

OPEN PEER REVIEW REPORT 1

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-20-00282

Title: Continued Development of Azithromycin as a Neuroprotective Therapeutic for the Treatment of Spinal Cord Injury and Other Neurological Conditions

Reviewer's Name: Yong Hu

Reviewer's country: China

Date sent for review: 2020-4-2

COMMENTS TO AUTHORS

This review summarizes the advances in the application of azithromycin in the treatment of spinal cord injury and other neurological condition. The review also offers a perspective on the current challenges in clinical translation and implementation, such as limitations in patient enrollment, time window for treatment, and neurological function assessment, and provides recommendations on how some of these critical issues could potentially be overcome. Obviously, in the face of the current debate about the use of high-dose steroids to treat spinal cord injury and the lack of other alternatives, the development of new uses of old drugs are an economic and convenient strategy.

This article has synthesized these salient concerns and will thus serve as a valuable reference for future research on the treatment of SCI. Additionally, there are some necessary issues that need to be concerned and discussed in this article.

1. Experimental study on large animals before clinical translation

It should be noted that the current research results of azithromycin in the treatment of neurological diseases mainly come from rodents. Despite the safety merits, none of the clinical trials have confirmed the effectiveness of this treatment based on non-human primate models. Continued research is therefore needed to making progress on this significant issue.

2. Time window and dosage of azithromycin treatment

SCI treatment may require long-term administration to yield benefits. Low-dose and short-term exposure to azithromycin do not automatically cause irreversible damage, but prolonged treatment can lead to unnecessary neurodegeneration by altering the cell-surface receptor signals and autophagy of neurons. And the higher concentrations were used, the drug-induced effects occurred earlier and were more pronounced (Waetzig V. Neurodegenerative effects of azithromycin in differentiated PC12 cells[J]. EUR J PHARMACOL, 2017). Only modest effect of azithromycin producing on SCI may be related to this negative effect. It may be a feasible way to modify the molecular structure mentioned in the article to improve the efficacy.

OPEN PEER REVIEW REPORT 2

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-20-00282

Title: Continued Development of Azithromycin as a Neuroprotective Therapeutic for the Treatment of Spinal Cord Injury and Other Neurological Conditions

Reviewer's Name: Ke Xu

Reviewer's country: China

Date sent for review: 2020-4-2

COMMENTS TO AUTHORS

In current study, the author reviews the treatment of spinal cord injury with Azithromycin(AZM). According to the author's concept, the AZM could be developed into a safe, neuroprotective treatment for SCI. The author told us that we need to better understand AZMs underlying mechanisms, improve its efficacy by optimizing dosing paradigms, and begin developing approaches to detect therapeutic effects non-invasively in humans. This review is meaningful. But some issues have to be concerned as follow:

1. There are some grammar problems and some sentences are not clearly described, which hinder readers' understanding of their findings. Revising the manuscript carefully will improve the quality of this manuscript.
2. In this review, the author should introduce more about AZM for the treatment of spinal cord injury or other neurological diseases in the first paragraph.
3. The authors may add references but control the presence of references along the journal (<12).

OPEN PEER REVIEW REPORT 3

Name of journal: Neural Regeneration Research

Manuscript NO: NRR-D-20-00282

Title: Continued Development of Azithromycin as a Neuroprotective Therapeutic for the Treatment of Spinal Cord Injury and Other Neurological Conditions

Reviewer's Name: Saijilafu

Reviewer's country: China

Date sent for review: 2020-4-2

COMMENTS TO AUTHORS

In this review, the author mainly discusses the neuroprotective effect of azithromycin in spinal cord injury and stroke, and then analyzes the therapeutic window of azithromycin treatment that can be expanded by optimizing the administration mode. Further, the author also describes the evaluation methods of human efficacy after spinal cord injury. Overall, this is through review that would contribute to the current knowledge on neuroprotection after spinal cord injury. However, a number of issues need to be addressed before publication can be recommended.

1. What is the potential molecular mechanism that the neuroprotective effect of azithromycin treatment.
2. What's the function of immune system may contribute to the secondary pathophysiology? Why the reason that the 24hr time-point, AZM administration is ineffective after spinal cord injury.
3. Blood test and CSF examination is also invasive method.
4. Moreover, neuronal loss not only happens in the spinal cord injury but also in many nervous system diseases. It would be better to more detail explain the role of AZM in some other CNS diseases. But, if the author does want to focus on the spinal cord injury, then the title should be narrowed down.