Efficacy of rituximab in neuromyelitis optica: A meta-analysis

CURRENT STATUS: ACCEPTED

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DOI: 10.21203/rs.1.17/v1

SUBJECT AREAS
Internal Medicine Specialties
Abstract

Background: Neuromyelitis optica (NMO) is a severe autoimmune disorder of inflammatory central nervous system, which often resulting in paralysis or blindness. Rituximab (RTX) is a mouse-human chimeric monoclonal antibody specific for the CD20 antigen on B lymphocytes used to treat many autoimmune diseases. This review performed a meta-analysis of the efficacy of rituximab use in NMO. Methods: We searched through the databases of PubMed, Embase, and Cochrane Library. We compiled 28 studies in this meta-analysis: 19 used annualized relapse rate (ARR) ratio, 24 used Expanded Disability Status Scale (EDSS) score. Differences in the ARR ratio and EDSS score before and after rituximab therapy were the main efficacy measures. After a consistency test, the publication bias was evaluated and a sensitivity analysis was performed with mean difference (MD) of the efficacy of rituximab. Results: A meta-analysis of 28 studies with 613 participants total was conducted. NMO patients have antibodies against aquaporin 4 autoantibody (AQP4-Ab) were recorded in 440 of 613 (71.78%). 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. 345 of 563 patients (61.28%) reached a relapse-free state. 94 of 613 (15.33%) patients had adverse reactions. Conclusions: RTX has acceptable tolerance, reduces the frequency of relapse, and improves disability in most patients. 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.

Background

Neuromyelitis optica (NMO) is a severe demyelinating disease, predominantly affecting the optic nerve and the spinal cord. The pathogenesis of NMO is related to the aquaporin-
4 autoantibody (AQP4-Ab) [1-3]. Serum autoantibodies targeting AQP4-Ab have become sensitive and specific biomarker that enable early diagnosis of NMO and are found in most patients. Because the progression of NMO disability is related to the severity of the attacks, prophylactic treatment of NMO recurrence must be performed as soon as NMO is identified. Since studies have found that NMO patients have antibodies against AQP4-Ab, several studies have proposed treatment for B cells in NMO[4].

Rituximab (RTX) is a chimeric monoclonal antibody directed against CD20 epitope expressed on pre-B and mature B cells, and is used to treat B-cell-derived lymphoid neoplasms and antibody-mediated autoimmune diseases [5, 6]. The depletion of CD20 provides a theoretical basis for the treatment of autoimmune diseases in which B cells and autoantibodies play a key role, such as NMO, in which AQP4-Ab have been associated with the disease[7]. Here, we perform a meta-analysis to test rituximab efficacy is both well safe and tolerated, and examined the treatment efficacies using relapse rates and disability in NMO.

Methods

Literature search

This search was restricted only to articles published in English language. We searched for publications on the PubMed, Embase, Cochrane Library, without any temporal restriction. We did keyword and Medical Subject Heading (MeSH) searches for our theme, and MeSH terms, key words and their synonyms related to “rituximab” and “neuromyelitis optica”. After excluding duplicates (n = 85) and inappropriate articles (n =962), we retained for analysis 28 relevant studies published between 2008 and 2018. A flowchart of the search strategy is shown in Fig. 1. One of us used a standardized form of data extraction to extract data, another person checks it, and revisits the data that does not match, and resolves the
differences through discussion and consensus.

Inclusion and exclusion criteria for the literature

Studies were included if they fulfilled the following criteria: 1) Published in various journals on RTX in patients with NMO; 2) Patients with NMO do not limit their age, gender, ethnicity, and whether they have received treatment before; 3) Main variables include ARR and/or EDSS; Exclusion criterion: 1) Case reports and studies that included fewer than 2 patients, review, meta-analysis; 2) studies with incomplete data.

Main variables

Among the 28 articles selected, we extracted the values (means and standard deviations) of DESS and ARR directly available. Disability was measured by the EDSS. The ARR were calculated using the total number of relapses per patient-year. A comprehensive search of the literature was undertaken in order to identify research the efficacy of rituximab in NMO.

Statistical Analysis

Data analysis was performed using statistical software provided by the Cochrane Collaboration (RevMan 5.3). The heterogeneity across each effect size was evaluated with the I2 index, in which I2 > 50% was considered heterogeneous among included studies. If P>0.1, I<250%, a fixed-effect model was used for meta-analysis. When P<0.1, I>50%, a random-effect model was used instead and first analyzed the causes of heterogeneity, such as design, measurement methods, age, gender and other factors are consistent. A P value < 0.05 was considered as clinical significance.

Results
Study identification and selection

By searching PubMed, Embase, and Cochrane library database dated until August 2018. The database search identified 1075 records. After removing duplicates, 990 titles were initially screened and 146 theme-related abstracts were selected for further screening. Finally, 28 studies were included in this systematic review. 19 used ARR ratio, 24 used EDSS score.

Demographic and clinical characteristics

Table 1 lists detailed information from 28 included studies. The included studies were published between 2008 and 2018. The number of participants per study ranged from 3 to 100, with a total number of 613 (537 female and 69 male, with sex not specified in 7 patient). NMO patients have antibodies against AQP4-Ab were recorded in 440 of 613 (71.78%).

Efficacy on the ARR Ratio

Fig. 2 shows a forest plot of the mean difference in the ARR ratio before and after rituximab therapy. This finding suggested that the mean difference of ARR ratio after rituximab therapy was 1.59 (95% CI, 1.33 to 1.85). A random-effect model was used with I² of 81%.

In the subgroup analysis based on different rituximab doses, the 1000 mg infused twice during a 2-week interval has a greater degree of heterogeneity (I²=0%, P=0.74). Similar degrees of heterogeneity were demonstrated in the subgroup analyses by the 375 mg/m² infused once weekly for 4 weeks (I²=93%, P<0.001). The heterogeneity of 100 mg once per week for 3 consecutive weeks is low (I²=0%, P=0.55), the 375 mg/m² infused once weekly
for 4 weeks and/or 1000mg infused twice during a 2-week interval was moderate (I²=45%, P=0.09), and the not mention a clear dose was at least moderate (I²=57%, P=0.1) (Fig. 3).

Sensitivity analyses were performed by removing each study in turn and re-analyzed. We performed a sensitivity analysis on the 375 mg/m2 infused once weekly for 4 weeks group and found that Cabre 2018 significantly affected heterogeneity(I²=0%, P=0.78).

Efficacy on the EDSS Score

Fig. 4 shows a forest plot of the mean difference in the EDSS score before and after rituximab therapy. This finding suggested that the mean difference of EDSS score after rituximab therapy was 1.14 (95%CI, 0.95 to 1.33). The heterogeneity was moderate (I²=11%, P=0.31).

Safety

345 of 563 patients (61.28%) reached a relapse-free state. Adverse effects were recorded in 94 of 613 (15.33%) patients treated with rituximab. Twelve of the patients experienced severe adverse reactions, five patients developed severe pneumonia, two patients developed transit hyperpyrexia, two patients developed septicemia, one patient developed a severe allergic reaction, one patient had a urogenital infection, and one patient developed seborrheic dermatitis. Six patients died.

Publication bias

The funnel plot for studies on the incidence of ARR and EDSS were symmetrical. The funnel plots indicated an absence of publication bias. (Fig. 5)

Discussion
NMO is a relapsing disease with a high early mortality rate. Without employing appropriate immunosuppressant treatment, more than 50% of patients with NMO will be functionally blind, or will progress to wheelchair dependence, within 5 years [8, 9]. Its treatment options are based on case series and expert opinion, and immunosuppressive therapy is the main method to prevent recurrence and prevent disability. The successful use of RTX has been widely reported in NMO. However, there are no randomized controlled trials in NMO and there are currently no established guidelines for the treatment of RTX. Although rituximab is expensive, it can offset the cost of recurrence and plasma exchange with its good therapeutic effect [10, 11].

We performed a subgroup analysis of ARR and found that its heterogeneity was significantly correlated with drug dose. Sensitivity analysis of the subgroup revealed that Cabre 2018 [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. One obvious factor is the duration of RTX treatment. Differences in follow-up time, ethnic differences, and other immunosuppressive treatments in some patients before and after RTX treatment were important reasons for heterogeneity.

With the increasing number of treatment options, the choice of the right therapeutic agent for the right patient becomes more important. Monoclonal antibody therapies are perspective options for NMO patients to prevent relapses compared with traditional immunosuppressants, especially in refractory patients. Some studies have used RTX as a first-line treatment for prophylactic treatment, which can reduce the severity of disease recurrence [13, 14]. Quan et al. has reported that rituximab treatment is well tolerated and resulted in a gradual recovery of neurological function. Rituximab mainly exerted its
function through two stages. It not only eliminates or inhibits the pathogenic effector B cells to achieve early effects, but also regulates the proportion of functional B cells to make a more lasting improvement in efficacy [15].

Although AQP4-Ab is critical in the diagnosis of NMO, its involvement in the pathogenesis of the disease remains controversial[9]. Some studies suggest that AQP4-Ab is generally used as a marker of disease activity in an individual patient, and AQP4-IgG titers increase significantly during NMO recurrence period, but these indices decline during remission period [16, 17]. Therefore, there is a correlation between rises in antibody levels and clinical attacks, and treatment with RTX resulted in the most pronounced decline in AQP4-Ab levels. However, many studies have shown that AQP4-Ab is only a diagnostic marker for NMO, which can be detectable in serum during relapse as well as during remission. RTX can effectively reduce CD20 B cells in blood and cerebrospinal fluid, but it does not eliminate plasma cells in the bone marrow. This may be other mechanisms beyond AQP4-Ab to maintain disease stabilization, including inhibition of B cell/T cell interactions, increased regulatory T cells, and decrease of CD20 cells with reduction of proinflammatory cytokines, as well as modulation of the T cell compartment [18, 19]. Therefore, there is a lack of correlation between AQP4-Ab titers and clinical disease activity. Partial AQP4-Ab negative NMO patients still have a good response to the treatment of RTX [20].

Maintaining the consumption of memory B cells by repeated treatment may be the pivotal to the clinical effects of RTX in NMO patients [21]. Some studies have developed a personalized maintenance treatment program for CD19 + CD27 + memory B cell detection, and achieved good results. However, the increase in the relapses rate of NMO also occurs in the case of low levels of CD19+ B cells, which makes it difficult to control the disease [12, 14, 22-24]. Therefore, CD27+ memory B cells can better detect the therapeutic effect of
RTX relative to CD19 + B cells.

Yang et al. found that in Asian NMO, lower doses of RTX can achieve better reactivity with cost and availability advantages[25]. Low doses of RTX can effectively reduce the recurrence rate and improve the prognosis in most NMOs cases. Repeated RTX treatments are superior to single RTX doses for NMO therapy. Some patients required an increased frequency of RTX infusion to maintain low levels of CD19+ cells, and long-term use of lower dose RTX may lead to cost savings [19, 26].

Due to ethical issues, the current study of rituximab lacks a placebo control group [12]. However, Zhang et al. has investigated the NMO patients treated with RTX and acetazolamide (AZA), study has found that RTX is more effective in preventing NMO recurrence than patients treated with AZA and can improve symptoms [27]. The most common reported adverse drug reactions are infections. A decrease in immunoglobulin levels was observed in some patients following rituximab treatment, which may increase the probability of infection in patients [28, 29]. Relatively few reports of serious adverse reactions leading to death. In our meta-analysis, most of the 6 patients died due to serious illness and related complications. Not related to the treatment of RTX.

Our meta-analysis was not only to present efficacy data, but also to expand the knowledge about the safety of RTX treatments. Although RTX has significant benefits for the treatment of NMO, long-term benefits and risks remain to be determined. Moreover, most patients receive other immunotherapies before and after RTX treatment, so the benefits and risks of treatment are inaccurate due to a single drug [5, 20, 30, 31]. And it is unclear whether patients have the appropriate time to discontinue RTX treatment without the risk of further relapse.
Conclusions

RTX has acceptable tolerance, reduces the frequency of relapse, and improves disability in most patients. 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.

Declarations

Acknowledgements

None

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Availability of data and materials

All data analyzed during this study are included in this article.

Authors’ contributions

FLG, BYC: search and screen the literature, extract the data, drafting the manuscript. CG, RPW, TD, YPY: collate the data. YZ: revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.
Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Annovazzi P, Capobianco M, Moiola L, Patti F, Frau J, Uccelli A, et al. Rituximab in the treatment of Neuromyelitis optica: A multicentre Italian observational study. J Neurol. 2016; 263(9):1727-35.

2. Bedi GS, Brown AD, Delgado SR, Usmani N, Lam BL, Sheremata WA. Impact of rituximab on relapse rate and disability in neuromyelitis optica. Mult Scler. 2011; 17(10):1225-30.

3. Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85(2):177-89.

4. Bukhari W, Barnett MH, Prain K, Broadley SA. Molecular pathogenesis of neuromyelitis optica. Int J Mol Sci. 2012; 13(10):12970-93.
5. Ip VH, LauAY, Au LW, Fan FS, ChanAY, Mok VC, et al. Rituximab reduces attacks in Chinese patients with neuromyelitis optica spectrum disorders. J Neurol Sci. 2013; 324(1-2):38-9.

6. Mauer G, Du L, Vaßen R. Atmospheric plasma spraying of single phase lanthanum zirconate thermal barrier coatings with optimized porosity. Coatings. 2016; 6:49.

7. Valentino P, Marnetto F, Granieri L, Capobianco M, A B. Aquaporin-4 antibody titration in nmo patients treated with rituximab: A retrospective study. Neurol Neuroimmunol Neuroinflamm. 2016; 4(2):e317.

8. Birnbaum J, Kerr D. Optic neuritis and recurrent myelitis in a woman with systemic lupus erythematosus. Nat Clin Pract Rheumatol. 2008; 4(7):381-6.

9. Jacob A, Matiello M, Weinshenker BG, Wingerchuk DM, Lucchinetti C, Shuster E, et al. Treatment of neuromyelitis optica with mycophenolate mofetil retrospective analysis of 24 patients. Arch Neurol. 2009; 66(9):1128-33.

10. Chay J, Donovan P, Cummins L, Kubler P, Pillans P. Experience with low-dose rituximab in off-label indications at two tertiary hospitals. Intern Med J. 2013; 43(8):871-82.

11. A. J, B.G. W, I. V, N. M, L. K, R.J. F, et al. Treatment of neuromyelitis optica with rituximab: Retrospective analysis of 25 patients. Arch Neurol. 2008; 65(11):1443-8.

12. Cabre P, Mejdoubi M, Jeannin S, Merle H, Plumelle Y, Cavillon G, et al. Treatment of neuromyelitis optica with rituximab: A 2-year prospective multicenter study. J Neurol. 2018; 265(4):917-925.
13. Lin J, Xue B, Li X, Xia J. Monoclonal antibody therapy for neuromyelitis optica spectrum disorder: Current and future. Int J Neurosci. 2017; 127(8):735-744.

14. Olivieri G, Nociti V, Iorio R, Stefanini MC, Losavio FA, Mirabella M, et al. Rituximab as a first-line treatment in pediatric neuromyelitis optica spectrum disorder. Neurol Sci. 2015; 36(12):2301-2.

15. Quan C, ZhangBao J, Lu J, Zhao C, Cai T, Wang B, et al. The immune balance between memory and regulatory B cells in NMO and the changes of the balance after methylprednisolone or rituximab therapy. J Neuroimmunol. 2015; 282:45-53.

16. Jarius S, Aboul-Enein F, Waters P, Kuenz B, Hauser A, Berger T, et al. Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. Brain. 2008; 131(Pt 11):3072-80.

17. Yang Y, Wang CJ, Wang BJ, Zeng ZL, Guo SG. Comparison of efficacy and tolerability of azathioprine, mycophenolate mofetil, and lower dosages of rituximab among patients with neuromyelitis optica spectrum disorder. J Neurol Sci. 2018; 385:192-197.

18. Pellkofer HL, Krumbholz M, Berthele A, Hemmer B, Gerdes LA, Havla J, et al. Long-term follow-up of patients with neuromyelitis optica after repeated therapy with rituximab. Neurology. 2011; 76(15):1310-5.

19. Evangelopoulos ME, Andreadou E, Koutsis G, Koutoulidis V, Anagnostouli M, Katsika P, et al. Treatment of neuromyelitis optica and neuromyelitis optica spectrum disorders with rituximab using a maintenance treatment regimen and close CD19 B cell monitoring. A six-year follow-up. J Neurol Sci. 2017; 372:92-96.
20. Weinfurtner K, Graves J, Ness J, Krupp L, Milazzo M, Waubant E. Prolonged Remission in Neuromyelitis Optica Following Cessation of Rituximab Treatment. J Child Neurol. 2015; 30(10):1366-70.

21. Kim SH, Kim W, Li XF, Jung IJ, Kim HJ. Repeated treatment with rituximab based on the assessment of peripheral circulating memory B cells in patients with relapsing neuromyelitis optica over 2 years. Arch Neurol. 2011; 68(11):1412-20.

22. Tallantyre EC, Whittam DH, Jolles S, Paling D, Constantinescu C, Robertson NP, et al. Secondary antibody deficiency: A complication of anti-CD20 therapy for neuroinflammation. J Neurol. 2018; 265(5):1115-1122.

23. Cohen M, Romero G, Bas J, Ticchioni M, Rosenthal M, Lacroix R, et al. Monitoring CD27+ memory B-cells in neuromyelitis optica spectrum disorders patients treated with rituximab: Results from a bicentric study. J Neurol Sci. 2017; 373:335-338.

24. Collongues N, Brassat D, Maillart E, Labauge P, Ouallet JC, Carra-Dalliere C, et al. Efficacy of rituximab in refractory neuromyelitis optica. Mult Scler. 2016; 22(7):955-9.

25. Yang CS, Yang L, Li T, Zhang DQ, Jin WN, Li MS, et al. Responsiveness to reduced dosage of rituximab in Chinese patients with neuromyelitis optica. Neurology. 2013; 81(8):710-3.

26. Li T, Zhang LJ, Zhang QX, Yang CS, Zhang C, Li YJ, et al. Anti-Rituximab antibody in patients with NMOSDs treated with low dose Rituximab. J Neuroimmunol. 2018; 316:107-111.

27. Zhang M, Zhang C, Bai P, Xue H, Wang G. Effectiveness of low dose of rituximab compared with azathioprine in Chinese patients with neuromyelitis optica: An over 2-year
follow-up study. Acta Neurol Belg. 2017; 117(3):695-702.

28. Zéphir H, Bernard-Valnet R, Lebrun C, Outteryck O, Audoin B, Bourre B, et al. Rituximab as first-line therapy in neuromyelitis optica: Efficiency and tolerability. J Neurol. 2015; 262(10):2329-35.

29. Kim SH, Jeong IH, Hyun JW, Joung A, Jo HJ, Hwang SH, et al. Treatment Outcomes with Rituximab in 100 Patients with Neuromyelitis Optica: Influence of FCGR3A Polymorphisms on the Therapeutic Response to Rituximab. JAMA Neurol. 2015; 72(9):989-95.

30. Dale RC, Brilot F, Duffy LV, Twilt M, Waldman AT, Narula S, et al. Utility and safety of rituximab in pediatric autoimmune and inflammatory CNS disease. Neurology. 2014; 83(2):142-50.

31. Longoni G, Banwell B, Filippi M, Yeh EA. Rituximab as a first-line preventive treatment in pediatric NMOSDs: Preliminary results in 5 children. Neurol Neuroimmunol Neuroinflamm. 2014; 1(4):e46.

32. Lindsey JW, Meulmester KM, Brod SA, Nelson F, Wolinsky JS. Variable results after rituximab in neuromyelitis optica. J Neurol Sci. 2012; 317(1-2):103-5.

33. Ayzenberg I, Kleiter I, Schröder A, Hellwig K, Chan A, Yamamura T, et al. Interleukin 6 receptor blockade in patients with neuromyelitis optica nonresponsive to anti-CD20 therapy. JAMA Neurol. 2013; 70(3):394-7.

34. Gredler V, Mader S, Schanda K, Hegen H, Di Pauli F, Kuenz B, et al. Clinical and immunological follow-up of B-cell depleting therapy in CNS demyelinating diseases. J Neurol Sci. 2013; 328(1-2):77-82.
35. Kim SH, Huh SY, Lee SJ, Joung A, Kim HJ. A 5-year follow-up of rituximab treatment in patients with neuromyelitis optica spectrum disorder. JAMA Neurol. 2013; 70(9):1110-7.

36. Jeong IH, Park B, Kim SH, Hyun JW, Joo J, Hj. K. Comparative analysis of treatment outcomes in patients with neuromyelitis optica spectrum disorder using multifaceted endpoints. Mult Scler. 2015; 22(3):329-39.

37. Nikoo Z, Badihian S, Shaygannejad V, Asgari N, Ashtari F. Comparison of the efficacy of azathioprine and rituximab in neuromyelitis optica spectrum disorder: A randomized clinical trial. J Neurol. 2017; 264(9):2003-2009.

Table 1. Clinical And Demographic Characteristics Of 643 Patients From 29 Studies Included In The Systematic Review
| Reference (Study) | Research type | Patient No. | Sex (F/M) | Age (year) | AQP4-Ab (+) | Duration of disease (years/month) | Follow-up (years/month) |
|------------------|---------------|-------------|-----------|------------|-------------|-----------------------------------|-------------------------|
| Jacob [11] 2008  | Retrospective  | 25          | 22/3      | 38(7-65)   | 11          | 4.5(0.8-17)y                       | 19(6-40)m               |
| Jarius [16] 2008 | Retrospective  | 4           | NC        | 45(19-59)  | 4           | NC                                | 62(33-144)m             |
| Pellkofer [18] 2011 | Prospective  | 9           | 8/1       | 36.1(11.5) | 9           | 11(7.7)y                          | 29.6(14.5)m             |
| Gurdes [2] 2011  | Retrospective  | 23          | 21/2      | 37.1(14.6) | 15          | 114(13-266)m                      | 32.5(7-63)m             |
| Lindsey [32] 2012 | Retrospective  | 8           | 7/1       | 37.6(14.4) | 4           | 65.1(53.7)m                       | 39.9(40.7)m             |
| Yang [25] 2013   | Retrospective  | 3           | NC        | 34.3(8.5)  | 2           | 9.3(4)y                           | 12.7(0.6)m              |
| Ip [5] 2013      | Retrospective  | 7           | 6/1       | 52(22-62)  | 4           | 57(40-272)m                       | 24(1-42)m               |
| Ayzenberg [33] 2013 | Retrospective  | 3           | 3/0       | 35(7.8)    | 3           | 6.7(3.7)y                         | 14.7(15.1)m             |
| Gredler [34] 2013 | Observational  | 4           | 4/0       | 42.5(15.4) | 4           | 6.2(4.2)y                         | 3.1(2.1)y               |
| Chay [10] 2013   | Retrospective  | 6           | 4/2       | 37.8(20.6) | 3           | NC                                | NC                      |
| Kim [35] 2013    | Retrospective  | 30          | 27/3      | 38(23-58)  | 23          | 4.5(0.5-12.9)y                    | 60(9-82)m               |
| Longoni [31] 2014 | Retrospective  | 5           | 4/1       | 13.7(2.7)  | 5           | 3.2(0.3)y                         | 21.5(6.9)m              |
| Kim [29] 2015    | Retrospective  | 100         | 92/8      | 43(11)     | 94          | 11(5)y                            | 67(9-108)m              |
| Zephir [28] 2015 | Retrospective  | 32          | 27/5      | 45(12.1)   | 28          | 6.5(1-410)m                       | 28.7(21)m               |
| Weinfurter [20] 2015 | Retrospective  | 4           | 3/1       | 26.5(22.3) | 3           | 6.5(3.1)y                         | 6(1.2)y                 |
| Valentino [7] 2016 | Retrospective  | 7           | 6/1       | 38.3(16.6) | 7           | NC                                | 59.4(29.7)m             |
| Jeong [36] 2016  | Retrospective  | 55          | 50/5      | 42(15-68)  | 52          | 41.7(2.1-231.5)m                  | 64.7(6.2-99.8)m         |
| Annovazzi [1] 2016 | Retrospective  | 76          | 64/9      | 46.5(12.5) | 53          | 6(7.2)y                           | 35.6(27)m               |
| Collongues [24] 2016 | Retrospective  | 21          | 19/2      | 37.8(15.5) | 19          | 46.9(51.2)m                       | 31(18)m                 |
| Zhang [27] 2017  | Case-control   | 31          | 23/8      | 42.2(16.9) | 15          | 4.05(2.11)y                       | 27.45(11.68)m           |
| Nikoo[37] 2017   | RCT            | 33          | 29/4      | 35.33(8.98)| 13          | 6.23(4.29)y                       | >12m                    |
| Evange. [19] 2017 | Retrospective  | 5           | 5/0       | 54(10.21)  | 5           | 6.8(1.3)y                         | 6.6(0.9)y               |
| Cohen [23] 2017  | Prospective    | 40          | 33/7      | 40.2(22-62)| 20          | 40(2-165)m                        | 2y                      |
| Tallantyre [22] 2018 | Retrospective  | 5           | 5/0       | 36.6(14.5) | 5           | 11.5(9.4)y                        | 3.5(0.2-8.9)y           |
| Yang [17] 2018   | Prospective    | 20          | 19/1      | 40.7(11.4) | 10          | 11(0.2-240)m                      | 29(18-40)m              |
| Cabre [12] 2018  | Prospective    | 32          | 30/2      | 39.9(12.1) | 20          | NC                                | 2y                      |
| Li [26] 2018     | Retrospective  | 19          | 16/3      | 34.8(13.7) | 17          | 3.4(3.4)y                         | 2.5(1.7)y               |

RCT=randomized clinical trial, AQP4-Ab=aquaporin antibody,

NC=no clear
Figures

Figure 1
Flow chart presenting the process of the study selection for NMO meta-analysis.

Figure 2
Forest plot of the mean difference in the ARR ratio before and after rituximab therapy.

Figure 3
Forest Plot showing the ARR ratio of patients with NMO after rituximab therapy in the subgroup analysis based on different rituximab doses.

Figure 4
Forest Plot Showing the EDSS score of Patients with NMO after Rituximab Therapy.

Figure 5
Funnel plot showing the incidence of ARR and EDSS of Patients with NMO after Rituximab Therapy.