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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Dear Dr. Samuel Harris:

BMC Neurology

I wish to submit for your consideration the revised version of our manuscript entitled “Interstitial pneumonia and other adverse events in riluzole-administered amyotrophic lateral sclerosis patients: A retrospective observational study” (NURL-D-18-00685R1).

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,

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Reviewer 1:

>In this study the authors approached side-effects of riluzole treatment in a small population of ALS patients. They mention increased liver enzymes and interstitial pneumonitis as relevant observations. In my personal experience of over 1500 patients treated with riluzole, the amount of drop-outs have been quite small (<5%) and the number of patients stopping the drug due to liver problems have been insignificant (<2%).

In this report, the value of threshold for defining abnormal liver enzymes increase is not set (the proposed limit is 3 x upper limit of normal for ALT and AST).

Thank you for sharing your valuable input. The rate of elevated liver enzyme cases (5.4%) is similar to that previously reported (3%–7%). Most of these elevated liver enzyme cases are not serious themselves. However, 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 have added these descriptions in the Methods section of the revised paper, as given below:

“As 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) in the present case of liver dysfunction, we decided to discontinue riluzole.”
Interstitial pneumonitis as a complication of riluzole treatment is not part of my medical experience, but chronic food microaspiration (common in ALS) is a classical cause of Idiopathic Pulmonary Fibrosis (Sweet MP, Patti MG, Hoopes C, Hays SR, Golden JA. Gastro-esophageal reflux and aspiration in patients with advanced lung disease. Thorax. 2009;64:167-73). Other mentioned adverse-events are very vague or related to disease progression.

As the reviewer indicated, food microaspiration is a classical cause of idiopathic pulmonary fibrosis with a chronic clinical course. Conversely, our case of respiratory problem was not chronic, but acute. We therefore performed transbronchial lung biopsy, and our pathological analysis revealed organizational pneumonia—a type of interstitial pneumonia (IP). Thus, we diagnosed the patients with drug-induced IP and not aspiration pneumonia. We have added these descriptions to the Results section of the revised paper, as given below:

“Bronchoalveolar lavage showed 57.8% increase in the lymphocyte counts, and transbronchial lung biopsy was performed from the right upper and lower segmental bronchi; the pathological analysis revealed organizing pneumonia—a subtype of IP. As the clinical course was acute and different from that of food microaspiration-induced idiopathic pulmonary fibrosis (Sweet MP et al. Thorax 2009), we diagnosed the patient with drug-induced IP.”

There is no reason to stop riluzole treatment when FVC declines below 60% of the predicted value, this was an eligibility criteria in the original trial, but treatment was not interrupted when FVC decline below that value.

Thank you for your comment. Because riluzole is the only approved oral drug for ALS, discontinuing riluzole is could be a serious problem. Riluzole was proved to prolong survival in ALS patients with >60% FVC in the eligibility criteria of original clinical trial [Miller et al. 1999]. Most of the patients wished to continue riluzole despite having FVC score of <60%. In case nos. 3 and 6, the attending physician decided to discontinue riluzole under the discussion with the patient considering the surrounding environment of the patient. We do not recommend discontinuation of riluzole prescription when the FVC score is <60%. We have accordingly revised “declining of FVC (Under 60%)” to “progression of bulbar palsy” in Table 2 of the revised paper.

Clinical reports are very poorly written and Discussion is too long

Thank you for the critique. We attempted to revise these sections (revised content is underlined in the document).
Reviewer 2:

The authors reported a retrospective observational study on adverse events in riluzole-administered amyotrophic lateral sclerosis patients.

Although riluzole is approved since 1995, updates on drug-related side effects are interesting and for this purpose the authors have to add a recent reference on this issue (see Introna et al, Neuropsychiatric Disease and Treatment 2018) as well as regarding the benefit of riluzole (see Dharmadasa T, Kiernan MC, Lancet Neurol. 2018)

Thank you for your comment. The indicated aspect is important considering the benefits and the adverse effects of riluzole. I have added the following text to the Discussion section in the revised paper, as given below:

“Despite the survival benefit of riluzole remaining controversial, some reports have suggested early benefits including that rilzole can partially normalize cortical and peripheral axonal hyperexcitability in the early stage of ALS [Geevasinga et al. 2016.] or that riluzole can induce longer survival in the last clinical stage of ALS [Fang et al. 2018]. In the light of these reports, it is advisable to continue riluzole as long as possible unless QOL is affected by the adverse events.”

The paper might be interesting, but there are several aspects to revise

>First of all to better understand the presence and type of side effects, I suggest to specify both the absolute number and the frequency of each adverse event in the text and in the reference table. Number of patients with increased liver enzymes were 5/20 in the discontinued cases and 8/72 in continued cases, then the total number with liver dysfunction is 13/92 (that is 14% of all cases and not 5.4%)

In addition in Table 1 what does "1 dementia" mean in the continued cases? what type of dementia? different from the FTD?

We have revised our manuscript to specify both the absolute number and frequency of each adverse event in the text and reference table. We have referred to patients who had to discontinue riluzole because of the elevation of liver enzymes as abnormal elevated liver enzyme cases. The number and frequency of elevated liver enzymes in the results and tables in this manuscript are about abnormally elevated levels of liver enzyme cases. Continued cases include patients who only presented with elevated levels of liver enzymes without symptoms. We have clarified this in the manuscript.

In Table 1, we have revised 1 dementia to 1 FTD.
> On page 8 line 1 why the decline in FVC is a factor of discontinuation?

Because riluzole is the only approved oral drug for ALS, stopping riluzole can result in serious issues. Riluzole was proved to prolong survival for ALS patients whose FVC was >60% in the eligibility criteria of the original clinical trial [Miller et al. 1999]. Most patients wished to continue riluzole despite having FVC score of <60%. In case nos. 3 and 6, the attending physician decided to stop riluzole after discussion with the patient and due consideration of the patient’s surrounding environment. We however do not recommend that the prescription of riluzole should be stopped when the FVC score is <60%. We have accordingly revised the phrase “declining of FVC (Under 60%)” to “progression of bulbar palsy” in Table 2.

> In the discussion the authors argue on the mechanism of IP in riluzole-administered patient and they suggests: 1) a "possible influence of omeprazole". As reported by Cassiman D et al (Cassiman D et al., NEUROLOGY 2003) omeprazole might be protective versus IP, reducing the effect of riluzole by enhancing its metabolization via induction of cytochrome p450 1A2. Therefore what means "possible influence of omeprazole"? It is not clear.

2) "via a cell-mediated type of allergy which depends on dosage" What means?? Could hypothesize a possible influence with the cigarette smoking, considering that case 2 was a past smoker of 30 cigarettes per day for 25 years? The authors have to clarify these issues.

1) Thank you for your kind advise. As indicated, the given reason for possible influence of omeprazole is not scientific, and we have therefore removed the related content in the revised Discussion.

2) Drug-induced IP is hypothesized to be caused by cell-type allergy. Indeed, increased CD8-positive lymphocyte in bronchoalveolar lavage (BAL) and drug-induced lymphocyte stimulation test (DLST) are effective methods for the diagnosis of drug-induced IP. Both are tests for cell-mediated type of allergy.

Cigarette smoking could be one of the causes in our case because the patient had a smoking history of 30 cigarettes per day for the past 25 years.

We added the relevant descriptions to the Discussion section, as given below:

“The mechanism of IP in riluzole-administered patient is hypothesized via cell-mediated type of allergy that depends on dosage with increased CD8 positive lymphocyte in bronchoalveolar lavage (BAL) and DLST in the literature [5]. We have surmised our IP cases to have been caused by riluzole-induced allergy. In case 2, the long history of cigarette smoking may have been the cause.”
Another point that the authors have to better clarify is the cut-off of <18 months that they define as the more frequent period to occurring adverse events.

As suggested, we have revised the relevant text as given below:

“Because, the phase III clinical study and drug-use survey were performed for 18 months (Lancombe L. et al. 1996) and because the above reports demonstrate adverse events occurring in 7 days to 9 months, we set our follow-up period for a median 15.5 months and believe it to be sufficiently long. Indeed, in our cases, all adverse events occurred within 6 months after initiating riluzole.

Finally, the English form is often hard (e.g. see in discussion line 32-35 page 12, or line 21 and 24 page 13, or line 25 and line 32 page 16 etc etc … ).

The manuscript has been rechecked by a native speaker of English to revise grammar and English.