Reviewer's report

Title: Sodium vanadate combined with L-ascorbic acid delays disease progression, enhances motor performance, and ameliorates muscle atrophy and weakness in mice with spinal muscular atrophy

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Reviewer: Chien-Ping Ko

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Liu et al. evaluated the therapeutic potential of sodium vanadate combined with a vanadium detoxification agent, L-ascorbic acid, in a mild and late-onset type of SMA mouse model. The authors showed that combined treatment of L-ascorbic acid protected cells against sodium vanadate-induced cytotoxicity, which is associated with a decrease in the expression of Bax. In addition, combined treatment increased SMN expression in NSC34 cells and restored SMN nuclear body gems in fibroblasts derived from SMA patients. The mice with late-onset SMA received combined treatment from PND1 to PND30 showed enhanced SMN expression, reduced tail and ear necrosis, improved performance on accelerating rota-rod, increased motor neuron number and muscle size, and decreased expression of Bax. Furthermore, combined treatment reduced vanadium accumulation in the kidney, liver and blood. The authors concluded that combined treatment of sodium vanadate and L-ascorbic acid could serve as a feasible and practicable treatment for patients with late-onset SMA. The authors did an excellent job in conducting thorough and comprehensive analyses both in vitro and in vivo, as well as provided substantial evidence for the therapeutic potential of combined treatment. This reviewer has following concerns:

1. In Figures 1 and 2, the authors showed combined treatment reduced cytotoxicity and increased gem numbers in fibroblasts of SMA patients. However, SMN expression was examined only in NSC34 cells. It is still unclear whether combined treatment could restore SMN expression in SMA patient fibroblasts.

2. The method for evaluating cell viability is not provided in the manuscript.

3. To evaluate the in vivo effect of combined treatment, the authors set off to treat SMA mice from PND1 to PND30, and to conduct phenotypic analysis in SMA mice at PND30 and 90. The authors did not explain why they only treat animals for 30 days. Although the authors did state, “Based on these results, SMA mice received combined treatment for 1 month beginning on PND 1” (page 27), they based on results from the more severe SMA mice, which show symptoms much earlier than the mild mice that the authors used in this study. While early treatment is critical for mitigating disease phenotype in severe SMA mice, whether early intervention is also necessary for mild mice with late-onset SMA has not been established. Since the current study is to evaluate the therapeutic potential of combined treatment for late-onset SMA patients, ideally,
the authors should have started the treatments later (e.g. from PND 20, instead of PND 1) to mimic the potential benefits of later treatments to type II and type III SMA patients. The authors should at least comment on the feasibility of later treatment in their mouse model in Discussion.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.