Author’s response to reviews

Title: Evaluation of the muscle strength and motor ability in type II and III spinal muscle atrophy children treated with valproic acid

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Author’s response to reviews: see over
Dear Editor

Thank you for reviewing our manuscript. We are sending you a revised version of the paper. The point-by-point response and the corrections we have done to the text are presented below.

All the best,

Illora

**Point by point comments:**

**Major revisions:**

1) The authors should specify explicitly that not including a control group is a major limitation of their results. It is impossible to differentiate between a potential effect of the drug treatment and the natural history of the disease. Despite suffering from a progressive neurodegenerative disease, individual patients with SMA II/III may well show short term improvements of their motor status. In addition, 3 out of 9 SMA III patients in this study were diagnosed at age 12 months or younger, which is very early for SMA III. If they were enrolled in the study relatively soon after diagnosis, this means that they may well have shown motor function improvements even if untreated. Unfortunately, the age at enrollment is only given as mean and as range in Table 2.

“It was added to the discussion the following statement as suggested by the reviewer. “The major limitation of our study was the non inclusion of a control group. Despite suffering from a progressive neurodegenerative disease, patients with SMA type II/III may show short term improvement of their motor status, in which it could be influenced by many factories including physical therapy, mental status and systemic diseases. However, in the period of evaluation, we could observe that no patient presented deterioration of their motor function, in which it would be expected considering the progressive course of the disease”.

2) The conclusion “Treatment of patients with VPA is a potential alternative to alleviate the progression of the disease” should therefore be phrased “treatment of SMA patients with VPA may be a potential alternative to alleviate the progression of the disease”, since no proof of therapeutic efficacy can be extracted from this uncontrolled study.
We made this changing on conclusion

3) The characterization of the patients should – for comparison with future studies – include the individual number of SMN2 gene copies for each patient. It would be desirable to reanalyze the data from table 3 according to SMN2 copy number and according to SMA type II versus III. If this is not possible, it should be made clear that this is a limitation of the present study.

In this study we included only SMA patients with types II and III, avoiding the inclusion of the most severe form of the disease (type I). However, unfortunately we did not measure the \textit{SMN2} copy number in our patients that would be very interesting to divide the patients in more homogeneous groups and for a better comparison of our results with future studies.

\textbf{Minor essential and discretionary revisions:}

All corrections suggested by the reviewer were done.

In addition

We included this article because of the importance: Recently, Swoboda et al (2010) [20] assessed 61 subjects randomized 1:1 to placebo or treatment with VPA and L-carnitine for six months, no benefit was demonstrated. Then, the efficacy of VPA is still controversial. In this study, we quantified the muscular strength and motor function of patients with SMA type II and III treated with VPA and assessed the side effects of the medication.

5) Background: 3\textsuperscript{rd} paragraph, 2\textsuperscript{nd} last sentence: “However, phase III clinical trials have not had their results disclosed yet”. There have as yet not been initiated any phase III clinical trials for SMA. Which trial the authors have in mind?

We removed from the text that statement

7) RESULTS: The authors should provide information on the VPA serum concentrations that were achieved at 20 mg/kg/d

We included in the text the sentence: “All 22 patients achieved the 20 mg/kg/d of the VPA serum concentration in the period of the study.”

PS: we measured the VPA level at the 6\textsuperscript{th} and 12\textsuperscript{th} month.

11) \textbf{TABLE 1; 4\textsuperscript{th} column from the left “age at diagnosis”: the unit should be given as “years unless specified otherwise”}.

This information was included on Table 1.
12) TABLE 2; what does “Q1-Q3” stand for?

We excluded this information from the Table 2.