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German open label trial of riluzole 50 mg b.i.d. in treatment of amyotrophic lateral sclerosis (ALS)

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Abstract

Riluzole is currently the only drug that holds any hope of prolonging life in amyotrophic lateral sclerosis (ALS) by slowing the rate of disease progression. *Methods and results:* Between 1995 and 1997 a total of 7916 ALS patients in 39 countries, were given 100 mg riluzole per day for a mean of 7.2 months. The present report focuses on the German results in comparison to the total population. Nine hundred and nineteen patients were treated in 25 German centres; 162 (17.6%) died from the disease during the course of the study. Serious adverse events attributed to the study medication occurred in 16 patients (1.7%). Most frequently these were reversible changes in liver enzymes (0.9%) occurring during the first 3 months, none resulted in death. In all, 413 patients (44.9%) reported an adverse event. The most frequent were reduced lung function (7.3%), nausea (7.1%), asthenia (5.8%), pneumonia (2.5%) and abdominal pain (2.5%). *Conclusion:* The results of the study allow the conclusion that riluzole is well tolerated. The majority of adverse events were symptoms of the underlying disease and were not attributed to riluzole. Overall the safety profile found in the German centres was very similar to the profile seen in the total patient population and was more favourable than in the two published double-blind studies [New Engl J Med 330 (1994) 585; Lancet 347 (1996) 1425].

Keywords: Riluzole; Amyotrophic lateral sclerosis (ALS); Liver enzymes; Adverse events; Germany

1. Introduction

While the exact cause of ALS is still unknown, it is assumed that the primary excitatory neurotransmitter of the central nervous system, the amino acid glutamate [3], plays a key role in the pathogenesis of the disease. Toxic concentrations of glutamate accumulate in the synaptic cleft, where they result in the destruction of the neurones [4–7]. The finding that glutamate metabolization is abnormal in ALS patients [4–7], with changes in leukocytic glutamate dehydrogenase [8] and a reduction in the capacity for glutamate uptake in the spinal cord and synaptosomes of the motor cortex [9], has confirmed the pathogenic role of glutamate in ALS.

In preclinical studies, riluzole, a benzothiazole, proved to be an antagonist of glutamatergic transmission [10,11]. However, riluzole does not bind to any known receptors, but exerts an inhibitory effect on the spontaneous release of glutamate. The neuroprotective activity of riluzole [12,13] is presumably mainly attributable to a presynaptic inhibition of glutamate release resulting from inactivation of voltage-dependent sodium channels and activation of processes that are dependent on G-protein [14–17].

In a first controlled study in 155 ALS patients [1] a significant increase in the survival rate and less decrease in muscular strength in comparison to the placebo group were found after 12 months of treatment with riluzole. In a subsequent dose-finding study in 959 ALS patients [2] the efficacy of riluzole in prolonging the duration of survival was confirmed. A dose of 100 mg/day proved to be optimal as regards the risk–benefit ratio. In general riluzole was well tolerated. The occurrence of adverse events was dose-dependent and the most frequent adverse events were nausea, asthenia and reversible increases in transaminases.

The aim of the present multicentre, open-label treatment

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study was to make riluzole available to a larger number of ALS patients and to collect additional data on safety. The safety profile is compared to that seen in the two previous studies [1,2].

2. Patients and methods

Riluzole was made available to a total of 10 000 out- and inpatients in a multinational, uncontrolled study between 1995 and 1997. The patients were treated with a daily dose of 100 mg riluzole (50 mg orally twice daily) for not less than 1 year (or until the preparation received marketing authorization in the respective country). Adverse events and changes in laboratory parameters were recorded. In Germany the study was conducted as an open Phase III study in accordance with the recommendations of the Declaration of Helsinki and the European Guidelines for 'Good Clinical Practice', and approved by local ethics committees.

Men and women aged between 18 and 75 years and with a 'probable' or 'definite' diagnosis of ALS according to the definition of the World Federation of Neurology-Committee on Neuromuscular Disease [18] were accepted for the study. Further criteria for inclusion in the study were disease duration of less than 5 years and a respiratory vital capacity of not less than 60%.

Patients received 50 mg riluzole orally, twice daily. Reports of adverse events were elicited and recorded every three months. The serum concentrations of ALT and AST and hematological parameters were determined once a month during the first 3 months of treatment and once every 3 months thereafter. The last serological and hematological determinations were performed not later than 14 days after the end of the treatment. ALT and AST concentrations 3 and 5 times higher than their reference limits were considered pathological. A reduction in neutrophilic granulocytes to below 0.5 Giga/l was defined as severe neutropenia.

Descriptive statistics were compiled for both the entire intent-to-treat population which included all participants who received the medication at least once, and then for each country taking part in the trial.

3. Results

Between June 1995 and March 1997 a total of 7988 patients from 674 study centres in 39 countries were accepted for the trial. A total of 7916 of these patients (99.1%) received the study medication at least once. The mean duration of treatment with riluzole was 202.1 (1–630) days or 7.2 (0–23) months. A total of 3230 patients (40.4%) discontinued the study prematurely. The main reasons for discontinuation were death (19%), adverse events excluding death (9.3%), withdrawal of consent (4.5%), patient lost to follow-up (3.9%), study medication not effective (1.6%) and tracheostomy or intubation (0.5%).

In Germany a total of 919 patients from 25 centres took part in the study. Between 9 and a maximum of 98 patients were recruited by the individual centres. The mean age of the patients was 59.1 years and 58.5% were men. The onset of ALS had been in the extremities in the majority of the patients (73.8%) and 53.5% had a 'probable' ALS diagnosis and a duration of disease of between 6 months and 2 years (63.7%) at the start of the study. A family history of ALS was known for 22 patients (2.4%). The demographic data of the German patients deviated only slightly from those of the total study population.

The occurrence of adverse events was the main focus of the study. Table 1 gives an overview of the frequency of critical events.

One hundred and eighty-five patients (20.1%) experienced a serious adverse event at least once. The most frequent serious adverse events reported were reduced lung function (7.2%), pneumonia (2.5%) and apnea (2.0%). Only in 16 patients (1.7%), however, did an event occur that was attributed to drug and therefore constituted a serious adverse drug reaction. The most frequently reported serious adverse drug reactions were reversible changes in liver enzymes (see Table 2) and nausea. Death or an adverse event with the outcome of death occurred in 162 patients (17.6%) at the German centres during the course of the study. The study was prematurely discontinued owing to an adverse event (including death) in 188 cases (20.5%). A total of 413 patients (44.9%) experienced at least one adverse event. Adverse events classified as non-serious occurred in 279 patients (30.4%). However, only in 212 (23.1%) cases was an event rated as 'possibly' or 'probably' attributable to the study medication.

The adverse events most frequently observed at the German centres as seen in Table 2 were reduced lung function (7.3%), nausea (7.1%) and asthenia in 5.8% of the patients. The frequency and nature of the adverse events observed at the German centres differed only negligibly from those seen in the overall study population. These findings compare very favourably with the safety findings of previous studies with the same dose [1,2].

Table 3 provides a break down of the critical liver enzyme changes that occurred during the trial. The transaminase values of the great majority of the patients in the total population ($\geq$97.3%) were normal before the start of the study and remained so at all measuring times during the study period. Pathological changes in liver enzymes were observed particularly during the first 3 months of treatment in up to 2.5% of the patients. During the rest of the study the percentage of patients with enhanced transaminase levels showed a distinct decline ($\leq$0.8%). Changes in liver enzymes occurred in a total of 3.3% of all patients during treatment, 0.9% of which were assessed as serious adverse drug reactions. The changes in liver

Table 1
Total number of patients reporting adverse event and discontinuations due to adverse events, adverse events broken down into serious and non-serious events reported at least once and in each of these categories the number of the events thought to have been related to the compound (adverse drug reactions)[a]

Adverse events	German centres (n=919)		Patients worldwide (n=7916)		Bensimon et al. [1] (n=77)		Lacomblez et al. [2] (n=236[b])	
Total no. patients reporting:	No.	%	No.	%	No.	%	No.	%
Adverse events at least once (including death)	413	44.9	3668	46.3	71	92.2	216	91.5
Adverse events leading to discontinuation	188	20.5	1580	20.0	19	25.0	29	11.9
Non-serious adverse events reported at least once	279	30.4	2409	30.4	nd		nd	
attributed to drug	212	23.1	1621	20.5	nd		nd	
Serious adverse events reported at least once	185	20.1	1878	23.7	33	42.8	111	46.8
attributed to drug	16	1.7	150	1.9	nd		nd	
Deaths and events with death as outcome during or after the end of treatment	162	17.6	1621	20.5	23	30.0	73	30.9
Deaths and events with death as outcome during or after the end of treatment attributed to drug	0		0		2	2.6	2	0.8

[a] The number of deaths and patients with events leading to death is also included. Two studies from the literature employing the same dose are provided for comparison where the data are available. nd, not done.
[b] Only the 100-mg dose group.

Table 2
Incidence of the most frequently observed (≥ 2%) adverse events during treatment with riluzole (100 mg/day); patients at German centres and all study participants[a]

Adverse event (COSTART coding)	Patients at German centres (n=919)		Patients worldwide (n=7916)		Bensimon et al. [1] (n=77))		Lacomblez et al. [2] (n=236[b])	
	No.	%	No.	%	No.	%	No.	%
Reduced lung function	67	7.3	511	6.5	30[c]	39.0	32	13.6
Nausea	65	7.1	554	7.0	3	3.9	49	20.8
Asthenia	53	5.8	534	6.7	20	26.0	42	17.8
Abdominal pain	23	2.5	186	2.3	3	3.9	13	5.5
Pneumonia	23	2.5	151	1.9	1	1.3	11	4.7
Dysphagia	22	2.4	417	5.3	6	7.8	46	19.5
Dizziness	22	2.4	136	1.7	1	1.3	11	4.7
Dyspnea	19	2.1	170	2.1	1	1.3	13	5.5
Apnea	18	2.0	235	3.0	0		25	10.6

[a] Two studies from the literature employing the same dose are provided for comparison.
[b] Only the 100-mg dose group.
[c] Preferred term=respiratory disorders.

enzymes were reversible and did not result in death in any case.

At the German centres the ALT concentrations of 39 out of 919 patients (4.2%) were found to be greater than 3 times the upper reference limit at least once during the course of the study. They increased to over 5 times the upper reference limit in 12 (1.3%) of these patients. Increases in AST levels to higher than 3 times the normal

Table 3
Number of patients with transaminase concentrations greater than 3 or 5 times the upper reference limit during at least one visit after the start of treatment with riluzole (100 mg/day)

Increase in transaminase(s)	Patients at German centres		Patients worldwide	
	n	%	n	%
ALT	919	100	7804	100
Rise to more than 3× the upper reference limit	39	4.2	287	3.7
Rise to more than 5× the upper reference limit	12	1.3	55	0.7
AST	919	100	7843	100
Rise to more than 3× the upper reference limit	8	0.9	92	1.2
Rise to more than 5× the upper reference limit	2	0.2	19	0.2

range occurred in eight of the 919 patients (0.9%), two of whom (0.2%) had rises in AST to over 5 times the upper reference limit.

In the majority of patients hematological parameters remained within the normal range during treatment. In some patients reduced levels of white blood cells, hemoglobin, hematocrit, platelets or red blood cells were found during the course of the treatment which had generally already been diminished before the start of the study. In isolated patients, values that had previously been normal fell below the normal range during treatment. Three patients (0.05%) — one in Belgium and two in France — had severe neutropenia (<0.5 Giga/l) during the first 3 months of treatment. In all three cases the values returned to normal following withdrawal of the study medication.

4. Discussion

The results of this study in a very large number of ALS patients show riluzole to be very well tolerated. Most of the adverse events observed were attributable to the underlying disease, especially to deteriorations in lung function, not to riluzole. The overall incidence of adverse events in this multinational study was distinctly lower than that shown by the safety results of previous controlled riluzole studies [1,2]. Moreover, no new, previously unknown events were observed. Overall, the safety profile of riluzole in patients treated at the German centres differed only negligibly from the results for the study as a whole.

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