Riluzole and amyotrophic lateral sclerosis survival: a population-based study in southern Italy

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Riluzole is to date the only treatment that prolongs amyotrophic lateral sclerosis (ALS) survival. However, results on the efficacy of riluzole in observational population-based studies with a longer follow-up are conflicting and it is still unclear if the effect of the drug is limited to an early stage of the disease and to some specific subgroups of patients. The objective is: (i) to evaluate the effect of riluzole on ALS survival in a cohort of incident cases; (ii) to examine whether bulbar-ALS benefits from the medication to a greater extent and (iii) to assess the efficacy of the drug in elderly patients. Source of the study was a prospective population-based registry of ALS established in Puglia, Southern Italy. We examined survival of 126/130 incident ALS cases diagnosed during the period 1998–1999. Seventy-three patients were prescribed riluzole and the remaining 53 were not. Riluzole therapy increased survival rates at 12 months by approximately 10% and prolonged survival by 6 months (18.2 months vs. 12.4; peto-test: 2.78; $P = 0.09$). This beneficial effect was present amongst bulbar-onset ALS (peto-test: 4.11; $P = 0.042$), but not in subjects with limb-onset (peto-test: 0.48; $P = 0.4$). In patients aged >70 years riluzole treatment was associated with an 8 months longer median survival time [15.4 months vs. 7.1] and a reduction in mortality rate at 12 months by 27%, regardless of site of symptoms onset. In multivariate analysis, riluzole use was an independent predictor of survival at 12 months from the diagnosis with borderline significance ($P = 0.06$). Riluzole was effective amongst cases with bulbar-onset ALS ($P = 0.04$), whereas in subjects with limb-onset there was no effect on survival at 12 months ($P = 0.5$). In each model riluzole did not influence survival at 24 months. Conversely, riluzole use was associated with an improvement in survival amongst elderly patients both at 12 ($P = 0.07$), at 24 months ($P = 0.03$) and in the entire follow-up period ($P < 0.04$). In this population-based series, we found that riluzole therapy improves ALS survival. The efficacy of the drug was present amongst bulbar-onset ALS and older patients, but not in subjects with limb-onset. The favourable effect of the drug was transient, as it was lost in prolonged follow-up. Our observations support the use of riluzole at an early stage of ALS in bulbar and elderly patients. However, the appropriate duration of riluzole treatment remains to be established.

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative motor-neuron disorder of unknown origin, with no effective cure; the progression is rapidly progressive, leading to death within 3–5 years [1]. Riluzole is currently the only drug capable to improve survival of ALS patients, as evidenced by two randomized trials. 2,3].

Several issues regarding riluzole remain undetermined. First, is riluzole truly effective in increasing survival of ALS patients? Data from two population-based studies of ALS in Europe showed that riluzole was an independent predictor of survival [4] and that riluzole prolonged survival by at least 4 months [5]. These findings are in contrast to two other longitudinal population-based studies that showed a trend towards shorter or unchanged survival in the last decade, despite the introduction of riluzole, percutaneous endoscopic

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gastrostomy (PEG) and non-invasive ventilation (NIV) [6,7].

The second issue surrounding riluzole is the appropriate duration of the treatment. Two studies [5,8] have shown that the drug is ineffective in advanced ALS, suggesting that the medication should be started as early as possible and discontinued in the late stages of disease. This is in direct contrast to the AAN guidelines for riluzole [9] which state that the medication should only be prescribed for patients with probable or definite ALS by El Escorial criteria (EEC).

Finally, it is unclear whether specific subgroups of ALS patients benefit more from riluzole administration. A greater efficacy of riluzole on patients with bulbar-ALS was noted in the first clinical trial of riluzole ($n = 155$) [2,5], but this finding was not replicated in the larger subsequent placebo-controlled trial ($n = 959$) [3]. Interestingly, a recent observational study again found that riluzole was particularly effective in bulbar-onset patients, prolonging survival [5]. The effectiveness of riluzole in older patients is not well defined. Patients 75 years and older have been included in only one randomized clinical trial [8] which did not detect any difference in survival between the treatment groups.

The aim of the present study was three fold: (i) to evaluate the effect of riluzole on survival in a cohort of ALS incident cases from a population-based study conducted in Southern Italy and to eventually determine the appropriate duration of treatment, (ii) to examine whether riluzole is more effective in bulbar ALS and (iii) to assess if the drug exerts beneficial effects in elderly patients.

Material and methods

A prospective ALS registry, established in Puglia, Southern Italy, in 1997, was the source of cases for this study [10]. The surveillance began on January 1, 1998. The registry has several sources of information that have been described elsewhere [10].

The diagnosis of ALS was based on EEC [11] and their Airlie-House revised version of 1998 (AHC) [12]. Riluzole is provided free of charge to Italian ALS patients provided it is prescribed by a neurologist working within the National Health system. All patients with ALS diagnosis are eligible for riluzole treatment in Italy.

Using this multisource registry, we identified all newly diagnosed ALS cases resident in Puglia in the 2-year period 1998–1999. All cases were routinely followed-up during the course of their illness on average every 6 months by direct examination or by telephone. Data was collected on the medications and treatments provided to patients (e.g. riluzole, NIPV, PEG, tracheostomy). Date and cause of death was recorded and death certificates were obtained from the National Death Data Base Registry. Date of last follow-up for this study was 30 June 2004. Death status was checked at censoring date for all patients in the study.

Statistical analysis

All patients gave informed consent to participation in the study; data were stored in a centralized database with separate anonymous files. Comparison of demographic features between cohorts employed either Mann–Whitney, *t*-test or chi-squared test. Survival curves were estimated by Kaplan–Meier method and differences in survival were measured by Peto and log-rank tests. Survival interval is from time of diagnosis. Peto test was used to emphasize the information on differences at the beginning of survival curves [13]. Multivariate analyses of the risk for death associated with selected independent variables were performed using the Cox proportional hazard model. An intention to treat analysis was employed.

Results

During the 2-year study-period we identified 130 patients (81 males, 49 females); data concerning riluzole prescription were missing for four patients (3%). Of the remaining 126 patients, 73 (58%) were prescribed riluzole on at least one occasion and 53 (42%) did not receive riluzole at any stage of the illness. The choice for treatment was made by the neurologist member of the registry, with informed consent by the patient. No patient refused the treatment. In addition, no treatment withdrawal was referred during the entire follow-up period.

Demographic and clinical variables were similar amongst patients receiving and not receiving riluzole (Table 1). Riluzole could have been prescribed based on progression of the disease. We measured progression of the disease with the onset-diagnosis interval (ODI), that were similar in the two groups. (Fig. 1; chi square, 2.4; $P = 0.6$). Only a small percentage of our patients underwent PEG (6%) or NIV (2.5%; Table 1). PEG was generally initiated after 26 months in this group, much later than riluzole prescription.

Univariate analysis

Median survival time from diagnosis was 5.8 months longer amongst patients prescribed riluzole compared with patients that did not receive riluzole (18.2 months vs. 12.4). Riluzole administration reduced mortality rate at 6 and 12 months by 8.3% (6.8% vs. 15.1%) and 11.6% (20.5% vs. 32.1%; Peto, 2.78; $P = 0.09$; log-rank, 0.08; $P = 0.78$) respectively. At 18 months from

Table 1 Clinical features at diagnosis of riluzole and non-riluzole cohorts

Variable	Patients prescribed Riluzole ($n = 73$)	Patients not prescribed Riluzole ($n = 53$)
Median Age (range)	64.3 years (32–80.2)	66 years (19–80) Mann–Whitney, 0.002; $P = 0.9$
Gender (M/F)	43/30	35/18 Chi-square, 0.4; $P = 0.5$
Bulbar-onset	20 (27%)	13 (25%) Chi-square, 0.02; $P = 0.9$
Spinal-onset	53 (73%)	40 (75%) Chi-square, 0.02; $P = 0.9$
Time to diagnosis (range)	8.6 months (1–70.7)	10 months (1.2–52) *t*-test, 0.5; $P = 0.6$
Median survival time from the diagnosis (range)	18.3 months (1.8–48)	12.4 months (0.3–50) *t*-test, 1.4; $P = 0.2$
Possible + suspected ALS	31 (42%)	23 (43%) Chi-square, 0.06; $P = 0.9$
Probable + definite ALS	42 (58%)	30 (57%) Chi-square, 0.06; $P = 0.9$
NIV	3 (4%)	0 Chi-square, 0.8; $P = 0.1$
PEG	7 (10%)	1 (2%) Chi-square, 1.9; $P = 0.08$

NIV, non-invasive ventilation; PEG, percutaneous endoscopic gastrostomy; ALS, amyotrophic lateral sclerosis.

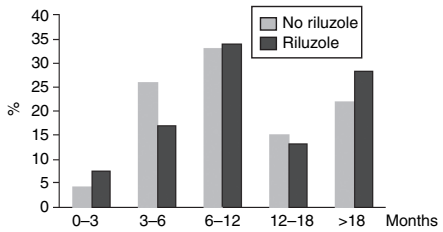

Figure 1 Histogram of onset–diagnosis interval distribution between amyotrophic lateral sclerosis patients treated with riluzole and untreated patients in Puglia ($n = 126$; chi-square, 2.4; $P = 0.6$).

the diagnosis mortality rate was 4.6% lower amongst the treated group. After the 18 month time point, there was no difference in mortality rates between the two groups (Fig. 2).

Patients with bulbar-onset disease ($n = 33$) benefited more from riluzole administration than patients whose symptoms started in the limbs. Riluzole prescription was associated with an 8 months longer median survival time amongst bulbar-onset ALS [17.1 months (range: 3.7–36.7) compared with 9.2 months (2.9–28.5)]. Mortality rates at 6 and 12 months were 5% (1/20) and 25% (5/20) in bulbar-onset ALS patients receiving riluzole, compared with the 31% (4/13; peto-test:4.11; $P = 0.04$; log-rank test, 1.1; $P = 0.29$) and 54% (7/13) of the non-treated group. This effect was lost after 18 months of follow-up (Fig. 2). There was no difference in median survival amongst limb-onset ALS patients receiving and not receiving riluzole. Demographics and clinical characteristics were similar amongst bulbar-onset receiving and not receiving riluzole (data not shown).

Riluzole had a beneficial effect on prognosis amongst Italian ALS patients aged > 70 years ($n = 34$). Median survival was prolonged by 8.3 months (15.4 months vs. 7.1 months) and 12 month mortality rate was slightly but not significantly decreased [57% (8/14) vs. 30% (6/20); peto = 0.33; $P = 0.5$; log-rank, 0.78; $P = 0.33$]. The beneficial effect of riluzole was present in elderly patients regardless of site of symptom onset. In patients who took riluzole this favourable effect was evidenced even when considering only limb-onset cases. Median survival amongst limb-onset cases >70 years taking riluzole was 18 months (1.8–22.6) compared with 8 months (1–12.5) amongst the same demographic not taking riluzole.

Riluzole did not have a beneficial effect on prognosis amongst patients with a rapidly progressive disease course or with a limited spread onset of the disease. Amongst the rapidly progressive subgroup (whose ODI was ≤ 6 months; $n = 91$), there was no difference in

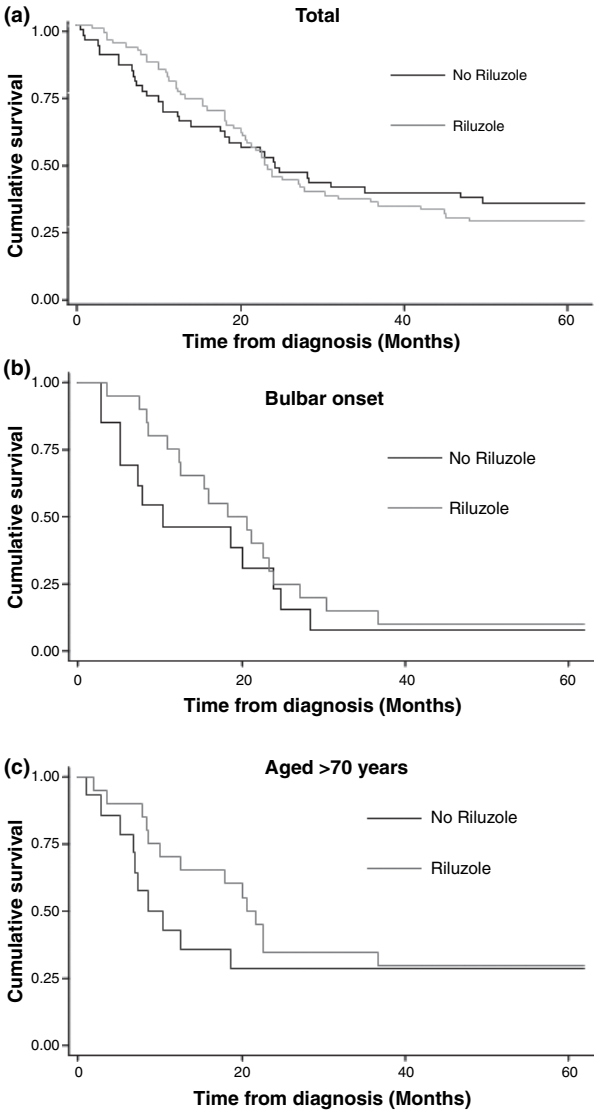

Figure 2 Kaplan–Meier survival curves from diagnosis for amyotrophic lateral sclerosis cases diagnosed in Puglia in 1998–1999, stratified according to riluzole use. Subtitles for the three graphs are as follows: (a) entire case series ($n = 126$; log-rank: 0.08; $P = 0.78$; peto: 2.78; $P = 0.09$); (b) bulbar onset cases ($n = 33$; log-rank: 1.1; $P = 0.29$; peto: 4.11; $P = 0.04$); (c) patients aged >70 ($n = 34$; log-rank: 0.78; $P = 0.37$; peto: 0.33; $P = 0.5$).

survival between patients treated and not-treated with riluzole [20.5 months (1.8–32; $n = 22$) vs. 18.8 (14–31; $n = 13$; log-rank, 0.07; $P = 0.8$)]. Finally, in patients with suspect and possible ALS by EEC ($n = 54$) survival rates at 12 months (78.1% vs. 73.9%) and median survival time were similar in the two groups (18.2 months vs. 16.3; log-rank, 1.5; $P = 0.2$).

Finally, as patients prescribed riluzole had more interventions, we examined the contribution on survival of more active interventions by ALS multidisciplinary clinics in our territory area. Despite a higher percentage of patients prescribed riluzole in the multidisciplinary clinics cohort than in the general neurology cohort (66% vs. 43%), we found no difference in median survival times of ALS patients attending ALS multidisciplinary clinics ($n = 84$) compared with those attending general neurology clinics ($n = 42$; 17.6 vs. 18 months; log-rank $= 0.11$; $P = 0.76$).

Multivariate analysis

Cox proportional model showed that riluzole use was a predictor of favourable survival at 12 months from the diagnosis in the entire case series with slight significance (HR: 0.51; 95%CI: 0.25–1.03; $P = 0.06$), after adjustment for age, gender, site of symptoms onset and ODI. This effect was stronger amongst bulbar-onset ALS, after adjustment for age and ODI (HR: 0.26; 95%CI: 0.07–0.92; $P = 0.04$); conversely, subjects with limb-onset treated with riluzole did not present favourable effects on survival at 12 months (HR adjusted for age and ODI: 0.72; 95%CI: 0.30–1.74; $P = 0.5$). In each model the positive effect of riluzole on survival was lost after 24 months.

Multivariate model revealed that riluzole use was associated with an improvement in survival even amongst elderly patients after adjustment for age, gender, site of onset and ODI both at 12 months (HR: 0.33; 95%CI: 0.1–1.07; $P = 0.07$), at 24 months (HR: 0.36; 95%CI: 0.1–0.92; $P = 0.03$) and in the entire follow-up period (HR: 0.36; 95%CI: 0.1–0.93; $P < 0.04$).

Discussion

In this population-based incident study riluzole treatment was associated with a 10% reduction in mortality at 1 year, corresponding to an increase in survival of 6 months. The beneficial effect of the drug was transient, as it was lost after 24 months of follow-up.

Although we did not find differences in survival with log-rank test, a trend towards improvement in survival was detected with peto-test, which emphasizes early survival. This observation is in contrast to a previous retrospecitve study [14], but consistent with the result of the Irish study [5] and may be related to the transient effect of the drug. In the retrospective clinical-based study [14], a stronger effect of riluzole was found but the subjects in the study were younger and the median survival time was longer (approximately 40 months) than in our cohort.

The improvement in ALS survival was most marked amongst patients with bulbar-onset of symptoms (8 months), whereas no significant effect was present

amongst patients with limb-onset. We found that riluzole administration is effective in prolonging survival amongst older patients, regardless of site of symptom onset. This is, to our knowledge, the first observational study to show an effect of riluzole amongst the elderly.

The ability of retrospective observational studies, such as the current study, in assessing drug efficacy is limited compared with double-blind, placebo-controlled clinical trials. The most important limitation of an observational study is the lack of control for unknown prognostic factors that can be differentially distributed in the treatment and non-treatment cohorts [15,16]; however, imbalances between treatment groups for important risk factors as age are not infrequent even in placebo-controlled double-blind trials [8]. Moreover, in our study, the two groups were similar in all measured clinical and demographic characteristics with prognostic value (age at onset and diagnosis, gender, site of symptom onset, ODI, classification according to EEC and AHC).

As in other studies [15], we had no data on vital capacity (VC); however the role of VC as prognostic indicator remains uncertain; some studies [17] found that VC at baseline is a predictor of survival, whilst others [18] did not. VC has some limitations as a measure for predicting respiratory failure in clinical practice, especially in bulbar-ALS and cases with more severe illness [19].

Furthermore, no differences were found in median survival times of patients who attended ALS multidisciplinary clinics compared with patients followed-up by general neurology clinics in this area only few patients underwent PEG or NIV and only in the latest stage of their illness. Finally, a placebo effect cannot be excluded, as both the patients and the physicians were unblinded. However, this seems implausible because survival was used as a measure of treatment efficacy.

The main strength of the population-based observational studies is that they are characterized by a broader range of clinical phenotypes compared with the selected subjects included in clinical trials in ALS tertiary centres. The findings are more probably to be representative of the drug's effectiveness in every day clinical practice, as subjects are more probably to reflect the management of ALS. Moreover, clinical trials are characterized by a short period of follow-up (18 months) compared with observational studies (5 years). This aspect of study design is important in the case of riluzole, as the beneficial effects of the medication appear to be lost after 18 months. Consistent with this hypothesis is a recent study carried out in a sample of long survival ALS (more than 10 years) from the King's Database [18] that found that only a few of the ALS long survivors received any interventions.

Our results of a favourable but transient effect of riluzole on ALS survival are similar to placebo-controlled trials [1,2] and to a population-based study in Ireland [5]. The lack of effect in the later stage of the disease (after 18 months) in our study is also consistent with the negative results of a randomized clinical trial carried out in ALS patients with advanced disease [8]. A study on transgenic rats demonstrated that the deficit in glutamate uptake becomes more severe by end-stage of the disease and is probably to be the cause for the loss of efficacy of the drug in advanced ALS [20].

In our case series, patients with bulbar-onset ALS benefit more from riluzole than patients with limb-onset disease. This observation has been previously reported [2,5]. and has been related to the shorter ODI of bulbar-ALS [4,5] and the earlier start of the drug, when the spread of motorneuron degeneration is limited; however, when we looked at cases characterized by a short ODI ($\leq$ 6 months) and limited spread of signs (restricting the analysis to possible and suspected cases), we did not find difference in survival, suggesting that neither of these two factors could explain the selective benefit of riluzole for bulbar-ALS; confirming these data, multivariate analysis revealed that the effect of riluzole was independent of ODI. An overall difference in glutamate uptake in different areas of the brain could explain the better efficacy of riluzole in bulbar-onset cases, characterized by less extensive deficit of glutamate transport capacity, compared with spinalonset cases [20].

Our study demonstrated that riluzole administration in patients $>$ 70 years associated with a 30% increase in survival at 12 months and an 8 months longer survival, regardless of site of symptoms onset. Despite the lack of significant effect of the drug on survival on univariate analysis, we observed a favourable effect of the drug on survival on multivariate analysis, after removing a possible confounding effect of gender, site of symptoms onset and ODI. These results indicate that riluzole exerts beneficial effects in older ALS patients.

The main limitation of our study, as in most ALS population-based studies, was the limited sample size that could have hampered the power of our analysis in some subgroups. Finally, we analysed the data with the intention to treat approach whilst compliance and duration of treatment were not considered.

In conclusion, even if randomized clinical trial is the unique gold standard for the evaluation of treatment, observational cohort studies like ours can give additional information about the use of riluzole in clinical practice. Our study supports the use of riluzole in the early stages of ALS because it improves surviv-

orship for a limited period of time. Bulbar-onset cases and elderly patients both experience significant benefits from therapy. Further studies are needed to establish if the interruption of riluzole should eventually be considered 2 years after the diagnosis.

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Appendix: Sclerosi Laterale Amiotrofica-Puglia (SLAP Registry)

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