PEER-REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-18-00325

Title: Safety of Wharthon's Jelly derived-Mesenchymal Stem Cells intrathecal injection in Amyotrophic Lateral Sclerosis therapy. Translational stem cell clinical study

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Reviewer's country: UNITED STATES

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Date reviewed: 2018-06-27

Review time: 12 days

1. Do you consider this paper is hotspots or important areas in the research field related to neural regeneration?

Yes

2. Which area do you think this paper falls into? Neurorepair, neuroprotection, neuroregeneration or neuroplasticity.

Neurorepair

3. Is the manuscript technically sound, and do the data support the conclusions?

Yes

4. Has the statistical analysis been performed appropriately and rigorously?

Yes

5. Is the manuscript presented in an intelligible fashion and written in Standard English?

The manuscript is well written and clearly presented

6. Your peer review comments will be published as an open peer review report. Do you agree to have your name included with the published article?

Yes

Manuscript Rating Question(s):	Scale	Rating
The subject addressed in this article is worthy of investigation.	[1-3]	2
The information presented was new.	[1-5]	4
The conclusions were supported by the data.	[1-10]	8

COMMENTS TO AUTHORS

Strengths:

- This work reported that intrathecal injections of WJ-MSC in 43 patients with ALS have a low incidence of SAE and well tolerability. Based on these claims, it is possible that the careful intrathecal administration of WJ-MSC alone (or in combination with the current drug therapies) could represent a promising new therapeutic approach to extend the life expectancy of patients with ALS.

Weaknesses:

-The work presented in this manuscript seems to only represent the initial stages of a larger clinical study.

The aim of this study is to assess the safety of intrathecal injections of Wharton's Jelly- derived mesenchymal stem cells in 53 recruited patients with amyotrophic lateral sclerosis (ALS). The authors reported no serious adverse effects during the clinical trial and the use of derived mesenchymal stems cells was well-tolerated among patients with ALS. However, some concerns about this study need to be explained before this manuscript can be considered for

publication.

Moderate/Minor concerns:

1- From the title: Based on the literature, the correct name of the experimental biological substance is Wharton's Jelly derived mesenchymal stem cells not Wharthon's Jelly derived mesenchymal stem cells (see Kalaszczynska et al 2015). Please revise and edit accordingly. Also, the word "Amyo-trophic" seems uncanny in the English medical literature.

2- In the introduction section, page 1, line 46-50: Although diseases such as ALS and frontotemporal dementia (FTD) shared common clinical features (see Ferrari et al 2011), it is really confusing why the authors described other motor neuron diseases with extensive genetic and neuropathology differences, such as primary lateral sclerosis (PLS) and spinal muscular atrophy (SMA) as subtypes of ALS. Actually, PLS and SMA are not mentioned in the reference [1] the authors provided (Turner et al 2013). Might be the authors are referring to the sporadic form of ALS (SALS) and the familiar form of ALS (FALS) with a FALS incidence of approximately 10%. The authors are invited to review and provide further clarifications (or references) for their statements in this section.

3- In the introduction section, page 2, line 17-18: The last sentence is disconnected to the rest of the paragraph. Please edit or delete.

4- In the material and methods section: Please state if any electromyography (EMG) testing was used to support the clinical diagnosis of ALS (previously mentioned in introduction section, page 2, line17-19) or if specific genetic testing was obtained to determine specific patterns of mutations related to ALS in this patient population.

5- In material and methods section, page 4, line 1-10: The authors claim to use intrathecal injects of Wharton's Jelly derived MSC (WJ-MSC) in patients under Riluzole treatment. Please explain if a control group (patients receiving Riluzole alone) was used to determine if the side effects reported were exclusively related to the intrathecal therapy and not to the drug administration .

6- In results section, page 4, line 51-53: The authors may describe the incidence of side effects as % of the total population (as stated in the discussion section for similar studies, page 6, line 9-11).

7- In the discussion section, page 6: The authors mentioned that the safety of intrathecal injection WJ-MSC in ALS patients has been tested by other groups (Sharma et al 2015 & Petrou et al 2016). Based in the extremely low incidence of serious adverse events (SAE) reported by this work, please explain in this section the differences between the author's technical approach (including molecular techniques to isolate the MSC material) and the work carried out by other scientific groups to explain such SAE differences.

8- In the discussion section: Please briefly state the potential, complications limitations or disadvantaged of the use of intrathecal injections of WJ-MSC in ALS and if the authors have any imaging protocol in place (CT or MRI) to assess any potential complications by the intrathecal delivery approach (hemorrhage, infections, etc.).