score (per 3 points)†	0.77 (0.68–0.86)	<0.001	0.82 (0.75–0.90)	<0.001
Stiffness scale (per 10 mm)‡	0.87 (0.78–0.96)	0.006	0.90 (0.83–0.97)	0.01
Tiredness scale (per 10 mm)‡	1.21 (1.07–1.37)	0.002	1.14 (1.04–1.24)	0.007

*Relative risks and 95 percent confidence intervals (CI) associated with the variables related to survival were determined with a stepwise Cox proportional-hazards regression model, stratified according to site of disease onset. For each variable, the relative risk was calculated after adjustment for the other covariates shown. P values were obtained by the Wald chi-square test and indicate the significance of the contribution made by the variable to the model. Relative risks represent the risk of death or tracheostomy in the period considered, with an increase in the variable by the unit indicated.

†The maximal score for bulbar function is 39 points; 3 points corresponds to normal functioning on one item of the scale.

‡Scores for tiredness and stiffness were measured on a visual-analogue scale on which the values ranged from 0 to 100 mm.

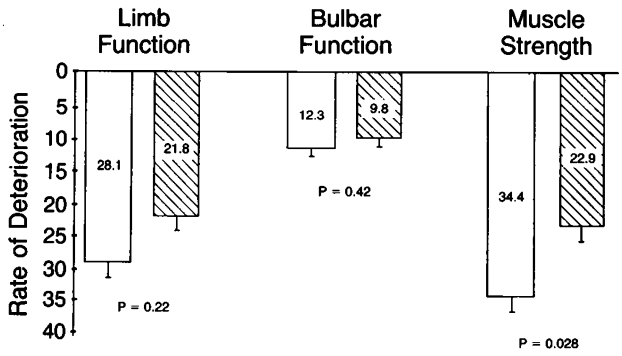


Figure 2. Mean (±SE) Annual Rates of Deterioration in Limb and Bulbar Functional Scores and Muscle-Testing Scores in Patients with Amyotrophic Lateral Sclerosis Given Placebo or Riluzole.

Seventy-five patients were studied in each group. Open bars denote the placebo group, and hatched bars the riluzole group. Numbers inside the bars are mean rates of deterioration per year. Slopes were estimated by the unweighted least-squares method. The difference between groups was 6.3±5.2 for limb function, 2.5±3.0 for bulbar function, and 11.5±5.2 for muscle testing.

(P = 0.005); it nearly reached significance at the end of the placebo-controlled period (P =0.058) (Table 2).

Functional Evaluations

During the 12 months of follow-up, 80 percent of all scheduled visits were completed. There were five patients with only one evaluation (three in the placebo group and two in the riluzole group) whose data could not contribute to estimates of the slope of the functional scores, but data on these patients were retained for the estimate of the initial value. For each functional score, the rate of deterioration was slower in the riluzole group than in the placebo group (Fig. 2). Only the slope of the muscle-testing score was statistically significant, however (P = 0.028), with a 33.4 percent reduction in the rate of deterioration of muscle function at 12 months. Treatment assignment, site of disease onset, and effects showing the interaction between these two factors were included in the model used in the analysis of slope. Only the effect of the treatment assignment was statistically significant, indicating that the effects of treatment were similar regardless of the site of disease onset. The same was also true for the scales measuring limb and bulbar function.

Adverse Drug Reactions and Withdrawal from Treatment

The clinically important adverse drug reactions reported included worsening of asthenia; worsening of spasticity; increases in alanine aminotransferase, aspartate aminotransferase, or both; and a mild-to-moderate increase in blood pressure (Table 3). Nineteen patients (6 in the placebo group and 13 in the riluzole group) had increases in aminotransferase levels. These increases occurred 42 to 267 days after randomization in the riluzole group, and 23 to 503 days after randomization in the placebo group. Increases in alanine aminotransferase to more than three times the upper limit of normal were observed in six patients in the riluzole group and in three patients in the placebo group. No patient had a value for alanine aminotransferase that was more than five times the upper limit of normal. Among the patients in the riluzole group who had increases in alanine aminotransferase, five were withdrawn from treatment, whereas one continued. In this patient the alanine aminotransferase level remained within two to four times the normal value. Eleven patients in the riluzole group and three in the placebo group had increases in aspartate aminotransferase. One patient in the riluzole group had an interruption of treatment, began treatment again, and remained in treatment until the end of the study, with aspartate aminotransferase values ranging up to four times the normal value; the alanine aminotransferase value remained less than twice the normal value. Concomitant increases in both aminotransferases occurred in five patients in the riluzole group but in none in the placebo group. In all patients assigned to riluzole who withdrew from treatment because of increases in aminotransferases, the levels returned to the base-line values within two months after the discontinuation of treatment. Overall, 44 patients discontinued treatment during the study (27 in the riluzole group and 17 in the placebo group). Among the 27 patients in the riluzole group, 19 discontinued treatment because of adverse experi-

Table 3. Most Frequent Adverse Drug Reactions during the First 21 Months of the Study, and Frequency of Withdrawal from Treatment as a Result.

Adverse Drug Reactions	Placebo Group (N = 78)		Riluzole Group (N = 77)	
	No. with adverse reaction	No. who withdrew from treatment	No. with adverse reaction	No. who withdrew from treatment
All*	71	9	71	19
Asthenia	11	2	20	8
Stiffness	3	1	8	2
Increased blood pressure	0	0	4	0
Nausea	3	1	3	2
Abdominal pain	0	0	3	2
Dysphagia	8	1	6	0
Incoordination	2	0	1	1
Fracture	2	0	1	1
Respiratory disorders†	33	2	30	1
Rhinitis	0	0	5	1
Pain	1	0	3	1
Fasciculations	0	0	1	1
Concurrent infections	3	0	6	0
Constipation	2	0	6	0
Depression	5	0	1	0
Increased ALAT or ASAT‡	6	2	13	5

*Patients with more than one adverse reaction were counted only once.

†Values shown do not include patients whose respiratory disorders were followed by death or tracheostomy within seven days.

‡ALAT denotes alanine aminotransferase, and ASAT aspartate aminotransferase. An increase in these values to more than three times the upper limit of normal was considered an adverse reaction.

ences, as compared with 9 of the 15 patients in the placebo group who discontinued treatment.

Discussion

Riluzole had a significant effect on rates of survival and muscular deterioration in this randomized, stratified, double-blind, placebo-controlled study of 155 patients with amyotrophic lateral sclerosis. We chose survival as a primary end point so that we could distinguish possible efficacy of the drug from a symptomatic effect on function that did not reduce motor-neuron loss. The favorable effect of riluzole on survival cannot be explained by other confounding factors. When we considered the previously reported predictive variables that influence survival in amyotrophic lateral sclerosis,[2-6] we could not identify any statistically significant difference between the placebo group and the riluzole group at entry. The effect of treatment on survival at 12 months remained significant after we controlled for other risk factors in a Cox proportional-hazards analysis.

To study representative patients with amyotrophic lateral sclerosis, we included patients in whom the duration of disease ranged widely. The mortality rate in the placebo group was in the range estimated when the study was planned and was in agreement with rates reported in other studies.[2-6,20] Our patients were representative of patients with amyotrophic lateral sclerosis and included approximately 5 percent of all such patients in France[25] at the time of the trial.

The favorable effect of riluzole on survival seems to depend on the site of onset of disease. A large and significant effect was observed in patients with amyotrophic lateral sclerosis of bulbar onset, whereas in those with disease of limb onset only a trend toward a positive effect was detected. Clearly, riluzole was less effective in patients with limb-onset disease, but at this point we cannot precisely account for the differences with respect to the pattern of onset. Such a striking difference between subgroups must, however, be interpreted carefully because, as Peto[26] has pointed out, such an effect can arise by chance. Regardless of the site of disease onset, the therapeutic effect of riluzole seems to be time-related, with a strong effect observed in the first 12 months and an apparent decrease in effect from month 12 to month 21 (the end of the placebo-controlled period). The higher rate of withdrawal from treatment in the riluzole group throughout the trial may have led to an underestimation of the actual benefit from the drug, since we used an intention-to-treat analysis.

Although the overall number of patients with at least one adverse reaction was similar in the two study groups, there was a significantly higher proportion of drug-related withdrawal from treatment in the riluzole group. The reason for these withdrawals included asthenia, stiffness, and increases in aminotransferase levels. Although aminotransferase elevations were more frequent with riluzole treatment, they were well tolerated even by the two patients who continued to receive the drug despite such elevations. On the whole, it appears that the reported adverse reactions to the drug do not outweigh its therapeutic effect on survival. Adverse drug reactions can worsen the quality of life, but such consequences may be outweighed by the effect of the drug on muscle function.

Riluzole has a positive effect on the rate of deterioration of muscle function. This suggests that the drug may interfere with the disease process (i.e., with motor-neuron degeneration) even though the mechanism of action remains unclear. Riluzole presynaptically inhibits the release of glutamic acid in the central nervous system[14,15] and interferes postsynaptically with the effects of excitatory amino acids in a number of experimental systems. However, it does not seem to interact competitively with any of the known receptors of glutamic acid, but rather to antagonize the effects of such neurotransmitters indirectly, possibly by interacting with voltage-dependent sodium channels[27] or G proteins.[28]

Whatever its mechanism of action, riluzole may be able to modify the course of amyotrophic lateral sclerosis. Deciphering the biologic effect responsible for the therapeutic activity of riluzole in amyotrophic lateral sclerosis may increase our understanding of the pathogenesis of the disease and open new therapeutic avenues. Further clinical trials, such as a study of dose ranges, are needed before riluzole can be offered as a treatment in amyotrophic lateral sclerosis.

We are indebted to Bernard Asselain for helpful statistical advice and discussion, to Claude Bensimon for translating the manuscript into English, and to Larry Powe and Phyllis Salzman for reviewing the manuscript.

Appendix

The following persons and institutions participated in the ALS/Riluzole Group.

Principal investigator: V. Meininger. *Methodologist:* G. Bensimon. *Coordinator:* L. Lacomblez. *Participating investigators:* V. Meininger, Paris; P. Bouche, Paris; C. Delwaide, Brussels; P. Couratier, Limoges; O. Blin, Marseilles; F. Viader, Caen; H. Peyro-St.-Paul, Toulouse; J. David, Toulouse; J.M. Maloteaux, Brussels; and J. Hugon, Limoges. *Senior investigators at each site:* Université de Louvain, Brussels: E.C. Laterre; Hôpital Purpan, Toulouse: A. Rascol and M. Clanet; Hôpital Dupuytren, Limoges: J.M. Vallat and A. Dumas; Hôpital de la Timone, Marseilles: G. Serratrice; Centre Hospitalier Universitaire de la Côte de Nacre, Caen: B. Lechevallier; and Hôpital de la Pitié-Salpêtrière, A.J. Puech. *Trial monitoring:* T. Nguyen and C. Shu, Rhône–Poulenc Rorer. *Biostatistical analysis:* G. Bensimon, Paris; P. Bastien, C. Papillon, and S. Durrleman, Rhône–Poulenc Rorer. *Coordination at Rhône–Poulenc Rorer:* E. Louvel and P. Guillet. *Data management:* L. Ledoux, Rhône–Poulenc Rorer. *Respiratory-functions advisory center:* E. Orvoen-Frija, Service de Pneumologie, Hôtel-Dieu, Paris. *Hôtel-Dieu biologic monitoring:* M. Dib (Centre SLA).

References

1. Charcot JM. Leçons sur les maladies du système nerveux faites à la Salpétrière. Paris: Progrès Médical, 1877:213-42.
2. Jablecki CK, Berry C, Leach J. Survival prediction in amyotrophic lateral sclerosis. Muscle Nerve 1989;12:833-41.
3. Norris FH, Denys EH, Sang K, Mukai E. The natural history of ALS in a specified population, with comments on risk factors, prognosis and symptomatic treatments. Clin Neurol 1989;29:1485-92.
4. Caroscio JT, Mulvihill MN, Sterling R, Abrams B. Amyotrophic lateral sclerosis: its natural history. Neurol Clin 1987;5:1-8.
5. Kondo K, Hemmi I. Clinical statistic in 515 fatal cases of motor neuron disease. Neuroepidemiology 1984;3:129-48.

6. Bensimon G, Rozier A, Dib M, Lacomblez L, Bouche P, Meininger V. Variables influencing the functional loss and the rate of evolution in amyotrophic lateral sclerosis. Neurology 1992;42:Suppl 3:202. abstract.
7. Rowland LP. Ten central themes in a decade of ALS research. Adv Neurol 1991;56:3-23.
8. Plaitakis A, Caroscio JT. Abnormal glutamate metabolism in amyotrophic lateral sclerosis. Ann Neurol 1987;22:575-9.
9. Plaitakis A. Altered glutamatergic mechanisms and selective motor neuron degeneration in amyotrophic lateral sclerosis: possible role of glycine. Adv Neurol 1991;56:319-26.
10. Hugon J, Tabaraud F, Rigaud M, Vallat JM, Dumas M. Glutamate dehydrogenase and aspartate aminotransferase in leukocytes of patients with motor neuron disease. Neurology 1989;39:956-8.
11. Rothstein JD, Martin LJ, Kuncl RW. Decreased glutamate transport by the brain and spinal cord in amyotrophic lateral sclerosis. N Engl J Med 1992;326:1464-8.
12. Plaitakis A, Smith J, Mandeli J, Yahr MD. Pilot trial of branched-chain aminoacids in amyotrophic lateral sclerosis. Lancet 1988;1:1015-8.
13. Testa D, Caraceni T, Fetoni V. Branched-chain amino acids in the treatment of amyotrophic lateral sclerosis. J Neurol 1989;236:445-7.
14. Mizoule J, Meldrum B, Mazadier M, et al. 2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission — I. Anticonvulsant properties. Neuropharmacology 1985;24:767-73.
15. Martin D, Thompson MA, Nadler JV. The neuroprotective agent riluzole inhibits release of L-glutamate and L-aspartate from slices of hippocampal area CA1. Br J Pharmacol 1991;104:Suppl:240P. abstract.
16. CPMP Working Party on Efficacy of Medicinal Products. EEC note for guidance: good clinical practice for trials on medicinal products in the European Community. Pharmacol Toxicol 1990;67:361-72.
17. Swash M, Leish N. Criteria for diagnosis of familial amyotrophic lateral sclerosis: European FALS Collaborative Group. Neuromuscul Disord 1992;2:7-9.
18. Brooks BR, Sufit RL, DePaul R, Tan YD, Sanjak M, Robbins J. Design of clinical therapeutic trials in amyotrophic lateral sclerosis. Adv Neurol 1991;56:521-46.
19. Rozier A, Lacomblez L, Chatelier G, Bensimon G, Bouche P, Meininger V. Interrater reliability of a new rating scale for amyotrophic lateral sclerosis. J Neurol Sci 1990;98:Suppl:316. abstract.
20. Lacomblez L, Bouche P, Bensimon G, Meininger V. A double-blind, placebo-controlled trial of high doses of gangliosides in amyotrophic lateral sclerosis. Neurology 1989;39:1635-7.
21. Freedman LS. Tables of the number of patients required in clinical trials using the logrank test. Stat Med 1982;1:121-9.
22. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966;50:163-70.
23. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
24. Wu MC, Carroll RJ. Estimation and comparison of changes in the presence of informative right censoring by modeling the censoring process. Biometrics 1988;44:175-88.
25. Durrleman S, Alperovitch A. Increasing trend of ALS in France and elsewhere: are the changes real? Neurology 1989;39:768-73.
26. Peto R. Statistical aspects of cancer trials. In: Halnan KE, ed. Treatment of cancer. London: Chapman & Hall, 1982:868-71.
27. Benoit E, Escande D. Riluzole specifically blocks inactivated Na channels in myelinated nerve fibre. Pflügers Arch 1991;419:603-9.
28. Doble A, Hubert JP, Blanchard JC. Pertussis toxin pretreatment abolishes the inhibitory effect of riluzole and carbachol on D-[3H]aspartate release from cultured cerebellar granule cells. Neurosci Lett 1992;140:251-4.

Silent Reflections EVERT LAMFERS, M.D.