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OUTCOME OF SPORADIC AMYOTROPHIC LATERAL SCLEROSIS TREATED WITH NON-INVASIVE VENTILATION AND RILUZOLE

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Abstract Sporadic amyotrophic lateral sclerosis (sALS) is a progressive degenerative motor neuron disorder lacking specific treatment. Riluzole is the only drug able to modestly slow down the course of the disease. Respiratory insufficiency is the main cause of death; non invasive ventilation (NIV) has shown to improve survival. Our aim was to evaluate the effect of NIV and riluzole on survival. Ninety seven patients with a diagnosis of sALS were assessed and followed up for 60 months. Twenty nine patients received NIV and 68 did not (nNIV). Overall median survival In the NIV group was 15.41 ± 7.78 months vs. 10.88 ± 7.78 months in the nNIV group (p= 0.028). Median survival time was not different in patients receiving riluzole (n=44), as compared with those who did not (n=53), although at month 4th and 5th riluzole treated patients showed a modest benefit. In those who only received NIV (n=11) or only riluzole (n=26), survival time was 13.45 ± 13.44 months and 11.19 ± 7.79 months, respectively. Patients who received both NIV and riluzole (n=18) had a median survival time of 16.61 ± 10.97 months vs. 10.69 ± 7.86 months for those who received only supportive treatment (n=42) (p= 0.021). NIV improved survival in our series of patients. Riluzole did not show any significant impact on survival when employed as the only therapy. Patients receiving both treatments simultaneously had a significant longer survival.

Key words: amyotrophic lateral sclerosis, survival, non invasive ventilation, riluzole

Resumen ***Sobrevida en pacientes con esclerosis lateral amiotrófica esporádica tratados con ventilación no invasiva y riluzole.*** La esclerosis lateral amiotrófica esporádica (sALS) es una enfermedad degenerativa para la que no existe tratamiento etiológico eficaz. El riluzole prolonga poco la sobrevida. La principal causa de muerte es la insuficiencia respiratoria. Uno de los tratamientos para esta última es la ventilación asistida no invasiva (NIV) con equipos de doble nivel de presión. El objetivo de este trabajo fue determinar el impacto en la sobrevida de estos enfermos combinando ventilación no invasiva y riluzole. Se evaluaron y siguieron durante 60 meses 97 pacientes con diagnóstico de sALS, según criterios definidos en El Escorial modificados, y fueron seguidos por 60 meses. Veintinueve pacientes recibieron NIV y 68 no (nNIV). En el grupo NIV la sobrevida media fue de 15.41 ± 7.78 meses vs. 10.88 ± 7.78 meses en nNIV (p= 0.028). La sobrevida media de los pacientes que recibieron riluzole (n=44) no fue diferente de la que no lo recibieron (n=53), aunque en el 4° y 5° mes los pacientes tratados con riluzole mostraron un escaso beneficio. Los pacientes que recibieron NIV y riluzole (n=18) tuvieron una sobrevida media de 16.61 ± 10.97 meses vs. 10.69 ± 7.86 meses para los que sólo recibieron tratamiento sintomático (n=42) (p= 0.021). La NIV prolongó significativamente la sobrevida en este grupo de pacientes. El riluzole, empleado como única terapéutica, no lo hizo. Los pacientes que combinaron los dos tratamientos tuvieron la mayor sobrevida.

Palabras clave: esclerosis lateral amiotrófica**,** sobrevida, ventilación no invasiva, riluzole.

Sporadic amyotrophic lateral sclerosis (sALS) is a fatal progressive degenerative motor neuron disorder, which combines upper and lower motor neurons symptoms[1]. Currently, there is no disease-specific therapy. Riluzole is the only approved drug which has been shown to slow down the course of the disease[2]. Symptomatic treatment includes non-invasive ventilation (NIV), which has been shown to prolong survival as well[3, 4].

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Ventilatory insufficiency in sALS is caused by respiratory muscle weakness, being the major cause of death (84%) in these patients[5, 6]. Dyspnea on exertion is the first respiratory symptom, eventually progressing to hypoventilation and leading to chronic respiratory failure[7]. Patients with sALS show a restriction pattern insufficiency on pulmonary function tests. Forced vital capacity is reduced. The most sensitive tests employed to assess global inspiratory and expiratory muscle strength are the static maximum pressures measured at the mouth[8]. Peak flow also appears to be useful to monitor expiratory muscle weakness[9].

We hypothesized that non-invasive ventilatory support may prolong survival either in those patients receiving

conventional treatment or in those others who, for different reasons, were not under the current pharmacological therapy employed for this disease. Therefore, the aim of our study was to evaluate survival in a series of sALS patients, assessing the efficacy of NIV and riluzole, when independently used, and combining both therapies. Also a group of patients receiving just supportive treatment was studied for comparison.

Materials and Methods

The study involved 97 patients with a diagnosis of sALS based on the El Escorial (modified at Arlie House) criteria[10, 11] who were assessed at the Hospital J.M. Ramos Mejía División Neurología, Sector Enfermedades de Neurona Motora, from December 1999 to December 2004 (60 months). There were 62 men (63.9%). Average age was 54.2 ± 13.12 years, ranging between 22 and 78 years.

Patients were studied by a neurologist and a pneumonologist. The initial evaluation included clinical assessment, spirometry, assessment of maximum pressures measured at the mouth and measurement of arterial blood gases (pO_2, pCO_2, pH, HCO_3, Sat O_2). The evaluation was repeated every 3 months. The American Thoracic Society predictive spirometry values were used as the normal standards[12, 13].

Criteria for submitting patients to NIV were based on the "Consenso Argentino para el diagnóstico y tratamiento de la esclerosis lateral amiotrofica"[14] and international guidelines[15]: These included symptomatic ventilatory impairment (dyspnea, morning headache, fatigue) and one of the following: $PaCO_2$ > 45 mm Hg or nocturnal oxygen saturation by pulse oximeter ≤ 88% for 5 continues minutes or maximal inspiratory pressure (PImax) < 60 cm H_2O or forced vital capacity (FVC) < 50%. All the patients when fulfilling these criteria were offered NIV and sixty eight patients refused.

Those patients who acepted NIV were treated with non invasive positive-pressure ventilation (with bilevel ventilation), using a nasal mask. Inspiratory pressures were individually adjusted until O_2 saturation was above 92% (positive inspiratory pressure of 13-25 cm H_20 with expiratory pressures between 5-9 cm H_20. Patients were admitted into the ward to start NIV, and caregivers were given instructions for its proper use.

Riluzole was offered to all patients but only 44 acepted to employ it.

Statistical analysis

Data are expressed as means ± 1 standard deviation (SD). Survival time was estimated as the time elapsed since the diagnosis to death or december 2004 and was calculated by employing the Kaplan-Meier method (16). Comparisons between groups were calculated by the chi-square and ANOVA for continuum variables tests; $p < 0.05$ was considered statistically significant. All statistics were carried out using SPSS software version 11.1 (SPSS Inc. Chicago, Il).

Results

Eighteen patients received NIV and riluzole (yRyV). Twenty six received only riluzole (yRnV), 11 received only

TABLE 1.– *Clinical characteristics of patients*

	N	Male	Average age	Bulbar involvement	Wheelchair use
nRnV	42	29	52.25 ± 11.44	23/35 (7)	18
yRnV	26	16	57.38 ± 12.57	9/22 (4)	11
yRyV	18	10	53 ± 15.46	12/17 (1)	13
nRyV	11	7	56.4 ± 15.5	6/10 (1)	7
Total	97	62	54.20 ± 13.20	50/84 (13)	49

nRnV: no riluzole no non invasive ventilation
yRnV: yes riluzole no non invasive ventilation
yRyV: yes riluzole yes non invasive ventilation
nRyV: no riluzole no yes invasive ventilation
( ) without data

TABLE 2.– *Overall median survival for different modalities of treatment*

Treatment	N	Survival mean ± SD (months)	Treatment	N	Survival mean ± SD (months)	p
nRnV	42	10.69 ± 7.86	yRnV	26	11.19 ± 7.79	0.798
			nRyV	11	13.45 ± 13.44	0.381
			yRyV	18	16.61 ± 10.97	0.021

nRnV: no riluzole no non invasive ventilation
yRnV: yes riluzole no non invasive ventilation
yRyV: yes riluzole yes non invasive ventilation
nRyV: no riluzole no yes invasive ventilation
SD: standard deviation

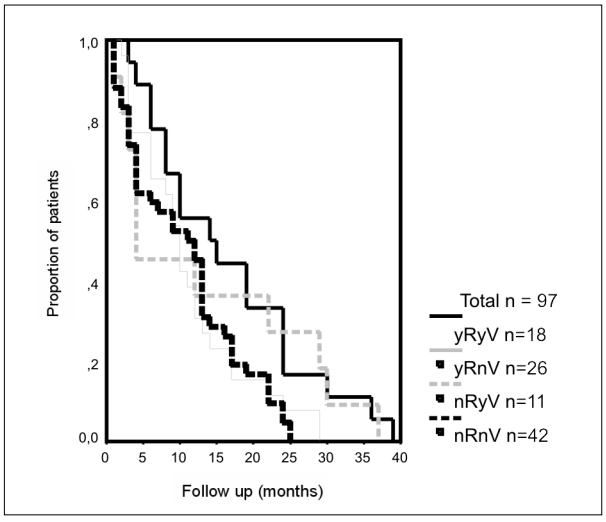

Fig. 1.– Impact of NIV and riluzole on survival time.
yRyV: patients with riluzole and NIV
yRnV: patients with riluzole and without NIV
nRyV: patients without riluzole and with NIV
nRnV: patients without riluzole and without NIV

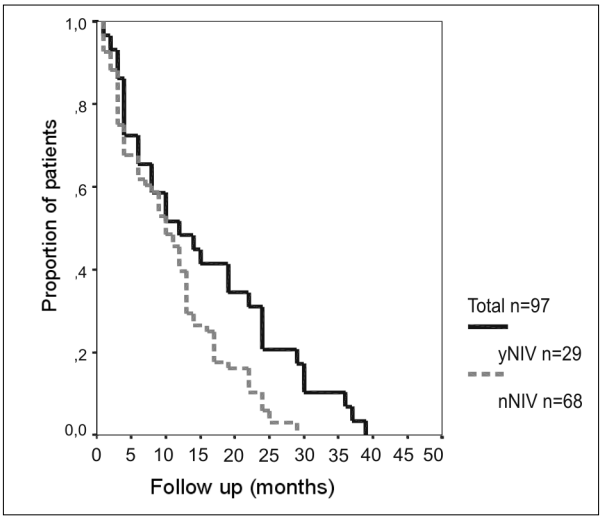

Fig. 2.– Impact of non invasive ventilation on survival.
yNIV: patients with NIV
nNIV: patients without NIV

NIV (nRyV) and 42 did not receive either riluzole or NIV (nRnV). This last group received only supportive care (Table 1).

The average survival times for each group are shown in Tables 2 while Kaplan Meier survival curves are depicted in Fig. 1 (Table 3). The largest significant difference in the average survival time was found when comparing groups yRyV and nRnV (yRyV= 16.61± 10.97; nRnV= 10.69 ± 7.86, p= 0.021) favouring the yRyV group.

Twenty nine patients were submitted to NIV (yNIV), while 68 were not (nNIV); independently of any associated pharmacological therapy, the average survival was 15.41 ± 11.83 months for the yNIV group and 10.88 ± 7.78 months for the other (nNIV) (p= 0.028). Statistical significant difference (p= 0.045) between groups appeared at month 16th along the follow-up (Fig. 2, Table 4).

Forty four patients were given riluzole (yRil) and 53 were not (nRil), independently of NIV use. The average survival was 13.41 ± 9.49 months for the yRil group and 11.26 ± 9.2 months for the other (nRil). A weak statistical significant difference (p= 0.013), favouring yRil, was found at months 4th and 5th (Fig. 3, Table 5).

Discussion

In our sALS patients cohort, the use of NIV was associated with longer survival, a finding which agrees with previous reports in the literature[3, 4]. When the patients were divided into two groups, yNIV and nNIV, independently

TABLE 3.– *Impact of NIV and riluzole on survival time*

Survival time (months)	yRyV N: 18		yRn N: 26		VnRyV N: 11		nRnV N: 42	
	ni	nd (%)	ni	nd (%)	ni	nd (%)	ni	nd (%)
0-10	18	6 (33)	26	12 (46)	11	6 (55)	42	20 (48)
11-20	12	6 (50)	14	10 (71)	5	1 (20)	20	15 (68)
21-30	6	3 (50)	4	4 (100)	4	2 (50)	7	7 (100)
>30	3	3 (100)			2	2 (100)		

ni: number of patients in the beginning of the period
nd: number of patients deceased during the period
yRyV: patients with riluzole and NIV
yRnV: patients with riluzole and without NIV
nRyV: patients without riluzole and with NIV
nRnV: patients without riluzole and without NIV

TABLE 4.– *Impact of non invasive ventilation on survival*

Survival time (months)	yNIV N:29		nNIV N:68	
	ni	nd (%)	ni	nd (%)
0-10	29	12 (41)	68	32 (47)
11-20	17	7 (41)	36	25 (69)
21-30	10	5 (50)	11	11 (100)
>30	5	5 (100)		

yNIV: patients with NIV
nNIV: patients without NIV
NIV: Non invasive ventilation
ni: number of patients at the beginning of the period
nd: number of patients deceased during the period

TABLE 5.– *Impact of riluzole on survival*

Survival time (months)	yRil N:44		nRil N:53	
	ni	nd (%)	ni	nd (%)
0-10	44	18 (41)	53	26 (49)
11-20	26	16 (62)	27	16 (59)
21-30	10	7 (70)	11	9 (82)
>30	3	3 (100)	2	2 (100)

yRil: patients with riluzole
nRil: patients without riluzole
ni: number of patients in the beginning of the period
nd: number of patients deceased during the period

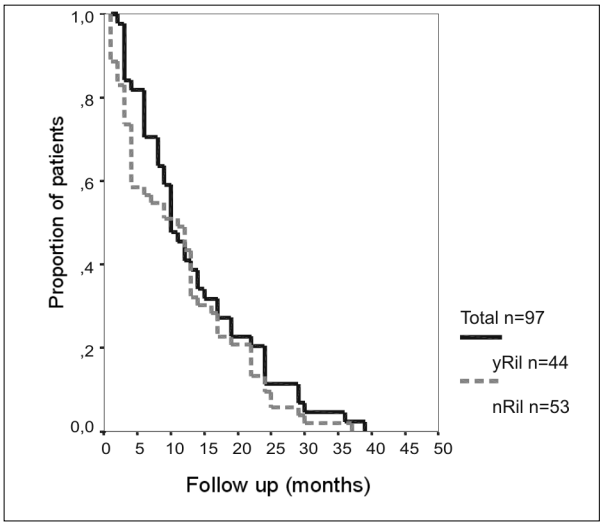

Fig. 3.– Impact of riluzole on survival.
yRil: patients with riluzole
nRil: patients without riluzole

of any other associated treatment, survival time was 15.41 ± 11.83 months for the yNIV group, while for the nNIV group mean survival was 10.88 ± 7.78 (p= 0.028). This significant difference appeared at month 16th after diagnosis, and was not related to the eventual pharmacological treatment received by the patients.

Riluzole, when employed as the only therapy, showed only a modest beneficial effect on survival at month 4th and 5th. This observation is partially at variance with the findings of Lacomblez and Bensimon[17, 18] who found that the major effect of the drug was observed after month 18th. This disagreement may be due to differences in the studied populations.

For a more detailed analysis we divided the patients in four groups: yRyV, yRnV, nRyV and nRnV. We observed that patients who received both riluzole and NIV had the longest median survival time when compared with those others who received only one modality of treatment or were only symptomatically treated. This findings was not reported before.

Therefore, NIV, a usually well tolerated procedure, may substantially prolong survival in sALS patients, either when employed as the only treatment modality or when combined with pharmacological therapy, being this last strategy the most convenient medical attitude.

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Would it not be better to draw a line below the past 50 years marked by unwarranted optimism, euphemism, and healthism? Would it not be better to cease to pretend that the fashioning of a colostomy, removal of parts of the brain, renal dialysis, and the treatment of heart failure constitute "health care"? Perhaps it would help us to concentrate minds if we discarded the designation of "health care workers" (a term which includes midwives as mortuary attendants). Perhaps we should stop talking about the "health budget" and "health expenditure" when an increasing portion of it is spent in chronic disease and disability.

¿No sería mejor trazar una línea debajo de los pasados 50 años marcados por un injustificado optimismo, eufemismo y "salutismo"? ¿No sería mejor dejar de pretender que hacer una colostomía, remover partes del cerebro, la diálisis renal y el tratamiento de la insuficiencia cardíaca constituyen "cuidados de la salud"? Tal vez nos ayudaría a concentrar las mentes si descartáramos la designación de "trabajadores de la salud" (un término que incluye tanto a las parteras como a los que atienden las morgues). Tal vez deberíamos parar de hablar de "presupuesto de salud" y de "gastos de salud" cuando una proporción cada vez mayor del mismo se gasta en enfermedades crónicas e invalidez.

Imre Loefler

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