OPEN PEER REVIEW

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Shiraz E-Medical Journal
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Peer Review Report for "Infusion-Related, Short-term, and Delayed Side Effects of Rituximab in Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder"

Author(s): Farzane Farzadfard, Maryam Poursadeghfard, Nahid Ashjazadeh

Review Timeline:

Submit Date: 17 Feb 2020
Revised Date: 27 Jun 2020
Accepted Date: 27 Jun 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0) — 10 Jun 2020

Dear AE,
This is an interesting pharmacovigilance study.
please the authors describe below items in your manuscript:
1- do not use any abbreviation at abstract
2- please describe your pharmacovigilance-ADR evaluation tools
3- Is it a questionnaire or checklist?
4- how you did reliability and validity of your tool?
Thanks

Abdorreza Naser Moghadasi: Reviewer | **Revision** (0) — 10 Jun 2020

Dear AE,
This is a valuable study but needs major revisions before publication:
1- The title should be changed to “Infusion-related, short term and delayed side effects of rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder”

2- The “introduction” should be rewritten again. This paragraph is wrong:
“Another issue is the safety and side effects of this drug, which has not been studied systematically and there is limited experience in this regard (1). Some studies have been conducted on the side effects of this drug in other diseases such as rheumatoid arthritis (RA), but due to differences in patient population and drug administration regimens, its generalization to MS patients should be considered cautiously (1, 9).”
There are multiple articles which describe the side effects of rituximab in multiple sclerosis and NMO.
3- In method section the authors should explain the checklist in details. How did they investigate the infections? Did they consider the CBC and LFT in follow up?
4- The authors should clarify which type of rituximab has been used in this study? Was it biosimilar? Mabtera, Zytux, Rituxan ….?
5- In the result section the comparison of first infusion related side effects between 4 described groups was not meaningful. The authors should perform this comparison between MS and NMO patients.
6- The authors should compare their findings with other Iranian study. You should consider below-mentioned studies:
Efficacy and safety of rituximab in patients with refractory neuromyelitis optica spectrum disorders: A prospective observation in Iranian cases. Seyed Ahadi M, Naser Moghadasi A, Asgari N, Sahraian MA.Caspian J Intern Med. 2020;11(2):155-162. doi: 10.22088/cjim.11.2.155.
Evaluating the efficacy and safety of ZytuxTM (Rituximab, AryoGen pharmed) in Iranian multiple sclerosis patients: An observational study.
Naser Moghadasi A, Darki A, Masoumi P, Hashemi SN, Ghadiri F. Mult Scler Relat Disord. 2019 Nov;36:101419. doi: 10.1016/j.msard.2019.101419. Epub 2019 Sep 27.
Efficacy and safety of biosimilar rituximab in patients with pemphigus vulgaris: a prospective observational study.
Toosi R, Mahmoudi H, Balighi K, Teimourpour A, Alaeen H, Shaghaghi M, Abedini R, Daneshpazhooh M. J Dermatolog Treat. 2019 May 28:1-8. doi: 10.1080/09546634.2019.1617831. [Epub ahead of print]
Long-term tolerability, safety and efficacy of rituximab in neuromyelitis optica spectrum disorder: a prospective study.
Shaygannejad V, Fayyazi E, Badihian S, Mirmosayyeb O, Manouchehri N, Ashtari F, Asgari N.
J Neurol. 2019 Mar;266(3):642-650. doi: 10.1007/s00415-019-09180-9. Epub 2019 Jan 11.
Thanks

REFEREE: Associate Editor | **Revision** (0) 16 Jun 2020

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (0) 16 Jun 2020

Dear Author,

The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.

Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear reviewers, thank you very much for your excellent scientific comments that definitely improve our article. It is our pleasure to edit the article according to your recommendations.

Reviewers' Comments:

Reviewer 1:

This is a valuable study but needs major revisions before publication:
1- The title should be changed to "Infusion-related, short term and delayed side effects of rituximab in multiple sclerosis and neuromyelitis optica spectrum disorder" This comment was made.

2- The "introduction" should be rewritten again. This paragraph is wrong:
"Another issue is the safety and side effects of this drug, which has not been studied systematically and there is limited experience in this regard (1). Some studies have been
conducted on the side effects of this drug in other diseases such as rheumatoid arthritis (RA), but due to differences in patient population and drug administration regimens, its generalization to MS patients should be considered cautiously (1, 9)."
There are multiple articles which describe the side effects of rituximab in multiple sclerosis and NMO. This paragraph was corrected and additional explanations were given.

3- In method section the authors should explain the checklist in details. How did they investigate the infections? Did they consider the CBC and LFT in follow up? It was explained in the method part. We also declared this point in our limitation.

4- The authors should clarify which type of rituximab has been used in this study? Was it biosimilar? Mabtera, Zytux, Rituxan ….? It was explained.

5- In the result section the comparison of first infusion related side effects between 4 described groups was not meaningful. The authors should perform this comparison between MS and NMO patients. We compared first and next infusions to investigate at what stage the side effects are more frequent. Also, we did not compare 2 groups of MS and NMO owing to low number of NMO patients (126 vs 9)

6- The authors should compare their findings with other Iranian study. You should consider below mentioned studies:

Efficacy and safety of rituximab in patients with refractory neuromyelitis optica spectrum disorders: A prospective observation in Iranian cases. Seyed Ahadi M, Naser Moghadasi A, Asgari N, Sahraian MA.Caspian J Intern Med. 2020;11(2):155-162. doi: 10.22088/cjim.11.2.155.

Evaluating the efficacy and safety of ZytuxTM (Rituximab, AryoGen pharmed) in Iranian multiple sclerosis patients: An observational study.
Naser Moghadasi A, Darki A, Masoumi P, Hashemi SN, Ghadiri F. Mult Scler Relat Disord. 2019 Nov;36:101419. doi: 10.1016/j.msard.2019.101419. Epub 2019 Sep 27.

Efficacy and safety of biosimilar rituximab in patients with pemphigus vulgaris: a prospective observational study.
Toosi R, Mahmoudi H, Balighi K, Teimourpour A, Alaeen H, Shaghaghi M, Abedini R, Daneshpazhooh M. J Dermatolog Treat. 2019 May 28:1-8. doi: 10.1080/09546634.2019.1617831. [Epub ahead of print]

Long-term tolerability, safety and efficacy of rituximab in neuromyelitis optica spectrum disorder: a prospective study.
Shaygannejad V, Fayyazi E, Badihian S, Mirmosayyeb O, Manouchehri N, Ashtari F, Asgari N.
J Neurol. 2019 Mar;266(3):642-650. doi: 10.1007/s00415-019-09180-9. Epub 2019 Jan 11.

We included these studies in the discussion part. However, these surveys are different with our study as studied population had pemphigus and NMO in 3 of them and in the 4th one, the main endpoint was efficacy (rather than safety) in MS patients.

Reviewer 2:
Dear Authors,
Thank you to submit your valuable manuscript to our journal.
this is an interesting pharmacovigilance study.
please describe below items in your manuscript:

1 do not use any abbreviation at abstract. Abbreviations used in abstract were deleted.

2-please describe your pharmacovigilance-ADR evaluation tools. This study was not a new clinical trial or case-control study with placebo comparison. There are many previous known side effects of rituximab in the other diseases. We just followed them in MS population with a fixed dose of medication. So, we did not use pharmacovigilance-ADR tool. However, we made plan to use Naranjo ADR form if we had newly recognized side effects aside from what has been reported before. Actually, our results were similar other reports.

3-is it questionnaire or checklist? We used a checklist in which we considered all side effects reported in the other studies; also new side effects we faced during the study.

4-how you did reliability and validity of your tool? It was only a checklist and prepared just for data collection.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: EIC | **Revision (1)** 27 Jun 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.