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SHORT REPORT

Stage-specific riluzole effect in amyotrophic lateral sclerosis: a retrospective study

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Abstract

Objectives: To estimate the effect of riluzole on the stage-specific risk of progression of ALS. *Methods*: Patients from the PRO-ACT dataset were staged employing two methods (King's and FT9). Hazard ratios associated with riluzole treatment were estimated for forward transition between stages, using unadjusted and adjusted Markov multistate models. *Results*: Of 1903 patients, 1587 had received riluzole. Riluzole-treated patients survived non-significantly longer than those who did not (median 22.9 months vs. 18.3 months from time of initial observation, log rank $p = 0.16$). After adjusting for age and ALSFRS-R slope at first visit, riluzole significantly reduced risk of the following transitions: (1) King's stages: 1->2 (hazard ratio (HR) = 0.81), and 2->3 (HR = 0.82), 4->death (HR = 0.57), and (2) FT9 stages: 1->2 (HR = 0.84), 3->4 (HR = 0.71), and 4->death (HR = 0.67). In contrast, the beneficial effect of riluzole in bulbar-onset patients was in early rather than late King's stages. *Conclusions*: This examination of cohorts closely followed in clinical trials finds a beneficial effect of riluzole that is predominantly but not exclusively in later stages of ALS. This analytic framework has utility to discern stage-specific treatment effects, and for refined health economic analyses.

Keywords: *Survival*, *prognostic*, *therapy*, *clinical trials*

Introduction

Observational and population-based studies confirm the survival benefit of riluzole originally demonstrated in randomized controlled trials (1–3). A recent re-analysis of original trial data employing King's staging (4) found that the survival benefit of the medication was exclusively through preventing death in advanced ALS (stage 4, patients already receiving or requiring noninvasive ventilation and/or gastric tube). Given relevance to clinical practice and health economic studies, it is desirable to revisit the question of the stage-specific effect of riluzole employing newer data, a different methodology and another staging approach. We report an analysis of riluzole effect in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database using Markov models, employing two staging methods (King's and Fine'til 9, or FT9). We were fortunate in finding an excellent balance between treated and non-treated subjects in regards to prognostic variables.

Methods

Data used in the preparation of this article were obtained from the PRO-ACT Database. In 2011, Prize4Life and Neurological Clinical Research Institute at Massachusetts General Hospital, in collaboration with the Northeast ALS Consortium, and with funding from the ALS Therapy Alliance, formed the PRO-ACT Consortium, whose members volunteered the data available in the PRO-ACT Database (5). The FT9 staging framework and Markov multistate modeling of ALS stages are

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Table 1. Characteristics of the cohort by treatment status.

	Riluzole (–) non-treated	Riluzole (+) treated	*p*-value
Number of patients, *n* (%)	316 (16.6%)	1587 (83.4%)	
Age (years) mean ± SD	56.1 ± 12.1	55.8 ± 11.4	0.61 NS
Female, *n* (%)	115 (36.4)	556 (35.0)	0.69 NS
Bulbar onset, *n* (%)	63 (19.9)	316 (19.9)	1.00 NS
Months from onset mean ± SD	20.5 ± 12.1	18.2 ± 9.6	<0.01
Pre-slope (points/month) mean ± SD	−0.61 ± 0.56	−0.64 ± 0.48	0.52 NS
Initial ALSFRS-R mean ± SD	38.7 ± 5.0	38.4 ± 5.3	0.43 NS
Bulbar SS	10.3	10.4	0.51 NS
Fine motor SS	9.0	8.5	<0.001
Gross motor SS	8.0	8.1	0.53 NS
Respiratory SS	11.4	11.5	0.46 NS
Initial King's stage, *n*			0.65 NS
(bulbar-onset in parentheses)			(0.15 NS bulbar)
King's 1	84 (15)	473 (110)	
King's 2	126 (26)	585 (89)	
King's 3	93 (15)	460 (87)	
King's 4	13 (7)	69 (30)	
Initial FT9 stage, *n*			0.76 NS
(bulbar-onset in parentheses)			(<0.05$ bulbar)
FT9 0	31 (4)	160 (41)	
FT9 1	128 (34)	611 (153)	
FT9 2	122 (20)	605 (56)	
FT9 3	29 (4)	185 (57)	
FT9 4	6 (1)	26 (9)	

Continuous and categorical variables compared using t test and Pearson's chi-squared test respectively ($Fisher's exact test used for testing significance). SD: standard deviation. NS: not significant.

described previously (6). FT9 counts the number of the revised ALS functional rating scale (ALSFRS-R) (7) subscores that are 9 or less. In addition to survival estimation, we conducted four analyses to examine stage-specific riluzole effect: (1) Unadjusted, (2) Adjusted for age and tertile of slope of ALSFRS-R at first visit (pre-slope), a powerful prognostic factor (3,8), Adjusted and stratified by site of onset (bulbar or extremity), and (4) Adjusted also for time from onset to enrollment. Significance threshold was set throughout at $p < 0.05$. R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) with additional packages (survival and msm) was used for analysis.

Results

Of 1903 patients who met inclusion criteria (age, onset date and riluzole exposure known, ALSFRS-R subscores measured at least twice), 1587 (83.4%) had received riluzole. Treated and non-treated patients were balanced for most prognostically important baseline features and disease stage (Table 1). Mean (±SD) follow-up was 10.9 (± 4.6) months during which 10.2 (± 4.3) ALSFRS-R measures were recorded per patient (19,445 total records). Median survival from first observation was 18.3 months (95% CI 16.2 to 23.5 months, 67 deaths) for non-treated patients and 22.9 months (95% CI 21.2 to 26.1 months, 276 deaths) for treated patients (log rank $p = 0.16$, Figure 1(A)). Figures 1(B,C) depict estimated stage-to-stage transition rates by treatment allocation, and HRs with riluzole, respectively. In unadjusted and adjusted models, riluzole had a greater effect on reducing hazard of death in stage 4 than on reducing the rate of earlier transitions by both staging systems. Among bulbar-onset patients, however, riluzole benefit occurred in earlier King's transitions but not in the transition from stage 4 to death. In unadjusted models, estimated stage durations in months for riluzole treated vs. non-treated patients were as follows: King's stages 1 (7.0 vs. 5.7), 2 (8.4 vs. 8.5), 3 (11.8 vs. 11.3), and 4 (17.1 vs. 12.7). FT9 stages 0 (3.4 vs. 3.2), 1 (7.5 vs. 6.0), 2 (11.9 vs. 11.5), 3 (11.9 vs. 8.8), and 4 (10.3 vs. 7.8).

Discussion

Employing two staging methods (King's and FT9), we confirm recent findings of riluzole benefit predominantly in advanced ALS (4), although with additional weaker effects in earlier stages (9). This inference is sensitive to staging method, not replicated with MITOS and other staging frameworks skewed towards advanced disease (9,10). Interestingly, by King's staging, riluzole benefit in bulbar-onset patients was early rather than late-stage.

Limitations of this study include non-randomized and unequal allocation, selection bias and heterogeneity from participation in diverse clinical trials, and possible confounding by other treatments (such as noninvasive ventilation) of which riluzole-treated patients may be more accepting.

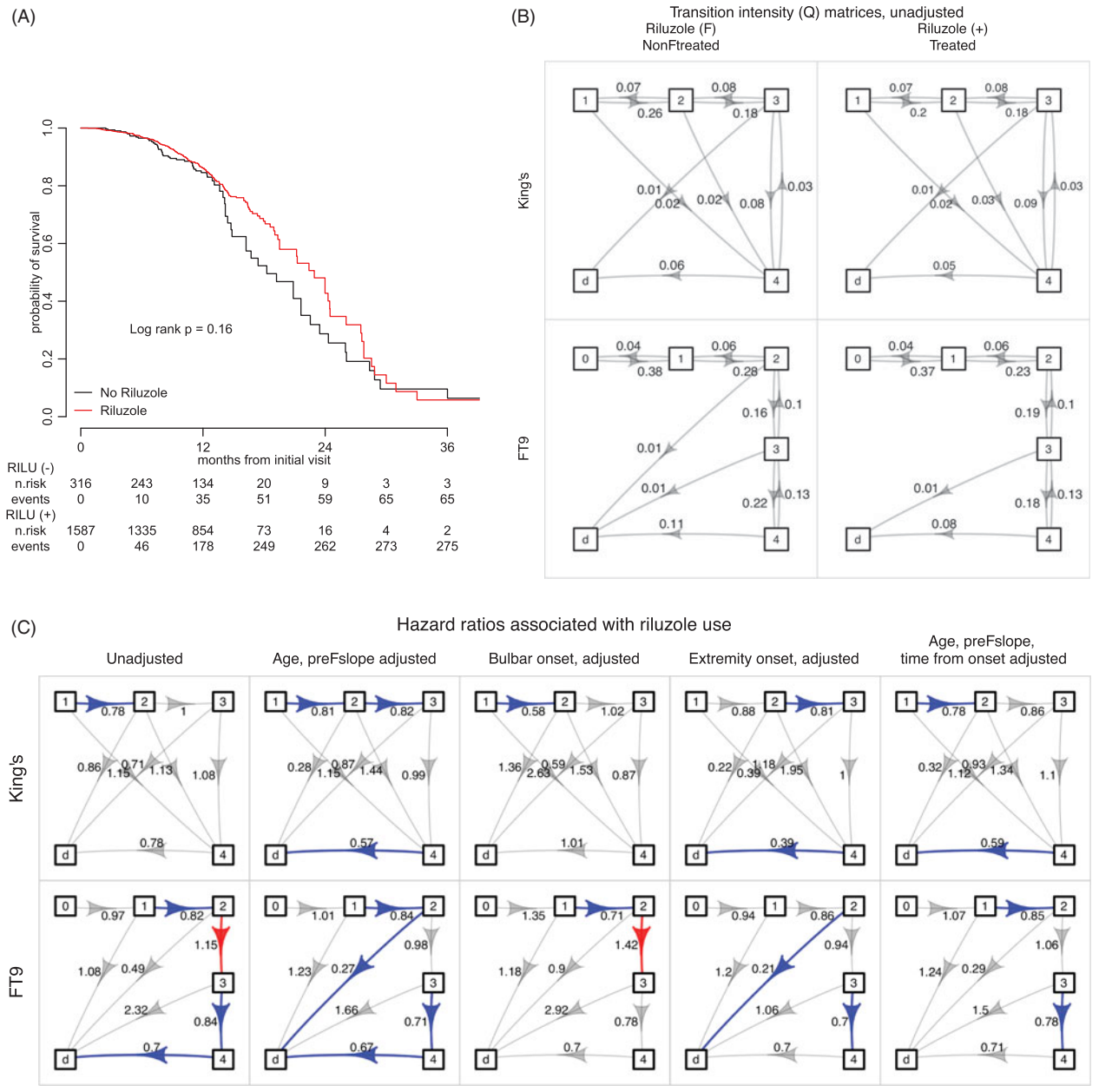

Figure 1. (A) Kaplan–Meier survival estimates of patients treated and not treated with riluzole. The median survival difference of 4.67 months was not significant. (B) Directed acyclic graphs depict transition intensity matrices (Q matrices) for King's and Fine'til 9 (FT9) staging systems without and with riluzole treatment (unadjusted). Numbers represent momentary risk of transitioning from stage to stage, expressed in units of transitions per month. Reverse arrows do not represent true reversal, rather allow for misclassification. Values rounded to <0.01 are omitted. Non-sequential transitions to King's stage 4 (needing gastric tube or noninvasive ventilation) were permitted, whereas non-sequential transitions were not permitted with FT9 staging except to death. Simulations driven by these Q matrices recapitulate observed survival in ALS (King's: untreated median survival from stage 1 31.1 months, 5-year survival 17.4%, riluzole-treated median survival from stage 1 36.0 months, 5-year survival 24.3%. FT9: untreated median survival from stage 0 30.8 months, 5-year survival 15.9%, riluzole-treated median survival from stage 0 36.9 months, 5-year survival 24.2%.). (C) Directed acyclic graphs depict effects of riluzole on different transitions. Rows 1 and 2 are for King's and FT9 systems. Columns 1 to 5 represent (1) unadjusted, (2) age- and pre-slope-tertile-adjusted, (3) and (4) adjusted and stratified by onset site, and (5) unconstrained age, pre-slope (square root transformed), and time from onset to enrollment (log transformed) adjusted models. Numbers represent hazard ratio (HR) point estimates associated with riluzole use for each transition. Bold arrow lines indicate significant HR values ($p < 0.05$), whereas gray arrow lines indicate non-significant HR values. Transition intensities with treatment (panel B, right column) are obtained by multiplying untreated forward transition intensities (panel B, left column) with corresponding unadjusted HRs from panel C, column 1.

Additionally, stage distribution imbalance among bulbar-onset patients may have biased the bulbar-specific inference noted above. Strengths of this study are the number of repeated measures, excellent balance of prognostic covariates between arms, use of comprehensive methodology that allows for competing/non-sequential transitions and panel data (exact transition time unknown), and absence of consistent stage-specific effect by allocation to investigational drug vs. placebo in

participating clinical trials (data not presented). Furthermore, our study provides a proof-of-concept for (i) utilizing Markov models to dissect out stage-specific treatment effects and (ii) FT9 staging. Transition rate matrices presented here (Figure 1(B)) have direct application in more granular health economic studies.

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Author contributions

NJT conceptualized the study, conducted the statistical analysis, interpreted the data, and prepared the initial manuscript. EPP and BRL interpreted the data and critically revised the manuscript for important intellectual content. All authors contributed equally to the approval of the final manuscript. Members of the PRO-ACT Consortium contributed to the design and implementation of the PRO-ACT Database and/or provided data, but did not participate in the analysis of the data or the writing of this report.

Declaration of interest

This study was not supported by any external or internal grant. There are no competing interests. Dr. Thakore reports grants from Novartis Pharmaceuticals Corporation, outside the submitted work. Dr. Lapin has nothing to disclose. Dr. Pioro reports grants from ALS Association and CDC/NIH, as well as personal fees from Avanir Pharmaceuticals, Inc., Biohaven Pharmaceuticals, Cytokinetics, Inc., ITF Pharma, Inc., MT Pharma America, Inc., and Otsuka America, Inc., outside the submitted work.

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