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ORIGINAL COMMUNICATION

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A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis

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Abstract Treatment with the neuroprotective drug riluzole has previously been shown to increase the probability of survival in patients with amyotrophic lateral sclerosis. This report describes a placebo-controlled, double-blind randomised clinical trial of riluzole carried out in ALS patients with advanced stage disease or aged over 75 years. The primary objective was to enable access to treatment to patients excluded from the pivotal trial which was run in parallel. Another goal was to assess the safety of riluzole in patients with advanced-stage disease. One hundred and sixty-eight patients were included, randomised to either riluzole 50 mg *b. i. d.* or to placebo, and treated for eighteen months. Riluzole was well-tolerated in this patient population, and the adverse events observed were similar in nature and frequency to those observed in previously published clinical trials in patients included in pivotal trials. The study could not include enough patients to reach adequate power to detect differences in survival between the two treatment groups, and no such difference was in fact observed. In conclusion, riluzole is well-tolerated in ALS patients with advanced stage disease.

Key words amyotrophic lateral sclerosis · riluzole · clinical trial · patients

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly evolving, fatal neurodegenerative disease resulting from the degeneration of cortical, bulbar and spinal motor neurons (Williams and Windebank 1991). Characteristic signs and symptoms include muscle wasting and weakness, spasticity, fasciculations and cramps. Signs of both upper and lower motor neuron dysfunction are required to establish the diagnosis. There is considerable variation in natural history. The disease progresses inexorably to death, usually due to failure of respiratory function, with a median duration of three years (Norris et al. 1993; Ringel et al. 1993; Brooks 1996). However, a longer survival is observed in a minority of patients, with a duration of over 10 years in around 5 % of the patients (Norris et al. 1993).

Riluzole is a benzothiazole derivative that interferes with glutamatergic neurotransmission in the central nervous system (Bryson and Benfield 1996). Its neuroprotective properties justified clinical investigations for the treatment of ALS. A double-blind, placebo-controlled study performed in 155 patients (Bensimon et al.

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1994), showed a significant improvement of both survival and functional outcome measures in patients treated with 50 mg of oral riluzole *b. i. d.* (100 mg/day). This study showed for the first time a potential therapeutic benefit of a drug in ALS.

To confirm the findings of this initial study, a larger dose-ranging study was initiated in a population of patients with similar baseline characteristics. The results of this study, which have since been published (Lacomblez et al. 1996), confirmed the beneficial effect of riluzole on survival seen in the first study.

Although the population investigated in both these studies corresponded to a large part of the natural ALS population, the entry criteria applied excluded certain patient groups: firstly, those older that 75 years, secondly, those presenting with signs of advanced disease (remaining vital capacity < 60 % or not assessable), and, thirdly, those whose disease had evolved for more than 5 years. The rationale for these limitations was to limit the variance in outcome. In addition, at a late clinical stage corresponding to pronounced and extended neuronal loss, less benefit might have been expected from a neuroprotective therapeutic intervention. Finally, survival might be too short in these patients to permit an effect of treatment to be revealed.

Nonetheless, in the first study, fifteen percent of patients were incorrectly included, since they did not meet the entry criteria with regards to age, disease duration and vital capacity (Bensimon et al. 1994). The high rate of improper inclusions may be attributed to a desire to give patients access to a potentially beneficial treatment in a previously untreatable condition. This pressure could be expected to be even greater in the second confirmatory trial, given the promising results of the first. In order to limit such protocol violations in the second study, it was thus decided to carry out in parallel another study in which could be included those patients not eligible for the pivotal trial. These patients were principally those with advanced stage disease. Apart from the inclusion criteria, the design of the two studies was identical. However, only the 100 mg/day dose was used.

This ancillary study was designed as a double-blind, placebo-controlled clinical trial, since having an open design would have interfered with enrolment in the pivotal study. The study was carried out in France and Belgium, and contemporaneously with the pivotal study in the same centers. Enrolment was stopped simultaneously with the end of enrolment of the latter.

This study also provided an opportunity to evaluate primarily the safety and secondarily the efficacy of riluzole 100 mg/day in a population of ALS patients with advanced stage disease. The current report describes the results obtained.

Methods

Participating institutions and study period

This study was carried out at eight centres in France and one in Belgium (see Appendix). The trial was performed in parallel with that described by Lacomblez et al. (1995). Inclusion started in December 1992, and terminated when the predefined patient population had been included into the pivotal trial (November 1993). The double-blind period terminated in January 1995.

Randomisation and treatment

Patients were randomly assigned to one of the two treatment groups (riluzole, one tablet (50 mg) orally twice daily and placebo, one tablet orally twice daily) according to a randomisation list balanced by center. Patients were stratified according to site of onset of the disease (bulbar or limb).

At the end of the study, patients were given the opportunity to receive riluzole 100 mg/day in an open-label, extension study. No information on the previously allocated double-blind treatment was given to the investigator or to the patient.

Inclusion and exclusion criteria

To be eligible for inclusion in the study, patients were required to present probable or definite ALS, according to the El Escorial criteria (Brooks, 1994), and meet one or more of the exclusion criteria of the pivotal study: age over 75 years, disease duration over 5 years since first symptoms, or forced vital ventilatory capacity below 60 % of the theoretical maximum value or not assessable. Patients had to be able to fully understand the study information given and give written informed consent. Patients presenting with only lower motor neuron signs (provided that in the course of the disease, upper motor neuron signs were documented), gastrostomised patients and patients with benign monoclonal gammopathy of undetermined significance could also be included. However, apart from three patients with benign monoclonal gammopathy, no such patients were in fact included.

Patients were not eligible for inclusion if they had undergone a tracheostomy or expected to undergo one within two months after study inclusion, if they had signs of dementia and/or major psychiatric disorders, and if they had another concomitant serious disease or handicap likely to interfere with their assessment or survival.

Patients were not eligible to enter this study if they presented at baseline with a creatinine plasma concentration above 200 µM, alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) activity greater than twice the upper limit of the normal range. Pregnant or lactating women were also excluded.

Contra-indicated drugs included those known to be hepatotoxic, enzyme-inducing or enzyme-inhibiting, anabolic steroids, calcium channel blockers, and drug cocktails containing amino-acids. Treatment with any of these drugs was to be discontinued one month before study initiation. Similarly, patients who had participated in another clinical trial with any investigational drug were to have had at least one month of washout or longer if specified by the previous trial protocol before study screening.

Safety evaluation

A physical examination was performed at baseline, and then every 2 months and at the post-treatment discontinuation visit. Height and weight were recorded at baseline and weight alone at the end of the study. A neurological examination was performed at baseline and every 6 months. Vital signs (heart rate and blood pressure) and an electrocardiogram were recorded at each visit.

Spontaneously reported adverse experiences and serious adverse experiences were recorded at each study visit. An adverse experience was recorded based either on the patient's comments after general questioning or on the investigator's observations.

Standard laboratory tests were performed. A complete hematology evaluation was performed every two months and in case of treatment discontinuation. In addition, during the first 6 weeks of treatment, red blood cell count, white blood cell count and platelet count were determined fortnightly. Electrolytes, blood chemistry and muscle enzymes were evaluated at baseline and every 6 months thereafter, as well as in case of treatment discontinuation.

Liver function was followed by monitoring ALT, AST, γ-GT, total and conjugated bilirubin and alkaline phosphatase every two months. In addition, ALT was measured every two weeks for the first six weeks. If the ALT value was above three times the upper limit of the normal range, viral hepatitis serology was checked, and all hepatic markers were monitored closely until normalisation. If the ALT value reached five times the upper limit of the normal range, study treatment was to be stopped and no rechallenge allowed.

Efficacy evaluation

The primary efficacy criterion was survival, defined as the time to failure during the 18 months (548 days) following randomisation where failure was considered as either death, tracheostomy or intubation with artificial ventilation.

The secondary outcome measures were the total scores for the manual muscle testing scale, the modified Norris bulbar and limb scales, the three items of the modified clinical global impression (CGI) scale, ventilatory function and the scores for the four self-assessments (fasciculations, cramps, stiffness, tiredness) by Visual Analogue Scales (Norris et al. 1974; Lacomblez et al. 1996). As far as possible, efficacy measures were assessed under the same conditions by the same investigator throughout the course of the study.

The modified CGI was subdivided into the following groups of items: severity of illness, global improvement and efficacy index. Patient rated visual analogue scales (VAS – 100 mm) assessed fasciculations, cramps, stiffness and tiredness.

Respiratory function (forced expiratory volume, slow vital capacity, and vital capacity ratio) was assessed by the Respiratory Function Department at each center. These tests was performed within the two months prior to the start of the study. Following enrolment, the patients were assessed every six months and at the post-treatment discontinuation visit.

Power calculations

Given the ancillary nature of the study, with patient accrual conditional to both (i) the unknown true prevalence of the population with these inclusion criteria and (ii) the unknown time length of patient accrual in the pivotal trial, the sample size could not be controlled. It was anticipated that about 200 to 300 patients would enter the study. The power available to detect a difference in survival of 10 % was calculated to be 44 % with 100 patients per group and 57 % with 150 patients per group. To detect a difference of 20 %, the power would be 89 % and 97 % respectively.

Statistical Analysis

The population to be considered for analyses was an "intent-to-treat" (ITT) population which included all randomised patients. The results are reported with two-sided p-values (with a significance level of 5 % being considered to be different) throughout this report.

In order to detect a potential treatment effect on survival, Kaplan-Meier survival curves were compared using Log rank and Wilcoxon tests. A stratification for bulbar or limb onset form of disease was performed. A Cox proportional hazard model was also used in order to take into account prognostic factors known to influence survival. These include onset form of the disease, age, duration of the disease, vital capacity ratio, total score of muscle testing scale, heart rate and scores of visual analogue scales. When data were missing, the mean (or mode for categorical variables) for the stratum was used.

For each of the functional scales (Muscle testing, Norris bulbar and Norris limb scales) and for each evaluation, a total score was calculated. Owing to loss to follow-up, failures and early study discontinuations, many patients did not complete the 18-month treatment period, and therefore did not have all evaluations in the functional scales. Unweighted least-square estimates of the rate of deterioration of the total score measured during treatment (slope of the total score versus time curve) were used as response variables in an ANOVA with respect to treatment, onset form of the disease and their interaction. Interactions were removed from the model if the associated p-value was higher than 15 %. If significant at this level, subgroup analyses by stratum were performed. All tests were two sided.

Ethics

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Clinical Practices (European Guidelines), and local regulatory requirements. Written informed consent was obtained from each patient (a spouse or caregiver was eligible to sign, in the presence of a witness, if the patient was physically unable to do so). Patients were free to withdraw from the study at any time for any reason, without effect on their medical care. The protocol and amendments were submitted to and approved by local Ethics Committees.

Results

Demographic and clinical characteristics at entry

One hundred and sixty-eight patients were enrolled into the study. Demographic characteristics of the subgroups at entry are shown in Table 1. When comparing the two treatment groups, there was a higher percentage of female patients in the riluzole group than in the placebo group (59 % *versus* 44 %); the patients in the riluzole group were also on the average significantly younger than in the placebo group ($p = 0.02$).

Mean disease duration tended to be shorter in the riluzole group (3.4 years) than in the placebo group (3.9 years), although this difference was not statistically significant. The proportion of patients with bulbar-onset disease was higher in the riluzole-treated patients (35 %) than in the placebo group (30 %). There was an imbalance in the number of patients assessable for vital capacity: 74 (86 %) patients were still assessable in the placebo group *vs* only 59 (68 %) in the riluzole group. This imbalance was particularly marked in the bulbar-onset group: 79 % assessable in the placebo group *vs* 48 % in the riluzole group.

Patients in the riluzole group had a significantly lower score on the muscle testing scale ($p = 0.03$). There was also a trend towards a lower score on the Norris bulbar and limb scales. The mean VAS scores for stiffness and tiredness were higher in the riluzole group than in

Table 1 Patient characteristics at baseline

	Placebo	Riluzole	All
N	86	82	168
Sex M/F	48/38	34/48	82/86
Age (years)[1]	62.8±1.4	57.8±1.4*	60.4±1.0
Weight (kg)[1, 2]	61.8±1.4 (12)	59.7±1.4 (12)	60.8±1.0 (24)
Disease duration (years)[1]	3.9±0.4	3.4±0.2	3.6±0.2
Limb/Bulbar onset	60/26	53/29	113/55
Sporadic/Familial	80/6	79/3	159/9
Definite/Probable diagnosis	51/35	51/31	102/66
Vital capacity ratio[1, 2]	55.1±2.6	51.9±3.1	53.7±2.0
VCR unassessable	12	23	35
Muscle testing scale[1] (max. score = 110)	70.3±2.8	63.8±3.2*	67.1±2.1
Norris bulbar scale[1] (max. score = 39)	20.5±1.3 (0)	18.9±1.4 (2)	19.7±1.0 (2)
Norris limb scale[1] (max. score = 63)	28.8±2.2	26.5±2.1	27.7±1.5
VAS Stiffness[1]	37.2±3.8 (17)	40.7±4.5 (23)	38.8±2.9 (40)
VAS Tiredness[1]	58.6±3.5 (17)	62.4±3.3 (24)	60.4±2.4 (41)
VAS Fasciculations[1]	37.2±3.4 (17)	35.5±3.7 (23)	36.4±2.5 (40)
VAS Cramp[1]	26.4±2.8 (17)	25.9±3.2 (23)	26.2±2.1 (40)

Demographic and clinical characteristics of patients at baseline. *VCR* Vital capacity ratio.
[1] Data are presented as mean ± s. e.m (number of missing values).
[2] Excluding patients not assessable. The asterisk indicates a significant difference between the two groups ($p < 0.05$; ANOVA).

the placebo group. Thus, overall, disease appeared to be more severe in the riluzole treated patients.

Description of patients included according to inclusion criteria

The majority of patients included (76.2 %) were characterised by impaired ventilatory capacity (VCR < 60 % or not assessable). The remainder were more or less evenly distributed between those over 75 years and those with a disease duration of over five years (Table 2). Ten patients did not meet inclusion criteria, and should have been enrolled in the parallel pivotal study.

Table 2 Inclusion criteria of patients

	Placebo (n = 86)		Riluzole (n = 82)		All (n = 168)	
Age > 75 years	19	22%	5	6%	24	14%
Disease Duration > 5 yrs	18	21%	14	17%	32	19%
VCR < 60%	49	57%	44	54%	93	55%
VCR unassessable	12	14%	23	28%	35	21%
Benign monoclonal gammopathy	2	2%	1	1%	3	2%
None (protocol violations)	4	5%	6	7%	10	6%

The different inclusion criteria are not mutually exclusive, so certain patients may figure more than once in the Table. VCR: Vital capacity ratio.

Treatment withdrawals

Thirty-five patients (13 in the placebo group and 22 in the riluzole group) discontinued treatment before the end of the study (Table 3). The primary reason for premature discontinuation was the occurrence of adverse events (excluding death), in a total of 23 patients (13.7 %). Discontinuation for adverse events was twice as frequent in the riluzole group than in the placebo group (18.3 % versus 9.3 %). Adverse events most frequently resulting in treatment discontinuation were commonly either related to impaired respiratory function (respiratory disorders, apnea, lung function decrease, bronchitis, hypoventilation, aspiration pneumonia) or liver enzyme elevations. Three patients in each group withdrew for perceived absence of efficacy, and three patients in the riluzole group withdrew their consent.

Seventy-four percent (124) of patients did not complete the eighteen month treatment period because they died or underwent a tracheostomy during the study period. At the end of the study, 23 % of patients only (20 in the placebo group and 19 in the riluzole group) were still alive and had been treated for the full 18 months.

Safety

Adverse events were reported in 152 patients out of the 168 included (90.5 %), 78 (90.7 %) in the placebo group and 74 (90.2 %) in the riluzole group (Table 4). These adverse events were classified as serious in 68 (79.1 %) in the placebo group and in 59 (72.0 %) patients in the riluzole group. 53 (61.6) patients died during the study in the placebo group, versus 41 (50.0) in the riluzole group. All these deaths were attributable to the terminal stage of the disease. The adverse events most frequently reported in both treatment groups were expected complications of ALS such as lung function decrease, dysphagia, bronchitis, respiratory disorders, apnea, dyspnea, aspiration pneumonia, sputum increase, hypertonia, accidental injuries, urinary tract infection, constipation. The adverse events (excluding death) reported more frequently in riluzole-treated patients than in placebo-

Table 3 Primary reasons for premature discontinuations from treatment

Reason for treatment discontinuation	Placebo n (%)	Riluzole n (%)	All n (%)
All	13 (15.1)	22 (26.8)	35 (20.8)
Adverse experiences			
– clinical	6 (7.0)	9 (11.0)	15 (8.9)
– laboratory	2 (2.3)	6 (7.3)	8 (4.8)
Lack of efficacy	3 (3.5)	3 (3.7)	6 (3.6)
Consent withdrawn	0	3 (3.7)	3 (1.8)
Cannot move	2 (2.3)	1 (1.2)	3 (1.8)

Table 4 Adverse events reported during the treatment period

	Number of patients reported		
	Placebo	Riluzole	All
Total number of patients	86	82	168
Patients with at least 1 AE (%)	78 (90.7)	74 (90.2)	152 (90.5)
Patients with serious AEs (%)	68 (79.1)	59 (72.0)	127 (75.6)
Adverse Event	n (%)	n (%)	n (%)
Death	53 (61.6)	41 (50.0)	94 (56.0)
Lung function decrease	28 (32.6)	18 (22.0)	46 (27.4)
Bronchitis	13 (15.1)	12 (14.6)	25 (14.9)
Dysphagia	18 (20.9)	9 (11.0)	27 (16.1)
Hypertonia	8 (9.3)	8 (9.8)	16 (9.5)
Respiratory disorder	15 (17.4)	7 (8.5)	22 (13.1)
Apnoea	9 (10.5)	7 (8.5)	16 (9.5)
Asthenia	6 (7.0)	7 (8.5)	13 (7.7)
Dyspnoea	2 (2.3)	7 (8.5)	9 (5.4)
Cardio-respiratory arrest	2 (2.3)	6 (7.3)	8 (4.8)
Lung disorder	6 (7.0)	5 (6.1)	11 (6.5)
Abdominal pain	3 (3.5)	4 (4.9)	7 (4.2)
Nausea	3 (3.5)	4 (4.9)	7 (4.2)
Aspiration pneumonia	2 (2.3)	4 (4.9)	6 (3.6)
Headache	2 (2.3)	4 (4.9)	6 (3.6)
Tachycardia	2 (2.3)	4 (4.9)	6 (3.6)
Diarrhoea	1 (1.2)	4 (4.9)	5 (3.0)
Accidental injury	6 (7.0)	3 (3.7)	9 (5.4)
Sputum increase	6 (7.0)	3 (3.7)	9 (5.4)
Hypertension	5 (5.8)	3 (3.7)	8 (4.8)
Pain	1 (1.2)	3 (3.7)	4 (2.4)
Syncope	1 (1.2)	3 (3.7)	4 (2.4)
Urinary tract infection	4 (4.7)	2 (2.4)	6 (3.6)
Constipation	4 (4.7)	1 (1.2)	5 (3.0)
Fever	4 (4.7)	0	4 (2.4)

All adverse events (AEs) occurring in more than two patients in either treatment group are listed in the Table.

treated patients were asthenia (8.5% *versus* 7.0%), dyspnea (8.5% *versus* 2.3%), abdominal pain (4.9% *versus* 3.5%), nausea (4.9% *versus* 3.5%), aspiration pneumonia (4.9% *versus* 2.3%), headache (4.9% *versus* 2.3%), tachycardia (4.9% *versus* 2.3%), diarrhea (4.9% *versus* 1.2%), pain (3.7% *versus* 1.2%), syncope (3.7% *versus* 1.2%), anorexia (2.4% *versus* 0%) and somnolence (2.4% *versus* 0%). Adverse events reported only in riluzole-treated patients never involved more than 2 patients (anorexia, emotional lability and somnolence).

Overall, no clinically significant changes were observed in mean values for blood pressure and heart rate at the different visits during treatment. No particular treatment group-related pattern of ECG abnormality was noted.

Abnormal laboratory test values deemed clinically significant by the investigator were reported in a total of 37 patients (22%), 17 of whom were in the placebo group (19.8%) and 20 in the riluzole group (24.4%). The most frequent hematological anomalies were hyperleukocytoses. Their frequency did not seem to be treatment-related. Anemias were also sometimes observed in the riluzole group, but these were not considered significant by the investigator. These anomalies appeared at various times after randomisation (from 2 to 8 months). In those patients with subsequent values available, the course of anemia was reversible. The most frequent biochemical anomalies were hepatic enzyme increases. The frequency of ALT elevations > 3 ULN was 5.8% in the placebo group *versus* 15.9% in the riluzole group and the frequency of ALT elevation > 5 ULN was 2.3% in the placebo group and 7.3% in the riluzole group. The duration of treatment before increase over 5 ULN values in the riluzole group was variable from 1 month to more than 15 months. Full recovery to normal or baseline value was usually observed within days or weeks, occasionally after several months.

Efficacy

Overall, the survival rate was similar in the two treatment groups at 18 months (25.6% and 26.8% in the placebo and riluzole groups respectively). The median survival time was approximately 200 days. No significant difference between placebo and treatment groups was detected either with the stratified Logrank test ($p = 0.77$) or the stratified Wilcoxon test ($p = 0.93$). Following adjustment for prognostic factors using the Cox proportional hazard model, the estimate of treatment efficacy is not significant, either in the total population ($p = 0.995$) or in the bulbar ($p = 0.19$) or limb strata ($p = 0.29$). However, there was a high frequency of patients with missing prognostic variables in the Cox model, significantly more so in the riluzole group (47 (57.3%) patients) than in the placebo group (34 (39.5%) patients)(chi square: p = 0.0215). The corresponding Kaplan-Meier curves are presented in Fig. 1. Sensitivity analyses (death as endpoint and censoring for treatment discontinuation) confirmed the lack of a statistically significant difference in survival rate between the two treatment groups.

Functional evaluations showed that the rate of deterioration of the muscle testing total score was not significantly different between the two treatment groups. On the other hand, the rate of deterioration of the score of the Norris bulbar scale was significantly slower ($p = 0.05$) in the riluzole-treated patients than in the placebo-treated patients.

Other functional parameters included VAS for fasciculations, cramps, stiffness and tiredness for which wide individual variations were observed. No conclusion could be drawn as to the effect of riluzole compared with placebo on these parameters (data not shown). No significant difference among groups was noted during treatment for the different parameters of the CGI (data not shown).

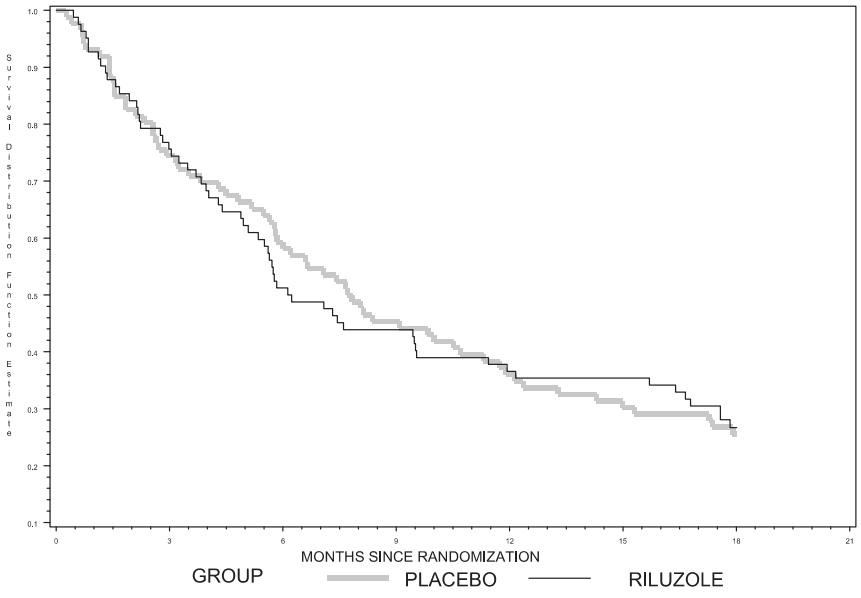

Fig. 1 Kaplan Meier survival curves. Patients were treated for 18 months with riluzole, 100 mg/day (–; n = 82) or placebo (–; n = 86).

	Inclusion	3 Months	6 Months	9 Months	12 Months	15 Months	18 Months
Placebo	0/86[a]	22/64	36/50	47/39	55/31	60/26	64/21
Riluzole	0/82	20/62	40/42	46/36	52/30	53/29	60/20

[a] Failures/patients at risk (i. e. patients alive without tracheostomy or intubation at each time interval)

Discussion

This report describes a double-blind, placebo-controlled, randomised clinical study of riluzole which included 168 patients with probable or definite ALS. The majority of these patients had advanced stage disease, as indicated by their impaired ventilatory function. The study was performed in parallel to that described by Lacomblez et al. (1996). The objective of minimising protocol violations due to improper inclusions in the latter study was achieved, since the treatment effect observed in the intent to treat analysis was maintained when protocol violations were excluded (Lacomblez et al. 1996b). In the pivotal study, there were in fact twenty protocol violations amongst the 444 patients in the centers participating in the two studies (4.5 %). This compares with fifteen percent in the previous study reported by Bensimon et al. (1994).

In the population studied, the frequency of adverse events was high. This can be expected given the advanced stage of disease in the individuals studied. The majority of the adverse events observed can be attributed to the progression of the disease process. This is notably the case for those affecting respiratory function and swallowing, which are signs of bulbar motor neuron dysfunction. In fact, the overall rate of mortality in this study was about three times higher than in the study by Lacomblez et al. (1996).

However, the adverse events reported specifically or excessively in the riluzole group as compared with the placebo group are both qualitatively and quantitatively similar to those seen in the two large trials of riluzole in less seriously ill patients (Bensimon et al. 1994; Lacomblez et al. 1996). These include asthenia, nausea and elevations in liver enzymes. It can be concluded that riluzole is relatively well-tolerated in ALS patients with advanced stage disease, and there is no specific safety issue associated with the use of riluzole in this patient population.

The currently available information on the efficacy of riluzole is derived from two studies with stringent inclusion and exclusion criteria (Wokke, 1997). This appraisal thus does not address efficacy in two important patient groups, those with early disease who do not yet fulfil the criteria for definite or probable ALS, and those with advanced stage disease. The current study provides an opportunity to evaluate the efficacy of riluzole in the latter population group.

The present study did not detect any beneficial effect of riluzole on survival. This, *prima facie*, contradicts the results of the two large randomised clinical trials in patients with less severe disease, where a decrease in the risk of failure (*ie* death or tracheostomy) of around

thirty percent was observed (Bensimon et al. 1994; Lacomblez et al. 1996). If indeed riluzole has a neuroprotective effect in ALS, it may be expected that this drug would have less effect in advanced state disease where there are few surviving motor neurons left to protect.

However, caution should be exercised in drawing conclusions about the lack of efficacy of riluzole in this patient population, since predetermined power specifications were not met. It had been anticipated that about 200 to 300 patients would enter the study. In fact, only 168 patients were enrolled. The statistical power is therefore lower than expected. It should also be noted that the two groups differed in certain major known prognostic factors at baseline (proportion with bulbar onset and ventilatory capacity). Furthermore, the number of missing values for important prognostic factors was high (> 50 %), and there was a significant imbalance favoring the control groups. It is known that in studies of ALS, missing values are informative, their presence being linked to the severity of the disease.

This study was performed in parallel with that reported by Lacomblez et al. (1996) conducted in the same centers, and the inclusion criteria for the two studies cover essentially all recruitable patients. Only those with potential hepatic insult, and those presenting with early disease (in whom a diagnosis of probable or definite ALS cannot be made) are excluded. It can thus be assumed that virtually all patients treated in the participating centres during the study period were included in one or other of the studies. From this exhaustive sample population it can now be inferred that results from the pivotal trials were obtained on a highly representative ALS population.

In conclusion, treatment with riluzole does not appear to expose the patients with advanced stage ALS to an additional risk, even though these patients are severely ill and have a very poor prognosis.

Appendix

Study Group:
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