Long term survival of participants in the mesenchymal stromal stem cells transplantation in amyotrophic lateral sclerosis.

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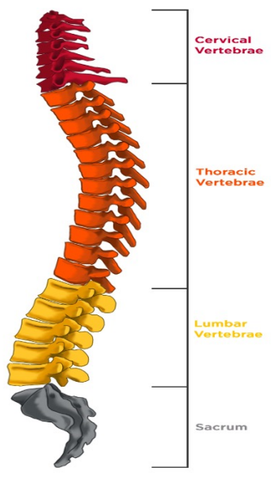
Background. Amyotrophic lateral sclerosis (ALS) is a fatal neurological disorder caused by motoneuron degeneration. No therapies can reverse the disease course. In recent years, cell-based therapies have generated interest as a potential treatment option. In this regard, **mesenchymal stem cells** (**MSCs**) are a promising approach due to their self-renewal ability, the capacity for multipotency maintenance, and paracrine function through secretion of immunomodulatory, anti-inflammatory, angiogenic, and pro-survival factors.

Rationale & aim. In the 2000s, our group conducted two phases I clinical trials evaluating the safety, eventual toxicity, and feasibility of transplanting MSCs into the lumbar spinal cord region. Both studies confirm that MSC transplantation in ALS patients is safe (no relevant adverse events). Furthermore, monitoring this cohort over the disease course, we observed an extended survival in some of these patients. So, to describe the potential beneficial effects of these cells in ALS patients and eventually justify a phase II/III trial, we evaluated the survival time for each patient in a long-term follow-up, compared with the predicted.

Methods - study population. We conducted two consecutive phases I prospective, open, pilot clinical trials, enrolling 19 ALS patients. All patients were diagnosed with definite or probable sporadic ALS according to the El Escorial Revised Criteria, had between 20 to 65 years, a spinal onset and no signs of respiratory failure. Patients over 65 were excluded due to a demonstration that cell growth of expanded in vitro MSCs is strictly related to the donor's age. We collected the ALS-Functional rating scale revised (ALSFRS-R), the Medical Research Council strength scale and the pulmonary function tests and for all disease duration after transplant. Autologous MSC isolated from bone marrow, expanded in vitro and suspended in about 1 mL of autologous cerebral spinal fluid, were surgically implanted.



second group: T4-T6

first group: T7-T9

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different number of injected cells

Methods - Statistical analysis.

Using the ENCALS prediction model (http://www.encalssurvivalmodel.org), we estimated the expected survival (death or tracheostomy) for each patient. Then, we compared the predicted with the observed survival, analyzing the patients at a sinlge subject level. Results were considered significant with a p-value ≤ 0.05. Data analysis was conducted with IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA) and GraphPad Version 8.0.

Patient	Group	Age at onset	Time to diagnosis	Sex	ALSFRS-R at diagnosis	FVC%	Site of onset	Definite ALS	C9orf72	Cognitive status	Predicted survival (m)	Observed survival (m)	Outcome
1	1	71	7	F	46	85	S	yes	no	ALS-no	32,2	70	D
2	1	60	8	M	42	100	S	no	no	ALS-no	32,2	77	D
3	1	45	3	F	47	108	S	yes	no	ALS-no	32,2	94	D
4	1	23	6	M	47	81	S	yes	no	ALS-no	91	292	D
5	1	44	16	F	45	82	S	yes	no	ALS-no	91	54	D
6	1	28	4	M	30	25	S	yes	no	ALS-no	91	121	D
7	1	20	2	F	46	50	S	no	no	ALS-no	91	303	A
8	1	37	6	M	45	100	B	yes	no	ALS-no	43,7	34	T
9	1	42	17	F	44	53	S	no	no	ALS-no	91	165	D
1b	2	32	10	F	45	73	S	yes	no	ALS-no	91	238	T
2b	2	17	3	F	45	51	S	yes	no	ALS-no	91	249	A
3b	2	35	3	M	47	105	S	yes	no	ALS-no	43,7	35	D
4b	2	27	9	M	46	80	S	yes	no	ALS-no	91	103	T
5b	2	45	44	F	47	94	S	no	no	ALS-no	91	111	T
6b	2	60	3	M	46	117	S	yes	no	ALS-no	25,3	34	T
7b	2	37	10	M	47	103	S	no	no	ALS-no	91	134	T
8b	2	45	21	M	44	84	S	yes	no	ALS-no	91	47	T
9b	2	56	7	M	48	115	S	no	no	ALS-no	91	38	T
10b	2	42	12	M	47	104	S	yes	no	ALS-no	91	58	T

Table 1. Demographic and clinical features of ALS participants.

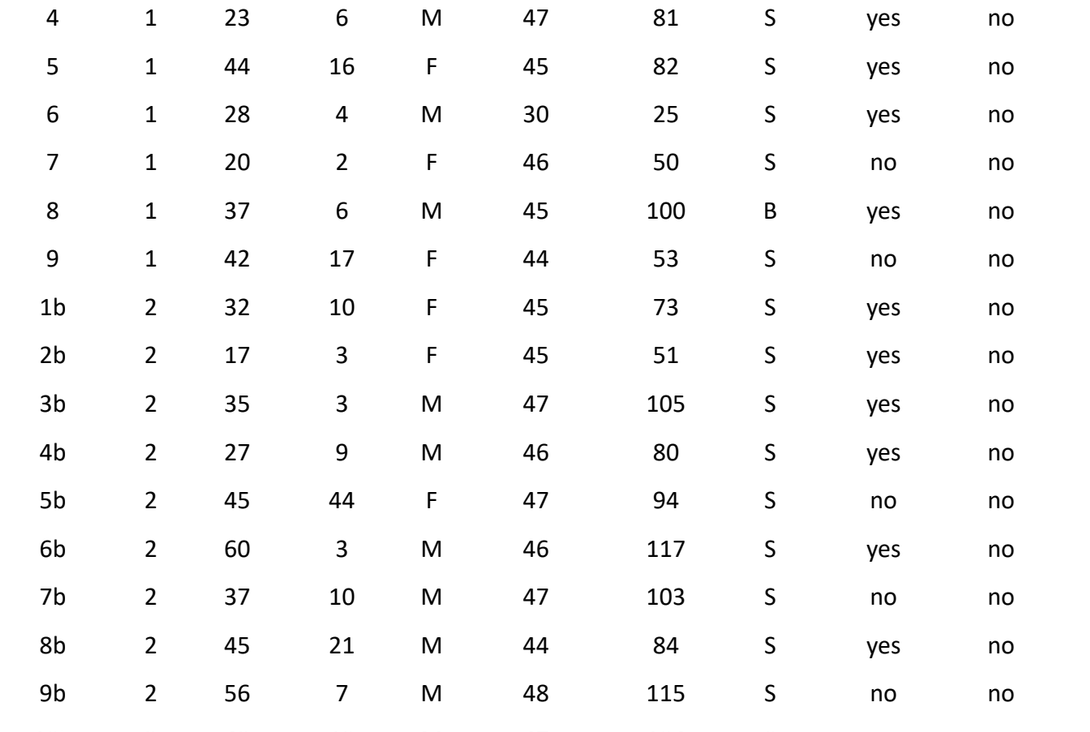

Figure 1. Predicted (yellow) and observed (red) survival.

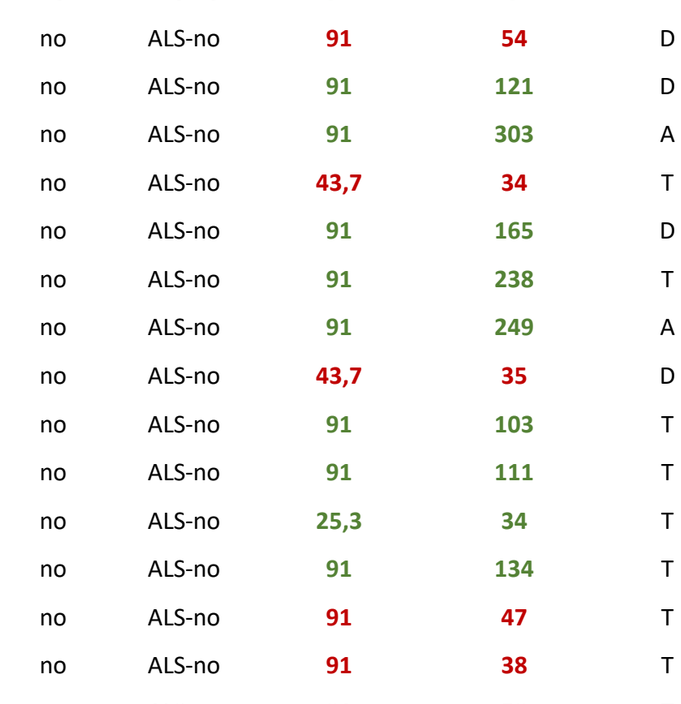

Figure 2. Trajectories of survival.

Results

The average participants' age at transplant was 43.37 (SD:14), with a median disease duration of 7 months (IQR:3-12) from symptoms onset to diagnosis and 38 (IQR:21-49) from onset to transplant. In safety analysis, no severe adverse events were reported. In enrolled patients, we predicted a short survival in one, an intermediate in three, a long in two and a very long one in 13. Of these, 12/19 had an observed survival time better than the predicted (*p*-value: 0.002) [Figure 1 - 2]. Patients with longer survival, were younger at transplant.

Four patients are still alive, of which one had no events over the monitoring period.

Discussion. For the first time, we observed a longer disease duration (compared to predicted) after MSC transplant. Long-term follow-up studies represent an essential part of the design of any clinical trial safety and efficacy evaluation.

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