Author’s response to reviews

Title: OBSERVATIONAL STUDY OF PATIENTS IN SPAIN WITH AMYOTROPHIC LATERAL SCLEROSIS: CORRELATIONS BETWEEN CLINICAL STATUS, QUALITY OF LIFE, AND DIGNITY

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Author’s response to reviews:

Dear editor,

In reference to the manuscript PCAR-D-17-00093 entitled “OBSERVATIONAL STUDY IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS IN SPAIN: CORRELATIONS BETWEEN CLINICAL STATUS, QUALITY OF LIFE AND DIGNITY” that is being considered for publication in BMC Palliative Care.

Please, find enclosed the detailed response to each reviewer point raised, describing exactly what amendments has been made to the manuscript text and where these can be viewed. All the references have been checked in order to be validated.

The present work has not been published and is not being considered for publication elsewhere.

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
No conflict of interest has been declared by the authors.

The study have been conducted in full accordance with the World Medical Association Declaration of Helsinki (2008).

Please find enclosed the answers to the reviewers point by point.

Dear professor Cheng:

1. The authors had divided their study in 2 parts. In the first part, observational study which included 43 ALS patients, they have found significant associations between BPAP usage and worse QOL and DoL, and PEG usage with worse QOL. These data should not be new to the literature. Therefore, the more interesting study findings would be the second prospective study part.

In reference to the first part of the study, the reviewer is right, the relation between quality of life and BIPAP and PEG have been already studied (Zamietra et al. 2012 and Bourke et al 2001)), in our opinion the difference in quality of life could be due more to the degree of progression of the disease (which requires the use of these procedures) than the procedures by themselves.

We have clarified this data in the manuscript (Discussion: Page 13 Line 2) and the references has been added (References: Page 20 line 24)

2. However, authors did not explain why only 23 patients were included in the second part of study, while 43 ALS patients were included in first part. Did patients refuse to take part, or their clinical status deteriorated too quickly? This bears major importance and needs further clarifications.

Patients are examined in our Unit every 3 months, that is, during a period of 4-5 months a total of 43 patients have been examined and 23 of them have been examined twice, which has allowed us to do a follow-up of the patient, during those three months. All patients agreed to continue with the study and only two could not be evaluated a second time as they died.

3. In the prospective study part of 23 ALS patients, authors have only included 3-months time frame as measurement, this is really inadequate for a good prospective study design, especially for neuro-degenerative disease, namely ALS which carries a relative chronic deterioration course. I would strongly suggest authors to reanalyze the data and include time frame of at least one year.

In our opinion, three months of evolution between the two evaluations are sufficient to be able to verify the functional deterioration secondary to the evolution of the disease (as explained in the manuscript) and therefore to be able to evaluate the changes in the quality of Life and dignity. In our opinion, the main problem of following a patient with ALS for a year is that we are in danger
of losing the follow-up of many of them due to the same evolution of the disease, since it has a very low survival rate, estimated between 20 and 48 months years from the onset of the disease (Reference 6; Chio A et al, 2000). However, in the future, a prospective study could be designed to follow patients for a longer period of time.

4. Otherwise, it is difficult to impress readers on the conclusion drawn, i.e. the significant clinical deteriorations in clinical status and QOL during the evolution of ALS; but DoL is not negatively affected and possibly derived from a multi-disciplinary approach to care.

The results of our work suggest a functional deterioration of ALS patients and their QoL without a significant deterioration of their DoL. In fact a discrete, but non significant, improvement of the DoL is found. We hypothesise that fact could be due, among other possible causes, to the multidisciplinary management of the disease. Evidently, this hypothesis is written in the manuscript as conditional. (Conclusions: Page 16, line 5): “The preservation of the sense of dignity appears to be multifactorial in nature, and may be due in part to the use of therapies derived from a multidisciplinary approach to the disease. “

Dear Professor Chang,

Abstract

1. According to the last paragraph of introduction and the methods section, this study had two major aims. Please correct the studyims of this study in the background paragraph of the abstract.

The abstract section (Page 4 Line 6) has been changed to: “Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease that exerts a significant impact on patients’ quality of life and dignity of life. The objectives are, first, to study the impact in quality of life and dignity of life in ALS patients and, second, their evolution throughout the duration of the disease.”

2. The methods section should be revised to match the study design.

In the abstract section, methods has been revised and changed to: “The first part of the study comprised an observational, descriptive, comparative trial of 43 ALS patients. Twenty healthy people with similar age and gender distributions formed the control sample. In the second part, a prospective cohort of 23 ALS patients was followed up for three months. All participants completed the three questionnaires about their functional status, quality of life (QoL) and dignity of life (DoL) (Abstract: Page 4 Line 11)

3. Please describe significant findings in the results section.
The significant results have been described in the abstract section: “Statistically significant differences were found in the QoL and DoL scales between ALS patients and healthy controls. (p=0.000). Statistically significant decline in clinical status (between the scores at time 0 of ALS Functional Rating scale and at three months with median scores of 30.95 points and 27.24 points respectively, p-value =0.0003) and QoL (with significant differences between the scores in the Amyotrophic Lateral Sclerosis Assessment Questionnaire at time 0 and at three months with median scores of 124.19 points and 131.81 points respectively, p-value =0.0062) were observed in the amyotrophic lateral sclerosis cohort during the three-month period. No decline of DoL was observed during the three-month period.” (Abstract, Page 4 Line 15)

4. Some contents of the results are different from the conclusions, please clarify this.

In the abstract, we have clarified the sentence in Page 5 Line 4.

Introduction

1. Please explain the importance of this study. What aspects of knowledge might be added on to previous researches?

In the best of our knowledge this is the first study in Spain trying to demonstrate the importance of focusing on control of quality and dignity of life as high as possible in some neurodegenerative diseases with lack of an effective treatment, such as ALS. (Introduction Page 9 Line 8)

These findings suggest that Dignity of Life may be an important target in the management and care of ALS patients alongside Quality of Life. (Conclusions Page 16 Line 7)

Both sentences have been added in the manuscript.

Methods

1. Please explain where and when the study was conducted and how the controls were selected.

We have added the required information in methods (Page 9 Line 16-19), trial design: “The first part of the study comprised an observational, descriptive, comparative trial of patients followed up at the ALS unit of our Center (UFELA) between December 2015 and April 2016. Twenty healthy people with similar age and gender distributions, chosen from authors’ (YMC, AL, CH, RA and DC) families and relatives, formed the control sample. In the second part, a prospective cohort of patients treated at the UFELA and diagnosed with ALS was followed up for three months. Three questionnaires – ALSFR, ALSAQ40 and PDI – were administered.”
Results

1. Please explain the power of each non-significant findings.

We have added the following information in results (Page 11 Line 13): “On one hand, no significant differences were observed with regard to QoL and DoL between gender (p=0.5626 and 0.4467 respectively), age of ALS onset (p=0.3982 and 0.3325 respectively), clinical onset (spinal –p=0.060 and 0.187 respectively, bulbar-p=0.126 and 0.995 respectively- or respiratory –p=0.340 and 0.058 respectively) and duration of the disease (p=0.660 and 0.3982 respectively). No significant differences were observed between PEG and DoL (p=0.5750).

Discussion

1. Please explain the strengths and limitations of this study.

We have added the following information in discussion (Page 15 Line 18), explaining the strengths and limitations of this study: “Unfortunately the number of patients (46 in the first part of the study and 23 in the second part) and the time of evolution (only 3 months) are low. However, on the other hand, it is a study with a prospective part in which, with that number of patient and that period of time, statistically significant changes can already be observed. Nevertheless, in the future, a prospective study could be designed to follow a higher number of ALS patients for a longer period of time.

Tables

Please revise tables according to the journal's style.

The tables have revised according the journal’s style

Sincerely

The Authors