Author’s response to reviews

Title: Effectiveness of rituximab in neuromyelitis optica: A meta-analysis

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Author’s response to reviews:

(Reviewer 1):

The paper is a meta-analysis of the effect of RTX in NMO patients.

Despite the previous publication of this meta-analysis in JAMA Neurol 2016 by Damato and colleagues, this confirmatory study includes more studies and offers additional data validating the use of RTX in this pathology.

Re : Thank you very much for your valuable comments.

Subgroup analysis includes a comparison of the RTX effect versus the dosage used. This dataset is not usable as presented here because the most important is clearly not only the dosage used during the induction phase, but also during the maintenance period. The comparison of the group according to that must be done (1g / 6months vs 2g / 6months for example).

Another subgroup analysis will be interesting and is currently being discussed in clinical practice which is the use of RTX in the first line or second line. This comparison will add substantial data to the knowledge in that field.

Re : We conducted a meta-regression on the heterogeneity of the article and corrected some of the content.
Please list the causes of death. I will be very surprised at the lack of relationship between RTX and this side effect.

Re: We supplemented the cause of the patient's death.

Please correct Ze'phir by Zephir

Re: This has been corrected

Discussion:

Please discuss the comparison between the submitted study and the Damato meta-analysis.

please correct: RTX is not expensive: in Europe, it costs about 700 euros the lot of 500 mg. This product has been biosimilarized.

please correct: no randomized trials in NMO: wrong, at least satralizumab and eculizumab have recently successfully completed a phase III study.

Re: We have corrected some of the content of the article.

(Reviewer 2):

The reviewed manuscript is a meta-analysis assessing the effectiveness of Rituximab (RTX) as therapy for Neuromyelitis Optica (NMO), based on studies published about it from 2008 to nowadays. The authors concluded RTX has acceptable tolerance, reduces the frequency of relapse, and improves disability in most patients.

While there are some problems with the writing of this manuscript, the issue is an important one, seems appropriate for BMC Neurology and could be of potential interest to readers. However, I am concerned that there has recently been a very similar publication using similar methodology, which may bring difficulties in the present study to add some new scientific element. In addition, I have other concerns that must be addressed, as following.

Re: Thank you very much for your valuable comments.

Title:

The pharmacological concept of efficacy involves studies that aim to know if a drug brings more benefits than impairments under ideal conditions, usually obtained in randomized controlled
trials (RCT). Effectiveness studies are those that evaluate benefits and prejudices, assessed in real world studies (RWS).(1,2) The meta-analysis in question seems to have basically evaluated RWS, since there are no RCTs assessing the issue RTX on NMO. Therefore, I believe that the word "effectiveness", not efficacy, would be more appropriate for the title.

Re: Thank you very much for your valuable comments. This has been corrected

Abstract:

It is mentioned that 28 studies were selected: 19 using ARR and 24 EDSS. It is not mentioned for what purpose these parameters were used in such studies. I suggest the inclusion of text: "To evaluate the effectiveness of RTX, the ARR and EDSS ..." or something like this.

In addition, the sum of the mentioned studies totals 43, but were selected 28. Although it is understood that some studies used the two criteria, to facilitate the reader's understanding this should be made explicit in the text.

"The mean difference of ARR ratio after rituximab therapy was 1.59 (95% CI, 1.33 to 1.85), and a mean difference 1.14 (95% CI, 0.95 to 1.33) reduction in the mean EDSS score."

- This passage seems confusing. It would be appropriate to rewrite it.

"However, the potential impact of early diagnosis of NMO and treatment with RTX in reducing health-care costs and improving functional outcome should be carefully addressed in future studies."

- Was this outcome assessed in the study? Was this outcome among the objectives? If positive, it should be mentioned in the Abstract in the Objectives topic, as it seems significant.

Re: We have corrected the abstract part of the article. Make some modifications based on your suggestions.

Background:

Autoantibodies are directed against astrocytic AQP4 and not against AQP-4ab. Again, I suggest changing the term efficiency to effectiveness.

Re: This has been corrected

Methods:
"After excluding duplicates (n = 85) and inappropriate articles (n =962), we retained for analysis 28 relevant studies published between 2008 and 2018"

- This text seems to be displaced here, referring already to the results of the bibliographical research and not to the methods themselves.

"Published in various journals 'on RTX' in patients with NMO…"

- I believe there is a misunderstanding in this expression.

Inclusion and exclusion criteria:

In the exclusion item, "studies with incomplete information", it is important to define previously what information was extracted from the studies, in order to define what a study with incomplete information is.

DESS: This acronym is incorrect.

'A comprehensive search of the literature was undertaken in order to identify research the efficacy of rituximab in NMO."

- This phrase seems misplaced at the end of the paragraph; I believe the paragraph should be rewritten.

Re: Based on your suggestions, we have corrected the method part of the article.

Statistical Analysis

When heterogeneities are identified in the treatment effect, one can opt for several approaches: (1) Ignore heterogeneity - use the fixed effect model in estimating the treatment effect. (2) Consider heterogeneity - use the random effects model to estimate the treatment effect. Another option is not to group all studies, because there may be two sources of variation: variation in studies (among patients) and variation between studies. (3) Explore heterogeneity - opt for subgroup analysis (subgroup of clinical trials or subgroup of participants) or for meta-regression (statistical analysis that relates effect size to study characteristics, eg average age, proportion of women, drug dose). (3,4,5)

In the present meta-analysis, two statistical methods were used, related to the presence or absence of heterogeneity in the included studies. However, these studies could not be weighted together in a meta-analysis, because this can induce bias. An alternative would be to divide the included studies into two different groups for analysis.

Interpretatively, an I2 value close to 0% indicates no heterogeneity between studies, close to 25% indicates low heterogeneity, close to 50% indicates moderate heterogeneity and close to
75% indicates high heterogeneity between studies. I believe that for the reader’s understanding this classification should be inserted in the statistical analysis text.

How were the causes of heterogeneity analyzed? There is no record of the use of statistical method for it, such as meta-regression.

The demographic, clinical, dose of infusion, and tolerability and safety parameters that were extracted from the included studies should be described in the methodology.

Re: Based on your suggestions, we have corrected the statistical part of the article.

Results:

Efficacy on the ARR Ratio:

There are several references to weak, moderate or strong I2 indices, but this classification was not mentioned in the methodology previously.

"... and found that Cabre 2018 significantly affected heterogeneity (I2=0%, P=0.78)."

- This is a meaningless phrase.

The sensitivity analysis assessed the dose regimen of RTX was performed using which statistical method?

The asymmetry of the funnel plot may be due to causes other than publication bias. Any influential covariates related to precision (or sample size) can induce such a pattern of confusion. Non-parametric and parametric methods of the Egger test, to formally test asymmetry, can be used. (4)

Re: Based on your suggestions, we have corrected the results of the article. We conducted a meta-regression on the heterogeneity of the article and corrected some of the content.

Discussion:

Data from previous studies by Kim et al were considered separately. However, this author describes the same patient population at different points in time.(6) I think that this created a certain overhead of total number of patients.

"We performed a subgroup analysis of ARR and found that its heterogeneity was significantly correlated with drug dose."

- Is it possible to conclude this? Are there no other factors influencing on heterogeneity? In a recent meta-analysis published, the meta-regression analysis performed showed that the
number of rituximab reinfusions does not affect the ARR ratios and EDSS scores in patients with NMO.\(^{(6)}\)

"Sensitivity analysis of the subgroup revealed that Cabre2018 [12] had a greater impact on heterogeneity. A careful reading of Cabre 2018 found that the baseline ARR of this document was lower than the baseline ARR observed in other literatures. The therapeutic effect of RTX varies among patients with different outcomes. Differences in follow-up time, ethnic differences, and other immunosuppressive treatments in some patients before and after RTX treatment were important reasons for heterogeneity".

- This paragraph seems confusing, and presents contradictions.

The paragraphs 3, 4, 5, 6 and 7th of discussion appear to be devoted to a review of the literature on pharmacological properties, biological effects and monitoring of RTX treatment, not correlating with the study objectives. In addition, it is redundant on aspects already addressed in the introduction of the study.

There is an absence of comparative with the results obtained in the current meta-analysis and previous publications with the same methodology. In addition, no discussion about what new contributions the present study brings to the topic to elucidate the effects of RTX therapy on NMO. The limitations of the study, such as the inclusion of only observational studies, with significant heterogeneity, or the absence of meta-regression evaluating, were not addressed. The meta-regression would be very important, suggesting that the observed heterogeneity may be due to the variability of sample sizes (ie, the number of patients enrolled) in the studies included. Also, the positive aspects, such as the inclusion of 11 new studies assessing the issue recently published and not included in a recently meta-analysis,\(^{(6)}\) were not highlighted or discussed.

Re: 1. Based on your suggestions, we have corrected the discussion section of the article.

2. The third, fourth, fifth, and sixth paragraphs of the discussion are further discussions of some of the secondary indicators in the treatment of RTX in NMO. So we think this is a necessary part.

3. We carefully interpret Kim's two articles and find that they are not the same study, so they are all included in the meta-analysis.

References:

There seems to be a problem with reference number 11.

Re: This has been corrected
Tables:

Table 1: were 28 or 29 studies selected?

Re: This has been corrected