Author’s response to reviews

Title: Interstitial pneumonia and other adverse events in riluzole-administered amyotrophic lateral sclerosis patients: a retrospective observational study

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Version: 3 Date: 28 Feb 2019

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Feb 28, 2019

Dear Dr. Samuel Harris,

BMC Neurology

I wish to submit the revised version of our manuscript entitled “Interstitial pneumonia and other adverse events in riluzole-administered amyotrophic lateral sclerosis patients: A retrospective observational study” for your consideration (NURL-D-18-00685R2).
In this revised paper, we have addressed all the reviewers’ comments and queries. Please find our rebuttal below. We hope that you will find our revised manuscript as significant contribution to BMC Neurology.

Best regards,

Aya Inoue-Shibui

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Reviewer 1:

> I do not agree with the following sentence on page 8 “Two cases had to discontinue the administration because of decline in forced vital capacity (FVC) to <60 %.” as the decline of the respiratory function is not a finding recommending to stop medication.

Thank you for your comment. As written in rebuttal letter on Jan 26, we do not recommend discontinuation of riluzole prescription just because of FVC score is <60%. In case no. 3 and 6, the attending physician decided to discontinue riluzole under the discussion with the patient considering the surrounding environment of the patient. We revised “Two cases had to discontinue the administration because of decline in forced vital capacity (FVC) to <60 %.” to “Two cases had to discontinue the administration mainly because of progression of bulbar palsy” in page 8 of revised paper.

> In addition, the report of a few exceptional cases of Interstitial pneumonia suggesting a possible link with the medication does not implies to recommend periodic chest x-ray in all treated ALS patients.
We agree that not all ALS patients have to take periodic chest X-ray, because it might be hard for some patients who have severe muscle weakness to go out and is too much for people who have no respiratory problem. Diagnosing riluzole-induced interstitial pneumonia is important because it could be treated and lethal.

We added these descriptions in the section of discussion and conclusion in page 18, as given below:

IP could be treated and lethal in most cases. All ALS patients need careful follow-up with through interviews after the beginning of riluzole especially within six months. If they complain of respiratory problem like dyspnea or dry cough, chest X-ray would be recommended.

Careful follow-up is important for the first six months after the beginning of riluzole with through interviews, chemical analyses, and chest X-rays, if needed.

Reviewer 2:

> In the Results section correct:

Pag. 7: 92 cases could be followed, … were followed (how long?)

ALS/front temporal dementia, ALS/fronto…

Thank you for your comments. We revised “92 cases could be followed” to “92 cases could be followed for 15.5 months (IQR, 9–22 months)” in the Result section in page 7.

We apologize the English form was incorrect. We revised “ALS/front temporal dementia” to “ALS/frontotemporal dementia” in page 7 and “FTD: front temporal dementia” to “FTD: frontotemporal dementia” in page 19.

> Pag 8 "all abnormal elevated enzymes case had some sort of medical history" change in All cases with abnormal elevated enzymes…. what means had some sort of medical history???

We are sorry for that the sentence in page 9 was vague. We revised the description as below.

All cases with abnormal elevated enzymes had medical histories of diabetes, hyperlipidemia and hypertension with medication (Table 2).
In the Discussion page 13 repeat the definition of abnormal

We decided to discontinue riluzole because the scores of ALT and AST were >3X of the upper limit of the normal scores [Introna et al. 2018, Bensimon G et al. 2004] or were accompanied by additional subjective symptoms (such as anorexia, nausea, and dizziness). We refer to those ALS patients as cases/patients with abnormal elevated liver enzymes and distinguish from those with score <3X or with no symptoms.

We added our paper in the Results section in page 8 as given below:

We refer to those ALS patients who with the scores of ALT and AST were >3X of the upper limit of the normal scores [Introna et al. 2018, Bensimon G et al. 2004] or were accompanied by additional subjective symptoms (such as anorexia, nausea, and dizziness) as cases/patients with abnormal elevated liver enzymes.

In table 2 page 33 and page 34: correct depressive

What means Clamydia pneumonia "s/o" (specify or add in end notes)

We thank your kind advisement and apologize that there were incorrect form of English. We revised to “depressive” in table 2.

We spelled out “s/o: suspected of” and “n/r/o: not ruled out” in list of abbreviations in page 19 and in end of table 2 in page 36.