ALS and other motor neuron disorders 2002 3, 23–29
 ISSN 1466-0822

Long-term safety of riluzole in amyotrophic lateral sclerosis

L Lacomblez[1], G Bensimon[1], PN Leigh[2], C Debove[3], R Bejuit[3], P Truffinet[3], V Meininger[1] and the ALS Study Groups I and II

[1]Departments of Pharmacology (LL, GB) and Neurology (LL, VM), Hôpital de la Pitié-Salpêtrière, Paris, France
[2] Department of Neurology, Guy's King's and St Thomas' School of Medicine and the Institute of Psychiatry, London, UK
[3] Drug Innovation and Approval Division, Aventis Pharma, 92165 Antony, Cedex, France

Correspondence:
Professeur Vincent Meininger
Fédération de Neurologie Mazarin
Centre Hospitalier Universitaire Pitié-Salpêtrière
Assistance Publique Hôpitaux de Paris et
Université Pierre & Marie Curie
75013 Paris, France
Tel: 33 1 42 16 04 26.

Received 14 January 2002
Revised 10 March 2002
Accepted 12 March 2002

OBJECTIVES: This international, open-label, multicentre extension of riluzole pivotal studies was designed to assess the long-term safety of riluzole in the treatment of amyotrophic lateral sclerosis (ALS).

METHOD: The studies were carried out at 31 different centres, 23 in Europe and eight in North America. 516 patients with diagnosed probable or definite ALS and who had participated previously in one of two international multicentre randomized double-blind placebo-controlled, parallel-group trials, were enrolled in the extensions. 58 of these patients had taken part in a randomized phase II trial (placebo or riluzole 100 mg/day) and 458 in a randomized, dose-ranging phase III trial (placebo or riluzole, 50, 100 or 200 mg/day). All participants in the open-label continuation received 100 mg/day of riluzole (50 mg b.i.d.)

RESULTS: At the end of the open-label study, the average exposure time of the patients to riluzole was 28.7 ± 14.4 months, with a maximum exposure time of 81 months. Most of the adverse events recorded reflected the progression of ALS, in particular the deterioration of the respiratory status of the patients. No particular adverse event, or frequency of adverse event, appeared to be related to the dose level of the previous double-blind riluzole treatment. Nor were any adverse events associated with the switch-over from double-blind placebo to open-label riluzole.

CONCLUSIONS: This open-label extension study reinforces and extends the results of the preceding double-blind trials regarding the safety of riluzole and shows that the drug is well tolerated for long periods of up to almost 7 years. (ALS 2002; 3: 23–29)

Keywords: amyotrophic lateral sclerosis – follow-up study – long-term safety – open label – riluzole (Rilutek®)

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disorder, characterized by muscle wasting and amyotrophy.[1,2] Death usually occurs within 2–5 years after the onset of the first symptoms.[1,2] The exact causes of the disorder are unknown, although it has been hypothesized that glutamate toxicity at central neuronal synapses may lead to neuronal damage.[3–6] Riluzole (2-amino-6-trifluoromethoxybenzothiazole, Rilutek®) is a novel anti-excitatory agent, now licensed for the treatment of ALS. The drug showed neuroprotective properties in preclinical studies[7–9] and its activity is thought to be related to an inhibitory effect on glutamate neurotransmission.[10–12] In a transgenic mouse model of familial ALS, riluzole has been shown to extend survival and slow disease progression.[13,14]

Two international multicentre randomized double-blind, placebo-controlled, parallel-group clinical trials have demonstrated that orally-administered riluzole is safe, and well tolerated, and significantly extends survival time and/or the time to tracheostomy in patients with ALS.[15,16] The first of these studies was a phase II trial involving 155 outpatients with ALS who received 100 mg riluzole per day (50 mg *b.i.d.*).[15] The second study was a dose-ranging phase III trial conducted with 959 patients with probable or definite ALS, to determine the benefit-to-risk ratios of 50, 100, or 200 mg riluzole/day (25, 50 or 100 mg/day *b.i.d.*).[16] In both cases, orally administered riluzole was found to significantly prolong survival time and/or the time to tracheostomy. A dose of 100 mg/day (50 mg b.i.d.) was considered to give the optimal benefit-to-risk ratio.[16] A post-hoc analysis of disease progression from the second study showed that riluzole delayed the progression of patients from less severe to more severe health states.[17] However, results of the phase II trial,[15] showing that riluzole decreased the rate of deterioration of muscle-strength loss, were not confirmed in the phase

These two studies also demonstrated that riluzole was safe and well tolerated over the time-scale of the trials. Adverse events (AEs) were recorded for >90% of patients in both treatment groups but the majority were considered to be related to the progression of the disease, especially those linked to the deterioration of the respiratory system.[15,16,18] Among the most frequent AEs considered to be potentially drug-related in patients taking riluzole were asthenia, nausea and reversible increases in transaminase levels.

At the end of both trials, patients were offered the opportunity to enter an open-label long-term extension study whose main objective was to assess further the long-term safety of riluzole 100 mg/day (50 mg *b.i.d.*). The combined results of these extension studies are reported here.

Materials and methods

Overall study design

The study design for both extension studies was essentially the same. Those patients from both the phase II and phase III studies who agreed to participate in the open-label extension and satisfied the inclusion criteria were entered into the study and received open-label riluzole, 100 mg/day (50 mg *b.i.d.*, orally). The phase II extension study began at the cut-off dates for the double blind trial (12 March 1992). The patients in the phase III study were switched to the open-label extension after 18 months' treatment or at the cut-off (31 December 1994), whichever occurred first. The study ended on 11 and 21 April 1997 for patients entering from phase II and phase III, respectively.

Study centres

This was a multinational study conducted in 31 centres: 23 in Europe (France 9, UK 8, Germany 4, Belgium 1 and Spain 1) and eight in North America (USA 5 and Canada 3).

Inclusion criteria

Initial selection criteria for the double-blind phase[15,16,19] included a diagnosis of definite or probable ALS and involvement of at least three to four regions of the body, with clear lower motor neuron involvement and obvious signs of upper motor neuron dysfunction. These selection criteria were designed to prevent misdiagnoses and to differentiate between various other neuromuscular diseases with overlapping features. At enrolment, patients had to be between 18 and 75 years of age, have disease duration of <5 years, and a vital capacity of >60% of the predicted (or theoretical) value.

In order to be included in the ongoing open-label extension, patients had to have participated in the double-blind studies for a minimum of 18 months or up to the studies' cut-off dates. Written informed consent was obtained specifically for continuation with open-label riluzole. Reasons for non-inclusion were death, loss to follow-up and discontinuation because of AEs between the studies' cut-off dates and the switch-over visits.

Exclusion criteria

Patients were ineligible to enter the longer-term, open-label extension if they refused to give consent or were unlikely to comply with the protocol, unable to establish a rapid means of contacting the investigator in case of emergency, receiving drugs known to be hepatotoxic, enzyme-inducing or enzyme-inhibiting, or were pregnant or lactating women. They were also excluded if they had discontinued medication due to increases in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels to more than five times the upper limit of the normal (ULN) or because of a serious AE.

Ethics

The study was conducted according to the Declaration of Helsinki (Hong Kong Amendment), Good Clinical Practices, and local regulatory requirements. Written informed consent was required specifically for the open-label extension (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 affecting their medical care. No patient was offered financial inducement to participate in the study.

Outcome measurements

The life status of each patient was monitored and recorded as dead, tracheostomized, or alive without tracheostomy. Functional assessments included modified Norris limb and Norris bulbar scales, muscle testing, physical assessments, investigator's Clinical Global Impression (CGI), and the visual analogue scale (VAS) for fasciculations, cramps, stiffness, and fatigability).[16] Safety assessments, which are the focus of this report, included physical examination, electrocardiogram, AEs assessed at each visit, laboratory tests ('standard laboratory work-up'), and serum enzyme tests. In the phase II extension, all safety assessments were carried out at the time of switch-over to open-label and every 2 months thereafter, with the exception of the serum enzyme tests, which were carried out every 2 weeks for the first 2 months and then every 2 months. An amendment to the protocol, introduced on 29 April 1994, lengthened the period between study visits to 4 months apart. At all subsequent visits, the following were also recorded: occurrence of spontaneous AEs since the last visit, concomitant medication use, vital signs, life status assessment during treatment and after discontinuation (where applicable), and haematology and biochemistry tests. Respiratory function tests and ECG readings were carried out every 8 months.

In the phase III extension, all of the above assessments and measurements were made at the switch-over and final visits. Haematology, serum enzyme tests, and AEs were recorded every 2 weeks for the first 8 weeks and every 2 months thereafter. Biochemical tests were carried out also at week 2 and at months 6, 12, 18, and 24, and ECG readings taken at 6–8 weeks following the switch-over visit. Concomitant medications and vital signs were recorded also at month 4 and every 4 months thereafter.

Data analysis

Data gathered from the two open-label extension studies were either combined, or analysed for separate groups of patients termed Ril_{new}, Ril_{50}, Ril_{100} and Ril_{200}, i.e. patients who had received placebo or 50, 100 and 200 mg of riluzole/day respectively, in the preceding double-blind trials.

Survival analysis was based on data collected up to the cut-off dates of 11 April 1997 for the phase II study (end-of-study dates for patients not lost to follow-up and not prematurely discontinued ranged from 10 February 1997 to 11 April 1997), and 21 April 1997 for the phase III study. Descriptive statistics have been used for both survival and safety analysis, but no statistical inference (*P*-value) has been drawn from the data. The population taken into account in the intent-to-treat analysis of survival comprised the 1114 (155 and 959) patients initially included in the double-blind studies. The other evaluation parameters were either assessed from the 516 patients in the extension studies or the number of patients in each group (Ril_{new}, 141; Ril_{50}, 114; Ril_{100}, 144 and Ril_{200}, 117). Dates of death or tracheostomy before the last visit were taken as endpoints in the analysis of survival. For patients who were still alive without tracheostomy at the end of the study, survival was censored at the final study visit. For patients lost to follow-up, the date of last news was used.

Results

Demographics

A total of 516 patients from the two randomized double-blind placebo-controlled multicentre studies described above were entered into this study. Of the 155 patients originally included in the phase II study, 71 were still alive on 12 March 1992. Of these, 58, 29 of whom had received riluzole 100 mg/day (50 mg *b.i.d.*), and 29 who had received placebo were included in the open-label extension. Of the 959 patients originally included in the phase III study, 458 entered the open-label trial. Of these, 112 had received placebo, 114 riluzole 50 mg/day (25 mg *b.i.d.*), 115 riluzole 100 mg/day (50 mg *b.i.d.*) and 117 riluzole 200 mg/day (100 mg *b.i.d.*). The baseline characteristics of the patients at the time of entry into the open-label study are shown in Table 1.

Duration of treatment

For all patients combined ($n = 516$), the mean duration of treatment at the end of the open-label study was 28.7 months (SD, 14.4 months; range, 0–81 months). The duration data for the individual groups are given in Table 2. Patients whose initial symptoms were bulbar had a mean duration of treatment of 26.4 months (SD, 13.0 months; range, 1–77 months), and those who entered with limb symptoms had a mean duration of treatment of 29.4 months (SD 14.8 months; range, 0–81 months). Figure 1 depicts the duration of exposure of all patients to riluzole.

Discontinuations

Altogether 302 patients (58.9%) discontinued the study. The main reasons for discontinuation were death, adverse clinical experience or consent withdrawn. Reasons for discontinuation are summarized in Table 3.

Parameter	Ril_{new} (n = 141)	Ril_{50} (n = 114)	Ril_{100} (n = 144)	Ril_{200} (n = 117)	All (n = 516)
Numbers participating	141	114	144	117	516
Male : female	91 : 50	71 : 43	90 : 54	70 : 47	322 : 194
Mean age (years)	52.3 ± 12.0	54.4 ± 11.0	54.1 ± 11.4	54.0 ± 11.6	53.7 ± 11.5
Age range (years)	19–76	28–73	24–73	28–75	19–76
Mean weight (kg)	69.7 ± 12.6	71.3 ± 13.5	70.1 ± 13.5	69.1 ± 11.6	70.0 ± 12.8
Mean disease duration (years)	2.0 ± 1.7	2.1 ± 1.3	1.9 ± 13	1.8 ± 1.2	2.0 ± 1.4
Form at onset:					
Bulbar	25 (17.7 %)	27 (23.7%)	37 (25.7%)	29 (24.8%)	118 (22.9%)
Limb	116 (82.3%)	87 (76.3%)	107 (74.3%)	88 (75.2%)	398 (77.1%)
Mean forced expiratory volume (%)	92.6 ± 20.3	89.7 ± 19.9	90.5 ± 21.9	90.7 ± 20.3	90.9 ± 20.6
Mean vital capacity ratio (%)	92.9 ± 17.6	91.8 ± 18.8	92.8 ± 19.6	92.8 ± 18.9	92.6 ± 18.7

Ril_{new}: patients who received placebo in the preceding double-blind trials; Ril_{50}, Ril_{100} and Ril_{200}: patients who received 50, 100 and 200 mg of riluzole/day respectively, in the preceding double-blind trials.

Table 1
Baseline characteristics of patients at double-blind baseline (unless otherwise indicated the data are given as means ± SD).

Original Research

Parameter	Ril_{new} (n = 141)	Ril_{50} (n = 114)	Ril_{100} (n = 144)	Ril_{200} (n = 117)	All (n = 516)
Duration from randomization (months)	35.26 ± 14.25	34.11 ± 10.49	32.46 ± 9.44	35.13 ± 13.75	34.34 ± 12.46
Extent of exposure to riluzole (months)	16.7 ± 14.3	33.7 ± 10.5	34.1 ± 13.8	31.7 ± 9.4	28.7 ± 14.4
Range of exposure to riluzole (months)	0–60	17–51	16–81	17–50	0–81

Ril_{new}, patients who received placebo in the preceding double-blind trials; Ril_{50}, Ril_{100} and Ril_{200}, patients who received 50, 100 and 200 mg of riluzole/day respectively, in the preceding double-blind trials.

Table 2
Duration of treatment and extent and range of exposure to riluzole from randomization into the double-blind studies to the end of the open-label extension study. (Data are given as means ± SD).

	No. (% total)
Entered the study	516 (100)
Completed the study	214 (41.5)
Did not complete the study	302 (58.9)
Reasons for withdrawal:	
Death, tracheostomy or intubation	229 (44.4)
Adverse events	25 (4.8)
Test drug ineffective	8 (1.6)
Other, including consent withdrawn	33 (6.4)
Lost to follow-up	7 (1.3)

Table 3
Reasons for withdrawal from the open-label extension study.

Survival

Kaplan-Meier survival curves for patients entering the open-label study from the phase II and phase III trials are shown in Figure 1. In both cases the curves show a relative stabilization in all groups after the switch-over to open-label. At the end of the study, 61 of the 516 patients were alive without tracheostomy. For 12 of those patients, who switched from the phase II trial, the time lapse since initial randomization was 6 years, and for the remaining 49 patients, who switched over from the phase III study, the time lapse was 4 years.

Safety

Clinical adverse events with onset during the extension study

Adverse events with onset during the open-label period were reported in a total of 444 patients (86.0%) (Table 4). The most frequent of these, other than death, were respiratory AEs, considered to be related to the ALS condition of the patients. In order of decreasing frequency, AEs occurring in ⩾10% of the patients were bronchitis (17.8%), apnoea (16.7%), lung function decrease (14.1%), and dysphagia (14.0%). Treatment was discontinued in 32 patients (6.2%) because of AEs, the most frequent of these being nausea (1.0%), apnoea (1.0%) and asthenia (4, 0.8%).

Three hundred and six patients (59.3%) had serious AEs reported with onset during the open-label treatment (Table 5). The most common serious AEs (in decreasing order and excluding death) were apnoea, decrease in lung function, dysphagia, bronchitis, and heart arrest. Serious

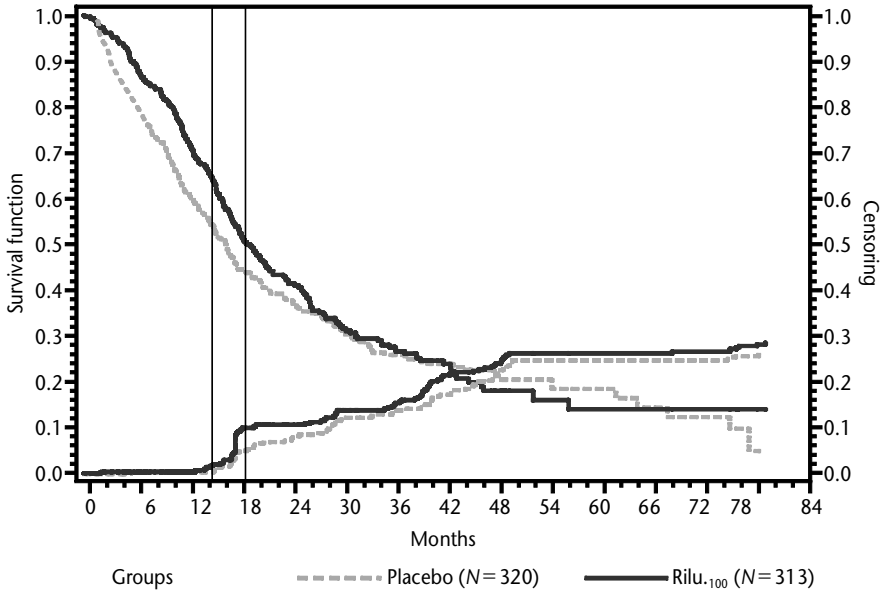

Figure 1
Kaplan-Meier survival curves for patients who participated in the open-label long-term study and who had participated previously in the phase II and the phase III double-blind trials. The first vertical line indicates the time the first patients switched over to open-label treatment and the second vertical line corresponds to the median duration from randomization to open label. The groups shown are those who were previously treated with placebo and riluzole, 100 mg/day.

Body system	Event	No. of patients (%)
Body as a whole	Accidental injury	50 (9.7)
	Abdominal pain	34 (6.6)
	Asthenia	28 (5.4)
	Pain	25 (4.8)
	Aggravation reaction	17 (3.3)
	Injection site inflammation	17 (3.3)
	Headache	16 (3.1)
	Reaction unevaluable	15 (2.9)
	Back pain	14 (2.7)
Cardiovascular system	Heart arrest	21 (4.1)
Digestive system	Dysphagia	72 (14.0)
	Nausea	37 (7.2)
	Constipation	36 (7.0)
	Diarrhoea	26 (5.0)
	Dyspepsia	22 (4.3)
Metabolic and nutritional disorders	Peripheral oedema	14 (2.7)
Musculoskeletal system	Arthralgia	11 (2.1)
Nervous system	Insomnia	21 (4.1)
	Depression	19 (3.7)
	Increased salivation	16 (3.1)
	Hypertonia	13 (2.5)
Respiratory system	Bronchitis	92 (17.8)
	Apnoea	86 (16.7)
	Lung function decrease	73 (14.1)
	Dyspnoea	40 (7.8)
	Rhinitis	31 (6.0)
	Pneumonia	24 (4.7)
	Respiratory disorder	19 (3.7)
	Sputum increased	16 (3.1)
	Cough increased	15 (2.9)
	Pharyngitis	13 (2.5)
Skin and appendages	Rash	20 (3.9)
Urogenital system	Urinary tract infection	17 (3.3)

*COSTART = coding symbols for thesaurus of adverse reaction terms.

Table 4
Most commonly reported adverse events (excluding death), by body system and COSTART* term (frequency >2.0%), with onset during the open-label extension study. (Percentages are calculated as a function of the total number of participants (516). A patient with one or more AE linked to the same COSTART term [or the same body system] is only counted once.)

AEs resulting in death were reported in 218 patients (42.2%) (Table 5).

There were no major differences in the frequencies of AEs or body systems affected between those patients who had received placebo during the double-blind phase and were therefore newly exposed to riluzole during the open-label extension study and those who had received riluzole previously at whatever dose (data not shown).

Laboratory adverse events

Clinically significant laboratory test results were observed sporadically. Low haematological values (anaemia) were observed in three patients, leading to one patient discontinuing treatment, and high gamma glutamyltransferase (gamma-GT) values led to discontinuation in another patient. Reversible hepatic enzyme elevations were observed in four patients, two of whom discontinued treatment: one with ALT levels >5 × ULN after 72 days of riluzole treatment, and one with ALT levels >7 ULN after 689 days on riluzole.

High blood pressure was recorded on at least one occasion in eight patients who entered the open-label phase from the Phase II study (systolic, SBP ⩾ 150 mmHg with diastolic, DBP ⩾ 100 mmHg) and in 12 patients who entered from the Phase III study (SBP ⩾ 160 mmHg with DBP ⩾ 100 mmHg). Low blood pressure (SBP ⩽ 100 mmHg with DBP ⩽ 50 mmHg) was recorded on at least one occasion in five patients who entered the open-label phase from the Phase III study. Hypertension was listed as an AE in three patients and as a serious AE in one patient. The investigators considered the results of ECG as abnormal in 59 patients, but no specific pattern was observed.

Deaths

Two hundred and fifty-eight deaths were reported, of which 181 occurred during open-label treatment and 77 after treatment had been discontinued. In most of these cases, death was the outcome of a se

Event	No. of patients with serious adverse events (%)	No. of patients with serious adverse events resulting in death (%)
Apnoea	86 (16.7)	80 (15.5)
Lung function decrease	68 (13.2)	51 (9.9)
Dysphagia	39 (7.6)	39 (7.6)
Bronchitis	28 (5.4)	10 (1.9)
Heart arrest	21 (4.1)	21 (4.1)
Pneumonia	21 (4.1)	6 (1.2)
Dyspnoea	17 (3.3)	6 (1.2)
Aggravation reaction	16 (3.1)	11 (2.1)
Accidental injury	15 (2.9)	–
Respiratory disorder	15 (2.9)	13 (2.5)
Heart failure	8 (1.6)	7 (1.4)
Lung disorder	6 (1.2)	–

Table 5
Serious adverse events (COSTART classification) with onset during the open-label extension study and serious adverse events resulting in death (frequency >1% of the total population). (Percentages are calculated as a function of the total number of participants (516). A patient with one or more serious AE linked to the same COSTART term (or the same body system) is only counted once.)

during treatment (n=218) and was related to an advanced phase or the terminal phase of ALS. This was also true for deaths that occurred after treatment had been discontinued (n=36). Only one death, resulting from respiratory failure after over one year on riluzole treatment, was considered to be potentially a result of the treatment medication.

Discussion

This study reviewed the safety of riluzole in patients with ALS who had been treated for a mean of 28.7 months (range, 0-81 months). Approximately 10% of the patients had been treated for ⩾48 months, 31% for ⩾36 months, 63% for ⩾24 months, and 89% for ⩾12 months. To date, this is the longest duration of a trial of a drug to treat ALS. It should be noted that the declining number of patients with longer treatment duration (Figure 1) not only represents deaths and discontinuations, but also reflects enrolment over a 5-year period, relative to a fixed study termination date.

This study permitted the switch-over of patients formerly on placebo to active treatment, giving the potential for detecting drug-related symptoms appearing for the first time. However, analysis of the results did not suggest the emergence of any new AEs in those patients formerly receiving placebo. Most of the clinical AEs recorded in all patients reflected the progression of ALS, especially the deterioration of respiratory status. In addition, the incidence and profile of AEs associated with open-label riluzole were similar to those observed in the double-blind studies.[15,16] For example, excluding death, the most frequent AEs reported during the double-blind phase II trial were respiratory disorders followed by asthenia,[15] whilst in the patients on 50 mg (*b.i.d.*) in the phase III trial, they were nausea, dysphagia, and asthenia.[16] This compares to bronchitis, apnoea, lung function decrease and dysphagia in the open-label phase (Table 4). The most frequently reported serious AEs in this study (Table 5) were also similar to, although not in the same relative order as, those reported in the double-blind trials.[15,16]

Laboratory abnormalities were not increased in frequency when compared to the double-blind trials. In particular, low haemoglobin values were observed in two patients throughout the open-label extension period. However, these two patients already had consistently low haemoglobin values during the double-blind phase II study when one was receiving riluzole (50 mg *b.i.d.*) and the other placebo. Among patients from the phase III study, the incidence of low values of haemoglobin (34.9%) was comparable to those observed in the double-blind study, 40.3%.

Among the patients entering from the phase II study, one discontinued treatment due to an ALT increase >7 ULN and an AST increase >6 ULN. These increases were partially reversed one month later and totally reversed after 3.6 months. In addition, two other patients, one previously treated with riluzole (50 mg *b.i.d.*) and the other with placebo, showed increases in ALT >3 ULN and AST >3 ULN, respectively. In both cases these increases were reversible despite continuing with treatment. In the latter case, isolated AST elevations >3 ULN were also observed during double-blind treatment with placebo. One patient from the phase III trial discontinued treatment due to a reversible increase of ALT of >5 ULN.

Indeed, the 58 patients from the phase II double-blind study had slightly better prognosis factors than the 155 initially randomized.[15] At baseline they were, on average, younger (54 *vs.* 57 years), with a higher proportion of limb-onset ALS (84.5% *vs.* 79.4%) and a slightly higher mean vital capacity (94% *vs.* 89%). The mean disease duration was similar (2.3 years *vs.* 2.1 years). Prognostic factors were even better in the 12 patients still alive 6 years after randomization, who were again, on average, younger (51.7 years), with a higher proportion of limb-onset ALS (91.7%), and a mean vital capacity of 95.3%. The mean duration of the disease was 3.3 years.

Similarly, the 458 patients who entered the open-label extension from the phase III study tended to exhibit a better prognosis than the 959 patients initially randomized.[16] At baseline they were, on average, younger (53.6 *vs.* 56.7 years), with a higher percentage of limb-onset ALS (76.2% *vs.* 69.2%) and a higher mean vital capacity (92.4% *vs.* 88.2%). The mean disease duration was similar (2.0 years *vs.* 1.8 years). Prognostic factors for the 49 patients still alive 4 years after randomization were even more favourable. These patients were, on average, younger (52.4 years), the proportion with limb-onset ALS was 71.4%, and vital capacity ratio was 98.7%. On the other hand, disease duration was slightly greater, at 2.7 years. Whether the observed prolongation

function of the natural slowing of disease progression or whether it is an effect of riluzole is unclear. It is clear, however, that long-term exposure (*i.e.* for more than 2 or 3 years) of patients with ALS to riluzole 100 mg/day does not cause any unexpected AEs and is associated with increased patient survival.

Conclusions

Most of the patients included in this open-label long-term extension study of the safety of riluzole were exposed to the drug for 2–3 years, and some for almost 7 years at the time of the cut-off date. Overall, the prolongation of the long-term riluzole treatment from double-blind to open-label and the switch-over from long-term double-blind placebo to open-label riluzole in patients with ALS were not associated with any particular AE nor any change in the frequency of AEs. Most of the AEs recorded reflected the progression of ALS, in particular the deterioration of the respiratory status of the patients. In conclusion, this open-label extension study reinforces and extends the results of the preceding double-blind trials regarding the safety of riluzole and shows that the drug is well tolerated for long periods of up to almost 7 years.

References

1. Brown Jr RH, Meininger V, Swash, M eds. Amyotrophic Lateral Sclerosis. London: Martin Dunitz, 2000.
2. 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: 1485–1492.
3. Meldrum BS. Amino acids as dietary excitotoxins: a contribution to the understanding of neurodegenerative disorders. Brain Res Rev 1993; 18: 298–314.
4. Rothstein JD. Excitotoxic mechanisms in the pathogenesis of amyotrophic lateral sclerosis. Adv Neurol 1995; 68: 7–20.
5. Leigh PN, Meldrum BS. Excitotoxicity in ALS. Neurology 1996; 47(suppl 4): S221–S227.
6. Ince PG, Eggett C, Shaw PJ. The role of excitotoxicity in neurological disease. Rev Contemp Pharmacother 1997; 8: 195–212.
7. Malgouris J, Bardot F, Daniel M et al. Riluzole, a novel antiglutamate, prevents memory loss and hippocampal neuronal damage in ischemic gerbils. Neurosci 1989; 9: 3720–3727.
8. Pratt J, Ratuad J, Bardot F et al. Neuroprotective actions of riluzole in rodent models of global and focal ischaemia. Neurosci Lett 1992; 140: 225–230.
9. Malgouris C, Daniel M, Doble A. Neuroprotective effects of riluzole on N-methyl-D-aspartate- or veratridine-induced neurotoxicity in rat hippocampal slices. Neurosci Lett. 1994; 177: 95–99.
10. Couratier P, Sindou P, Esclaire F, Louvel E, Hugon J. Neuroprotective effects of riluzole in ALS CSF toxicity. NeuroReport 1994; 5: 1012–1014.
11. Doble A. The pharmacology and mechanism of action of riluzole. Neurology 1996; 47(suppl 4): S233–S241.
12. Doble A. Effects of riluzole on glutamatergic neurotransmission in the mammalian central nervous system and other pharmacological effects. Rev Contemp Pharmacother 1997; 8: 213–226.
13. Gurney ME, Cutting FB, Zhai P et al. Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis Ann Neurol 1996; 39: 147–157.
14. Gurney ME, Fleck TJ, Himes CS, Hall ED. Riluzole preserves motor function in a transgenic model of familial amyotrophic lateral sclerosis. Neurology 1998; 50: 62–66.
15. Bensimon G, Lacomblez L, Meininger V. ALS/Riluzole study group. A controlled trial of riluzole in amyotrophic lateral sclerosis. N Engl J Med 1994; 330: 585–591.
16. Lacomblez L, Bensimon G, Leigh PN, Guillet P, Meininger V. for the Amyotrophic Lateral Sclerosis/Riluzole Study Group II. Dose-ranging study of riluzole in Amyotrophic Lateral Sclerosis. Lancet 1996; 347: 1425–1431.
17. Riviere M, Meininger V, Zeisser P, Munsat T. An analysis of extended survival in patients with amyotrophic lateral sclerosis treated with riluzole. Arch Neurol 1998; 55: 526–528.
18. Haas JF. The tolerability and AE profile of riluzole. Rev Contemp Pharmacother 1997; 8: 265–273.
19. Meininger V. Efficacy of riluzole in the treatment of amyotrophic lateral sclerosis. Rev Contemp Pharmacother 1997; 8: 255–263.