PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica Spectrum Disorders ：a protocol for systematic review and meta-analysis.
AUTHORS	han, mengyu; Nong, Luqi; Liu, Ziqiang; Chen, You; Chen, Yang; Meng, Huan; Qin, Yali; Wang, Zhijun; Jin, Ming

VERSION 1 – REVIEW

REVIEWER	Marilena Durazzo Department of Medical Sciences, University of Turin, Italy.
REVIEW RETURNED	11-Jun-2020

GENERAL COMMENTS	The paper is a protocol for systematic review and meta-analysis concerning safety and efficacy of mycophenolate mofetil in treating neuromyelitis optica spectrum disorders. The protocol is clear and well designed. I hope to see it put into practice soon.

REVIEWER	Niyaz Mostafa University of New South Wales Australia
REVIEW RETURNED	17-Jun-2020

GENERAL COMMENTS	Good protocol

REVIEWER	Carlos de Cabo de la Vega Hospital General de Albacete, Spain
REVIEW RETURNED	25-Jun-2020

GENERAL COMMENTS	The present paper proposes a protocol for systematic review and meta-analysis to assess the efficacy and safety of mycophenolate mofetil for the treatment of Neuromyelitis optica spectrum disorders. The topic is pertinent and interesting. The paper is generally well written and the methodology they propose is well described and appropriate for their purpose. MAIN POINTOF CONCERN: My main concern is with the originality of the proposed study. Two systematic review and meta-analysis papers have been recently published covering this topic: - Huang W, Wang L, Zhang B, Zhou L, Zhang T, Quan C. Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-

	analysis. Mult Scler Relat Disord. 2019 Oct;35:246-252. doi: 10.1016/j.msard.2019.08.009. Epub 2019 Aug 9. PMID: 31425902. - Espiritu AI, Pasco PMD. Efficacy and tolerability of azathioprine for neuromyelitis optica spectrum disorder: A systematic review and meta-analysis. Mult Scler Relat Disord. 2019 Aug;33:22-32. doi: 10.1016/j.msard.2019.05.011. Epub 2019 May 22. PMID: 31136907. The authors should explain in what way their study in a valuable new contribution to the field different from the already existing studies. MINOR POINTS: 1- Page 23, 3rd paragraph, lines 2 and 3 (coordinates 51-52): "There are no systematic reviews and meta-analysis yet that evaluated the effects of MMF against other therapies in patients with NMOSD." In accordance with my main point, this sentenced has to be downplayed and acknowledge the existence of previous systematic reviews. 2- Page 4, end of the first line: the acronym "CBM" needs to be described. 3- The English is generally good, but needs some revision. For example, but not only: -Page 5, line 9: "NMO of positive AQP4-IgG" should be "AQP4-IgG positive NMO" - Page 5, line 18: "incidence of female is about 10 times that of male" should be "incidence IN femaleS is about 10 times that of maleS" - Page 6, lines 9-10: the meaning of the sentence: "Immunosuppressive agents are often used in the latter to prevent recurrence and reduce the progression of neurological disability" is not clear. It needs to be re-written. - Page 6, lines 15-16. The sentence"… rituximab has also been reports of infusion reactions…" needs to be re-written. - Page 6, last sentence before "Methods" : "It is therefore timely to perform a systematic review and meta-analysis to assess the efficacy and safety of MMF on current research for its potential use in clinical practice in treating NMOSD" needs to be re-written. Among others…

VERSION 1 – AUTHOR RESPONSE

Dear reviewer:

Thank you very much for your review and evaluation. I'm going to answer your main point of concern as follows:

Article I : "Efficacy and tolerability of azathioprine for neuromyelitis optica spectrum disorder: A systematic review and meta-analysis"

This review aimed to determine the efficacy and tolerability of azathioprine (AZA) compared to other interventions in patients with neuromyelitis optica spectrum disorder (NMOSD) by performing a systematic review and meta-analysis of available efficacy and safety data from various relevant studies. A total of 9 literatures were included. There are 5 observational studies concerning MMF. They concluded that AZA improves relapses and disability in patients with NMOSD but this regimen is associated with relatively frequent adverse events based on limited published evidences. More well-conducted clinical trials are necessary to establish with certainty the beneficial and harmful effects of AZA in patients with NMOSD. In assessing the efficacy of MMF in the treatment of NMOSD, the paper noted “Efficacy data were very limited in the comparison of AZA to mycophenolate mofetil (MMF), to cyclophosphamide, and to interferon-β for patients with NMOSD.” and “Performance of meta-analysis of efficacy data in the included studies was not possible due to the remarkable heterogeneity of the comparator groups.”

Therefore, this paper did not actually quantitatively evaluate the efficacy of MMF in the treatment of NMOSD.

In terms of the safety of MMF in the treatment of NMOSD, although the article mentioned “Occurrence of any adverse event, elevated liver enzymes/hepatoxicity, leukopenia and hair loss associated with AZA use were significantly greater compared to MMF, which may lead to medication noncompliance.”

However, this paper did not compare the adverse events of MMF with other drugs in the treatment of NMOSD, so the safety of MMF in the treatment of NMOSD could not be fully evaluated.

Hence, the purpose of our upcoming study is to directly evaluate the efficacy and safety of MMF in the treatment of NMOSD using available evidence, and I believe that this issue will be fully addressed with the implementation of our paper.

Article II：“Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis”

A total of 6 literatures were included in this study, 3 of which were related to MMF (Chen et al., 2016; Xu et al., 2016; Zhang et al., 2017), and this paper evaluated the difference in efficacy of immunosuppressants such as rituximab (RTX), MMF and AZA in the treatment of NMOSD.

The analysis concluded that the following: “RTX and MMF may be recommended as optimal treatments to prevent relapse in NMOSD. Low-dose cyclosporine A could be a promising alternative therapy.”

Nevertheless, there is no further evidence in the literature that which (MMF or RTX) is the most suitable prescription medication for NMOSD, and this question could be addressed if it is included in this report.

Another disadvantage of this paper is that the forms of literature used in the review included 1 randomized controlled trial (RCT) and 5 observational studies, which made their study lacking in research design methodology. Typically, the network meta included only the RCT or controlled clinical trial (CCT) for review, which makes us skeptical of its conclusion.

Furthermore, the literature related to MMF in this paper are three observational studies that made the number of included studies and closed loops per comparison were few, which might lower reliability of the findings. The number of articles included was limited, and new clinical trial data was updated after development, and some recent retrospective papers were not included.

The conclusion of our paper will be the direct evaluation evidence for the efficacy and safety of MMF in the treatment of NMOSD, which is also the verification and supplement of their contents and conclusions

About our article：

First of all, I would like to point out that there have been no conventional meta-and systematic studies specifically evaluating the effectiveness and safety of MMF in the treatment of NMOSD.

In addition to the reasons stated above, I will focus on explaining the following reasons for the necessity of our research:

1. If our paper is completed, it will be a currently searchable protocol for a traditional meta-and systematic review that directly evaluates the efficacy and safety of MMF in the treatment of NMOSD.
2. The database we searched includes not only English database but also Chinese database. The retrieval time is limited to June 2020, so the number of included literatures is supplemented, which makes the retrieval literature more comprehensive：
   For example, we add 3 retrospective study involving 471 with NMOSD [1-3]**.**
3. Compared to the content of Article II, MMF will be included in the intervention group and the control group will consist of AZA and other medications, and while there will be some variation in the findings, we will contrast the efficacy and safety of different drugs not only with AZA, but also with drugs RTX, cyclophosphamide, methotrexate, Mitoxantrone, Tacrolimus, and cyclosporine.
4. The conclusions of the previously published literature are inconsistent. Poupart argued that RTX was clinically better tolerated than MMF [2]. But Huang et al argued that MMF had the best drug tolerance and was superior to RTX [4]; We expect our research to help solve this problem as well.
5. In this paper, the sources of heterogeneity and different subgroups of the articles will be analyzed to comprehensively evaluate the efficacy and safety of MMF in the treatment of NMOSD, and to

increase the credibility of the article content and conclusions.

Reference

[1]. Zhou Y, Zhong X, Shu Y, et al. Clinical course, treatment responses and outcomes in Chinese paediatric neuromyelitis optica spectrum disorder. Mult Scler Relat Disord. 2019;28:213-220. doi:10.1016/j.msard.2018.12.038.

[2]. Poupart J, Giovannelli J, Deschamps R, et al. Evaluation of efficacy and tolerability of first-line therapies in NMOSD. Neurology. 2020;94(15):e1645-e1656. doi:10.1212/WNL.0000000000009245.

[3]. Shi Z, Du Q, Chen H, et al. Effects of immunotherapies and prognostic predictors in neuromyelitis optica spectrum disorder: a prospective cohort study. J Neurol. 2020;267(4):913-924. doi:10.1007/s00415-019-09649-7.

[4]. Huang W, Wang L, Zhang B, Zhou L, Zhang T, Quan C. Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis. Mult Scler Relat Disord. 2019;35:246-252. doi:10.1016/j.msard.2019.08.009

VERSION 2 – REVIEW

REVIEWER	Carlos de Cabo de la Vega Hospital General de Albacete, Spain
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	The present paper proposes a protocol for a systematic review and meta-analysis to assess the efficacy and safety of mycophenolate mofetil for the treatment of Neuromyelitis optica spectrum disorders. The topic is pertinent and interesting. The paper is well written and the methodology they propose is sound, well described and appropriate for their purpose. The authors have thoroughly revised the English and the paper has much improved in that regard. However, I regret to say that MY MAIN POINT OF CONCERN HAS NOT BEEN ADDRESSED AT ALL by the authors. In my previous report I stated my concern that the paper may not be original, since two systematic review and meta-analysis papers have been recently published covering this topic: - Huang W, Wang L, Zhang B, Zhou L, Zhang T, Quan C. Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis. Mult Scler Relat Disord. 2019 Oct;35:246-252. doi: 10.1016/j.msard.2019.08.009. Epub 2019 Aug 9. PMID: 31425902. - Espiritu AI, Pasco PMD. Efficacy and tolerability of azathioprine for neuromyelitis optica spectrum disorder: A systematic review and meta-analysis. Mult Scler Relat Disord. 2019 Aug;33:22-32. doi: 10.1016/j.msard.2019.05.011. Epub 2019 May 22. PMID: 31136907. This last paper is actually already on the “Reference” list, but it is only cited to support the Method. I will try to make myself clearer this time. THE AUTHORS MUST:

	1- INCLUDE this reference in their “Reference” section in their manuscript: - Huang W, Wang L, Zhang B, Zhou L, Zhang T, Quan C. Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis. Mult Scler Relat Disord. 2019 Oct;35:246-252. doi: 10.1016/j.msard.2019.08.009. Epub 2019 Aug 9. PMID: 31425902. (The Espiritu and Pasco paper is already on the “Reference” list, but it is only cited to support the Method.) 2 –EXPLAIN both in the In the “Introduction” section and in the “Discussion “ section of their manuscript IN WHAT WAY THEIR PROPOSED STUDY IS DIFFERENT from the systematic reviews and meta-analyses already published by Huang et al, 2019 and Espiritu and Pasco 2019. Only one year has gone by since those studies were published, so, in principle, it would be too soon to do another study on the same topic. What is the new contribution from the proposed paper that justifies another systematic review and meta-analysis on this topic so soon? What is different/ better/ more complete… from what it has already been published? What did the other papers missed? Are the authors searching other databases? Are the authors using a different analysis? All this needs to be explained in the paper by the authors both in the INTRODUCTION and the DISCUSSION, perhaps also in the ABSTRACT. MINOR POINTS: 1- Page 2, Abstract. Introduction. lines 3 (coordinate 31): “higher incidence in women and Asian.” This sentence seems incomplete. Do they mean: “higher incidence in women and Asian PEOPLE”? 2- Page 5, lines 10-11 (coordinates 22-23) “myelosuppression that result in drug withdrawal or replacement of patients with NMOSD. Rituximab has also been reported in recent years as infusion reactions…” The meaning is not clear. Do they mean “myelosuppression that resultS in drug withdrawal or replacement of THESE DRUGS IN patients with NMOSD. OTHER AEs FOR Rituximab HAVE also been reported in recent years SUCH as infusion reactions…”? 3- Page 5, Line 22 (coordinates 43-44) “At present, ONLY LOW EVIDENCE exists concerning comparative treatment efficacy of MMF with other drugs” This lines needs to be change to acknowledge the publications from Huang et al 2019 and Espiritu and Pasco 2019. 4- Page 9, Line 20 (coordinate 43) “the issue of a unit of analysis” should be “a unit of analysis issue” 5- Page 10, Lines 9-10 (coordinate 20-21): “Where meta-analysis is not feasible due to lack of clinical trials or heterogeneity, systematic narrative synthesis is adopted.” The tenses are not correct: “Where meta-analysis MAY NOT BE not feasible due to lack of clinical trials or heterogeneity, systematic narrative synthesis WILL BE adopted.”

VERSION 2 – AUTHOR RESPONSE

Dear reviewer:

Thank you again for your hard work in reviewing and evaluating my article. I'm going to answer your main point of concern as follows. Here, I first listed two published literature related to MMF,

respectively discussing the main content of their research and the similarities and differences with this research. Secondly, I also modified the introduction and discussion of my paper to clarify and improve the content of the research topic. Please refer to the manuscript for details. Finally, we explain here why our article is necessary.

Article I：“Efficacy and tolerability of azathioprine for neuromyelitis optica spectrum disorder: A systematic review and meta-analysis”

This review aimed to determine the efficacy and tolerability of azathioprine (AZA) compared to other interventions in patients with neuromyelitis optica spectrum disorder (NMOSD) by performing a systematic review and meta-analysis of available efficacy and safety data from various relevant studies. A total of 9 literatures were included. There are 5 observational studies concerning MMF. They concluded that AZA improves relapses and disability in patients with NMOSD but this regimen is associated with relatively frequent adverse events based on limited published evidences. More well-conducted clinical trials are necessary to establish with certainty the beneficial and harmful effects of AZA in patients with NMOSD. In assessing the efficacy of MMF in the treatment of NMOSD, the paper noted “Efficacy data were very limited in the comparison of AZA to mycophenolate mofetil (MMF), to cyclophosphamide, and to interferon-β for patients with NMOSD.” and “Performance of meta-analysis of efficacy data in the included studies was not possible due to the remarkable heterogeneity of the comparator groups.”

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8. Compared to the content of Article II, MMF will be included in the intervention group and the control group will consist of AZA and other medications, and while there will be some variation in the findings, we will contrast the efficacy and safety of different drugs not only with AZA, but also with drugs RTX, cyclophosphamide, methotrexate, Mitoxantrone, Tacrolimus, and cyclosporine.

9. The conclusions of the previously published literature about the clinical effect of MMF are inconsistent. Poupart argued that RTX was clinically better tolerated than MMF [2]. But Huang et al argued that MMF had the best drug tolerance and was superior to RTX [4]; We expect our research to help solve this problem as well.
10. In this paper, the sources of heterogeneity and different subgroups of the articles will be analyzed to comprehensively evaluate the efficacy and safety of MMF in the treatment of NMOSD, and to increase the credibility of the article content and conclusions.

Reference

[5]. Zhou Y, Zhong X, Shu Y, et al. Clinical course, treatment responses and outcomes in Chinese paediatric neuromyelitis optica spectrum disorder. Mult Scler Relat Disord. 2019;28:213-220. doi:10.1016/j.msard.2018.12.038.

[6]. Poupart J, Giovannelli J, Deschamps R, et al. Evaluation of efficacy and tolerability of first-line therapies in NMOSD. Neurology. 2020;94(15):e1645-e1656. doi:10.1212/WNL.0000000000009245.

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[8]. Huang W, Wang L, Zhang B, Zhou L, Zhang T, Quan C. Effectiveness and tolerability of immunosuppressants and monoclonal antibodies in preventive treatment of neuromyelitis optica spectrum disorders: A systematic review and network meta-analysis. Mult Scler Relat Disord. 2019;35:246-252. doi:10.1016/j.msard.2019.08.009

VERSION 3 – REVIEW

REVIEWER	Carlos de Cabo de la Vega Hospital General de Albacete, Spain
REVIEW RETURNED	08-Sep-2020

GENERAL COMMENTS	The authors have successfully addressed all my concerns. I believe that the paper is now ready for publication.