SUPPLEMENTARY MATERIAL

Effect of tauroursodeoxycholic acid on survival and safety in amyotrophic lateral sclerosis: a retrospective population-based cohort study

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Supplementary Table 1: Demographic and clinical characteristics of patient population (before matching) (N = 627)

Characteristics	**Oral TUDCA treatment**		**p-value**
	Yes N=86 n (%) m [SD]	**No N=541 n (%) m [SD]**	
Sex, male	64 (74·4)	297 (54·9)	**0·0006**
Age at onset, years	58·2 [9·3]	67·0 [11·4]	**< 0·0001**
Diagnostic delay, months	11·9 [10·2]	13·4 [11·3]	0·25
Site of onset			0·15
Bulbar	19 (22·1)	187 (34·6)	
Upper limb	35 (40·7)	166 (30·7)	
Lower limb	31 (36·0)	178 (32·9)	
Respiratory	1 (1·2)	10 (1·8)	
Phenotype			0·45
Bulbar	18 (20·9)	180 (33·3)	
Classic	52 (60·5)	269 (49·7)	
Flail arm and leg	12 (14·0)	48 (8·9)	
UMNp	3 (3·5)	35 (6·5)	
Respiratory	1 (1·2)	9 (1·7)	
Revised El Escorial criteria			0·12
Definite	22 (25·6)	181 (33·4)	
Clinically probable	28 (32·6)	173 (32·0)	
Probable lab-supported	16 (18·6)	74 (13·7)	
Possible	19 (22·1)	100 (18·5)	
Dementia at diagnosis	6 (7·0)	46 (8·5)	0·63
BMI at diagnosis (Kg/m²)	24·7 [3·7]	24·1 [3·9]	0·18
ALSFRS-R at diagnosis	41·8 [5·0]	38·5 (6·9)	**< 0·0001**
Disease progression rate (points/month) measured at diagnosis	0·62 [0·65]	1·1 (1·5)	**0·0034**
FVC at diagnosis, mean [SD]	86·4 [24·9]	92·9 [23·9]	0·12
MiToS stage at diagnosis	0·19 [0·58]	0·32 [0·77]	0·11
King's stage at diagnosis	1·55 [0·81]	2·01 [0·98]	**< 0·0001**
Riluzole treatment	82 (95·4)	477 (88·2)	0·047

SD: Standard Deviation; UMN-P: Upper Motor Neuron predominant; BMI: Body Mass Index; ALSFRS-R: ALS Functional Rating Scale – Revised.

Based on the nature of the clinical variable under investigation, the homogeneity between cases and controls was assessed by Student's T test or chi-square test. The resulting p-values are representative of good homogeneity of clinical features among tested groups.

Supplementary Table 2: Standardized mean differences after propensity score matching. Demographic and clinical characteristics of TUDCA-treated and non-TUDCA-treated patients with ALS after propensity score matching are reported in Table 1.

Clinical features	SMD
Sex, male	0·040
Months from onset to diagnosis, mean	0·036
Age at onset, mean	0·005
Phenotype	0·025
BMI at diagnosis, mean	0·071
ALSFRS-r at diagnosis, mean	0·022
Disease progression rate at diagnosis, mean	0·035
FVC at diagnosis, mean	0·025

BMI: Body Mass Index; ALSFRS-R: ALS Functional Rating Scale – Revised. FVC: Forced Vital Capacity.

Supplementary Table 3: Relevance of covariates included in Cox regression analyses as confounding factors on survival time.

Covariates	Hazard Ratio
	p-value
Survival Analyses (from onset to death/tracheotomy) performed on PSM cohort	
Level I: Survival: from onset to death/tracheotomy (treatment impact)	
• Patients treated with riluzole (n=234)	0·99
• Delay of TUDCA initiation from onset (n=86)	**0·0013**
• Delay of TUDCA initiation from diagnosis (n=86)	0·55
• FVC value at the baseline (n=125)	**0·0073**
Level II: Survival: from onset to death/tracheotomy (duration impact)	
• Patients treated with riluzole (n=234)	0·99
• Delay of TUDCA initiation from onset (n=86)	**< 0·0001**
• Delay of TUDCA initiation from diagnosis (n=86)	0·69
• FVC value at the baseline (n=125)	0·022
Level III: Survival: from onset to death/tracheotomy (dosage impact)	
• Patients treated with riluzole (n=234)	0·99
• Delay of TUDCA initiation from onset (n=86)	**0.0022**
• Delay of TUDCA initiation from diagnosis (n=86)	0.56
• FVC value at the baseline (n=125)	**0.0092**
Analyses performed on sub PSM cohort (excluding TUDCA < 1000 mg/day and their matched controls)	
Survival: from onset to death/tracheotomy (treatment impact)	
• Patients treated with riluzole (n=116)	0·99
• Delay of TUDCA initiation from onset (n=66)	**0·0062**
• Delay of TUDCA initiation from diagnosis (n=66)	0·22
• FVC[a] value at the baseline (n=64)	**0·015**

FVC: Forced Vital Capacity. The reported p-values estimate the relationship between selected covariates and survival probability. They were determined by using the same Cox regression model applied for estimating the Hazard Ratios of TUDCA treatment, duration and doses reported in Table 3.

Supplementary Table 4: Median survival and hazard ratio on patients' subgroups comparing high-dose TUDCA-treated patients and their propensity score-matched non-TUDCA-treated patients

Subgroups of patients	Survival	Hazard ratio		
	Median (CI)	*HR*	*95% CI*	*p-value*
Spinal patients not treated with TUDCA (n=103)	41·5 (33·1-50·5)	-	-	-
Spinal patients treated with TUDCA ≥1000 mg/day (n=54)	93·5 (43·1- 96·1)	0·44	0·26-0·76	**0·0029**
Bulbar patients not treated with TUDCA (n=29)	34·1 (22·4-44·2)	-	-	-
Bulbar patients treated with TUDCA ≥1000 mg/day (n=12)	31·8 (24·5- NA*)	0·81	0·26-2·49	0·71
Familial patients not treated with TUDCA (n=13)	30·5 (10·8- NA*)	-	-	-
Familial patients treated with TUDCA ≥1000 mg/day (n=7)	56·2 (20·3- NA*)	0·52	0·11-2·54)	0·42
C9ORF72 patients not treated with TUDCA (n=7)	11·4 (6·5-16·5)	-	-	-
C9ORF72 patients treated with TUDCA ≥1000 mg/day (n=5)	- (20·3- NA*)	0·13	0·15-1·16	0·068
Slow progressors not treated with TUDCA (n=50)	57·34 (41·6 - NA*)			
Slow progressors treated with ≥1000 mg/day (n=25)	96·2 (93·5-NA*)	0·17	0·05-0·60	**0·0065**
Intermediate progressors not treated with TUDCA (n=49)	41·6 (33·1-54·6)			
Intermediate progressors treated with ≥1000 mg/day (n=33)	43·0 (33·1-56·2)	0·90	0·45-1·76	0·75
Fast progressors not treated with TUDCA (n=33)	16·5 (13·0-19·9)			
Fast progressors treated with ≥1000 mg/day (n=8)	20·4 (3·9-NA*)	0·84	0·32-2·20	0·73
Intermediate and fast progressors not treated with TUDCA (n=82)	31·6 (23·8-38·6)			
Intermediate and fast progressors treated with ≥1000 mg/day (n=41)	41·7 (31·1-56·2)	0·58	0·34-0·98	**0·043**

NA: not available. CI: confidence interval. HR: Hazard Ratio. * the CI cannot be estimated because a low observations' size or a higher number of censored observations. Median survival times from Kaplan-Meier analyses and Hazard Ratio descriptors from univariable Cox regression analyses were reported, respectively. For analyses on progressor subgroups, the obtained results should be considered as suggestive of possible trends, due to possible biases because of the inhomogeneity of case/control groups due to their limited sample size as demonstrated by the Breslow-Day Test ($p<0.01$).

APPENDIX

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