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Review article

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

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ABSTRACT

Background: Several immunosuppressants or monoclonal antibodies have been used as preventive treatment for neuromyelitis optica spectrum disorders (NMOSD); however, the optimal therapies have not been clarified. In this study, we aimed to compare and rank the effectiveness and tolerability of all preventive therapies for NMOSD.

Methods: Qualified studies were identified in a search of MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov databases. We combined direct and indirect evidence via meta-analyses. The annualized relapse rate (ARR) was defined as the primary outcome. Secondary outcomes included the Expanded Disability Status Scale (EDSS) score and hazard ratios (HR) for the counts of adverse events (AEs).

Results: We identified one randomized controlled trial (RCT) and five observational studies including a total 631 patients with NMOSD. Among these, the follow-up time ranged from 12 to 40 months. For the primary outcome, rituximab (RTX) was hierarchically superior, with the significant standardized mean difference versus azathioprine (−0.86; 95% confidence interval: −1.60, −0.11). Mycophenolate mofetil (MMF) was ranked the most tolerable therapy, whereas cyclophosphamide was the least tolerable.

Conclusion: RTX and MMF may be recommended as optimal treatments to prevent relapse in NMOSD. Low-dose cyclosporine A could be a promising alternative therapy.

1. Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are devastating autoantibody-induced inflammatory diseases of the central nervous system that primarily affect the spinal cord, optic nerves, and brainstem, causing paralysis and blindness (Kremer et al., 2014; Wingerchuk et al., 2015). The main pathogenic autoantibody is astrocytic water channel aquaporin-4 immunoglobulin G (AQP4-IgG), targeting AQP4 on the membrane of astrocytes. This results in damage to and inflammation of astrocytes, as well as disruption of the blood–brain barrier, eventually causing oligodendrocyte injury and demyelination. Recently, anti-myelin oligodendrocyte glycoprotein antibody has been reported as another candidate pathogenic antibody in NMOSD (Kitley et al., 2014; Lechner et al., 2016).

Treatment strategies of NMOSD include those addressing acute exacerbations and relapse prevention. High-dose corticosteroids, plasma exchange, and intravenous immunoglobulin are widely used treatments for acute attacks (Katz Sand, 2016; Trebst et al., 2014). For relapse prevention, empiric therapies, such as with interferons, natalizumab, and fingolimod, have been shown to be ineffective and even harmful (Gahlen et al., 2017; Kleiter et al., 2012; Min et al., 2012; Shimizu et al., 2010). Immunosuppressive agents including azathioprine (AZA), mycophenolate mofetil (MMF), cyclophosphamide (CTX), and monoclonal antibodies, including rituximab (RTX), eculizumab, and tocilizumab, have been reported to be effective (Araki et al., 2014; Huang et al., 2018; Kim et al., 2013; Li et al., 2017; Pittock et al., 2013; Xu et al., 2016b). As there is no evidence regarding the optimal use of these drugs, we performed a systematic review and network meta-analysis (NMA) to compare and rank these immunotherapies in terms of effectiveness and tolerability in preventing NMOSD.

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2. Methods

2.1. Search strategy

The databases MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and ClinicalTrials.gov databases were independently searched by two reviewers (Wenjuan Huang and Liang Wang). Relevant terms were combined into a search formula applied for each database (Appendix). We considered all published and unpublished studies, updated to November 21, 2018, in English, covering all relevant immunosuppressive drugs and monoclonal antibodies.

2.2. Inclusion and exclusion criteria

We included all comparative studies, from randomized controlled trials (RCTs) to prospective cohort studies and retrospective studies, covering at least two interventions. We excluded case reports, reviews, and studies only involving one intervention. Two authors (Wenjuan Huang and Liang Wang) thoroughly read the studies to assess appropriateness for inclusion in this NMA. A third investigator (Baojingzi Zhang) arbitrated any disagreement, until consensus was reached. We followed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (Stroup et al., 2000) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The procedures followed in the literature search and the study selection are exhibited in **Fig. 1**.

2.3. Data extraction and outcome measures

We extracted accessible information covering study design, demographic and clinical characteristics of participants, as well as intervention and outcome measures. Demographic and clinical features comprised sample size, AQP4-IgG serostatus, number of female patients, patient age, and disease duration. The Oxford hierarchy of evidence 2011 was used to measure the levels of evidence in each included article (Howick et al., 2011).

Two reviewers (Wenjuan Huang and Liang Wang) extracted the published data using a standardized procedure and another reviewer (Baojingzi Zhang) re-examined the data. We contacted the corresponding authors regarding unpublished data. Any contradictory data were rechecked and discussed to reach consensus. In this NMA, the primary outcome was the annualized relapse rate (ARR). The Expanded Disability Status Scale (EDSS) score and hazard ratios (HR) for the counts of adverse events (AEs) were defined as the secondary outcomes.

2.4. Quality assessment: risk of bias

Using the Cochrane risk of bias tool and Newcastle–Ottawa Scale, two reviewers (Wenjuan Huang and Liang Wang) independently evaluated risk of bias in the included RCT (Higgins et al., 2011) and observational studies (Stang, 2010). Evaluation of the methodological quality of the RCT included random sequence generation, allocation concealment, blinding of participants, blinding of observers, incomplete outcome data, selective reporting, and other bias. As for observational studies, criteria covered selection, comparability, and outcome. A score of 5 or less (out of 9) corresponded to a high risk of bias. A comparison-adjusted funnel plot was used to examine small-study effects, including publication bias.

2.5. Statistical analysis

The present NMA was performed using a Bayesian Markov chain Monte Carlo model (Caldwell et al., 2005). Standardized mean differences (SMDs) for continuous variables, with 95% confidence intervals (CIs), were used to estimate the relative effectiveness of the compared interventions. Furthermore, the “metan” command was applied to

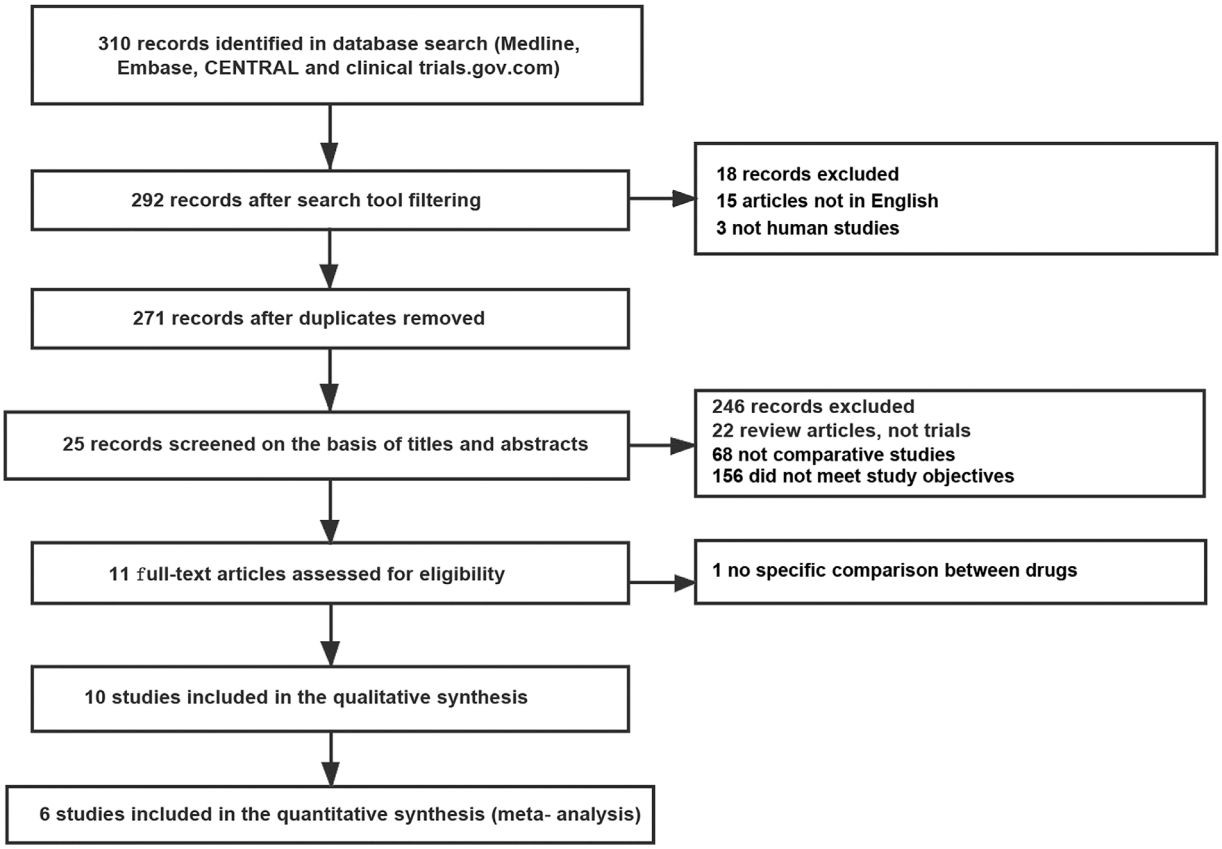

Fig. 1. PRISMA flow diagram.

perform traditional pairwise meta-analysis of random effects in each intervention. We determined the hazard ratios (HRs) for count variables with 95% CI using a random effects Poisson model. To evaluate convergence, we used a burn-in phase of 60,000 iterations after 20,000 iterations of the annealing algorithm. The surface under the cumulative ranking curve (SUCRA) was used to acquire the effectiveness hierarchy. Finally, network meta-regression would be performed with controlled intervention periods if the number of included studies exceeded 10.

We used the Higgins design-by-treatment interaction model to check for inconsistency (Higgins et al., 2012). We further verified the assumption of consistency using a node-splitting model (Dias et al., 2010). WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, UK), Stata 13.0 (StataCorp, College Station, TX, USA), and Revman 5.3 (Cochrane Collaboration, Oxford, UK) were used to perform this NMA.

3. Results

3.1. Description of included studies

A total 310 studies were identified after searching the databases. Studies with two or more treatment arms and complete data were included in the quantitative synthesis. Data from one study were excluded owing to lacking a specific comparison between drugs (Lin et al., 2018). Four studies were excluded as we were unable to obtain information regarding changes in standardization (i.e., SD) (Chen et al., 2017; Jeong et al., 2016; Mealy et al., 2014; Torres et al., 2015). Finally, a total of six studies were included in this NMA(Chen et al., 2016; Kageyama et al., 2013; Nikoo et al., 2017; Xu et al., 2016a; Yang et al., 2018; Zhang et al., 2017).

In total, 631 patients with NMOSD were included in the combined dataset. The median sample size was 70 (range 9–210) patients. A total 497 patients were seropositive for anti-AQP4 antibodies. The level of evidence was grade 2 for the RCT and grade 3 for the observational studies. The median follow-up time was 27.5 (range 12.0–40.0) months. Information of patients' clinical and demographic characteristics, the level of evidence, treatment regimens, and follow-up times is exhibited in **Table 1**.

3.2. Reduction of ARR

Reduction in the ARR was assessed in all six included studies, with reference to five drugs. A network plot is shown in **Fig. 2** and the estimated SMDs of relative effectiveness are listed in **Table 2**, with 95% CIs. Statistical significance was only calculated for RTX versus AZA (−0.91; 95% CI: −1.78, −0.038) in traditional pairwise mean analysis. According to the SUCRA, RTX was hierarchically superior versus AZA, with statistical significance (−0.86; 95% CI: −1.60, −0.11). Integral inconsistency was not demonstrated in the design-by-treatment interaction model ($p = 0.29$). The node-splitting model exhibited segmental inconsistency for MMF versus AZA and MMF versus RTX, which might be related to the quality of the studies. We did not perform network meta-regression with a controlled intervention period owing to an insufficient number of included studies.

3.3. Lowering of EDSS score

In the six included studies, the ability to reduce the EDSS score using immunosuppressive agents was evaluated. There was significant inconsistency, according to an integral inconsistency test ($p = 0.00$). **Table e1** (e-component) displays the estimated SMDs of relative effectiveness, with 95% CIs. Although heterogeneity was present, traditional meta-analysis yielded significant results for RTX versus AZA (−0.67; 95% CI: −0.97, −0.36), MMF versus CTX (−1.05; 95% CI: −1.53, −0.58), and AZA versus CTX (−0.56; 95% CI: −0.92, −0.20).

Table 1
Characteristics of the included studies.

Reference	Year	Study design	Level of evidence	Interventions	Sample size	Follow-up(mo)	AQP4+ *n*(%)	Female n(%)	Age(y)	Disease duration(mo)	Regimen	Outcome measures
Kageyama	2013	Retrospective study	3	1.CyA	9	32.0	9 (100)	9 (100)	45.0	72.0	150 mg/d po	ARR; EDSS
				2.AZA	9	40.0	9 (100)	7 (77.8)	55.0	96.0	100 mg/d po	
Chen	2016	Prospective study	3	1.MMF	105	16.8	89 (84.8)	97 (92.4)	44.0	22.8	20 mg/kg/d po	ARR; EDSS; Adverse events
				2.AZA	105	36.0	91 (86.7)	99 (94.3)	41.6	32.4	2 mg/kg/d po	
Xu	2016	Prospective study	3	1.MMF	38	15.2	33 (86.8)	32 (84.2)	31.6	14.3	1500 mg/d po	ARR; EDSS; Adverse events
				2.AZA	119	16.3	110 (92.4)	110 (92.4)	39.7	23.0	100 mg/d po	
				3.CTX	41	13.6	37 (90.2)	39 (95.1)	40.2	23.3	400 mg/w iv	
Zhang	2017	Retrospective study	3	1.RTX	31	27.5	25 (80.7)	23 (74.2)	42.4	48.6	100 mg/w iv	ARR; EDSS; Adverse events
				2.AZA	34	31.3	28 (82.4)	24 (70.6)	42.2	49.0	2 mg/kg/d po	
Nikoo	2017	RCT	2	1.RTX	33	12.0	13 (39.4)	29 (87.9)	35.3	74.8	1000 mg/2 w iv	ARR; EDSS; Adverse events
				2.AZA	35	12.0	20 (57.1)	28 (80.0)	32.4	73.4	2–3 mg/kg/d po	
Yang	2018	Prospective study	3	1.MMF	30	28.5	13 (43.3)	26 (86.7)	NA	9.5	1000 mg/d po	ARR; EDSS; Adverse events
				2.AZA	22	26.0	8 (36.4)	20 (90.9)	NA	9.0	2 mg/kg/d po	
				3.RTX	20	29.0	10 (50.0)	19 (95.0)	NA	11.0	100 mg/w iv	

CyA: cyclosporine A; AZA: azathioprine; MMF: mycophenolate mofetil; CTX: cyclophosphamide; RTX: Rituximab; ARR: annualized relapse rate; EDSS: expanded disability status scale; po: per os; iv: intravenous; NA: not available.

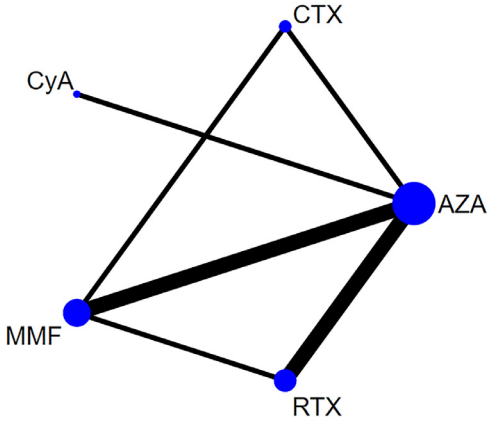

Fig. 2. Network plot of eligible comparisons for reduction of the annualized relapse rate in neuromyelitis optica spectrum disorders. CyA: cyclosporine A; AZA: azathioprine; MMF: mycophenolate mofetil; CTX: cyclophosphamide; RTX: rituximab.

3.4. AEs

AEs were counted during the follow-up periods, together with the number of participants. AEs for CyA were not accessible, and therefore only four interventions were analyzed. Values of HRs are listed in **Table 3**, with 95% CIs. The most tolerable therapy was MFF, with the lowest counts of AEs; CTX was the least tolerable agent. The combined results for ARR and AEs are presented in **Fig. 3**.

3.5. Risk of bias

The overall quality of the included studies is summarized in **Table 4** and **Fig. 4**. Three studies received eight stars and two studies received nine stars, indicating a high quality of the observational studies. Apart from blinding in the RCT, the risk was low for the domains of random sequence generation, allocation concealment, incomplete outcome data, and selective reporting. We therefore considered the RCT to be a moderate-quality study. The publication bias was not investigated as there were fewer than 10 included studies.

4. Discussion

In this NMA, we assessed six comparison studies including 631 patients, representing the most comprehensive data regarding preventive therapy in NMOSD. Our main findings comprise the following. First, RTX and MMF can be recommended as optimal therapies in refractory NMOSD. Second, low-dose CyA may be an option as an alternative therapy. Third, the effectiveness of AZA and CTX may be limited owing to multiple AEs.

Our findings indicate that RTX could be the most efficacious therapeutic option for patients with NMOSD, with the second fewest AEs. Several reports point to B cell-mediated humoral immunity in the pathogenesis of NMOSD (Bennett et al., 2015; Etemadifar et al., 2017). Rituximab (RTX) is a chimeric monoclonal antibody targeting the CD20 antigen on B cells, producing rapid and profound depletion of circulating CD20+ B cells (Cabre et al., 2018; Maurer et al., 2016). RTX is recommended in various B-cell hematologic malignancies (Salles et al., 2017) and is widely used to treat autoimmune diseases (Schioppo and Ingegnoli, 2017). RTX has been empirically used as first-line treatment in highly active NMOSD (Kim et al., 2013; Longoni et al., 2014; Radaelli et al., 2016). Remarkably,the only RCT included in this NMA investigating RTX and AZA may reveal its actual effectiveness. In line with the results of some excluded studies, RTX exhibited the best effectiveness according to the SUCRA (Jeong et al., 2016; Mealy et al., 2014; Torres et al., 2015). In a comparison of RTX with AZA for reducing ARR, significant differences were detected in both the NMA (−0.86; 95% CI: −1.60, −0.11) and traditional pairwise meta-analysis (−0.91; 95% CI: −1.78, −0.038). RTX had the second lowest HR for AEs, making it superior to both AZA (3.48; 95% CI: 0.71, 18.71) and CTX (6.09; 95% CI: 0.42, 110.50). Most AEs reported in the included studies were mild anaphylactoid reactions. Notably, RTX possesses some other advantages, including easily tracked adherence and rapid onset of action within two weeks, whereas MMF and AZA require 3 to 6 months for therapeutic effects to develop (Weinshenker and Wingerchuk, 2017). Therefore, B-cell depletion might be the most reactive therapy for treatment of NMOSD.

MMF is a prodrug of mycophenolic acid (MPA). MPA has a potent cytostatic effect on lymphocytes and can suppress primary antibody responses as well as T-lymphocytic responses to antigens (Allison and Eugui, 2000). MMF is recommended to prevent allograft rejection and treat some autoimmune diseases (Dai et al., 2017; Xiao et al., 2014). Treatment for NMOSD with MMF was first supported in some retrospective studies that showed a reduction of the absolute relapse rate (Huh et al., 2014). In our study, MMF had the best drug tolerance with the lowest HR for AEs and was superior to RTX (1.31; 95% CI: 0.15, 9.67), AZA (4.47; 95% CI: 0.94, 20.33), and CTX (7.82; 95% CI: 0.74, 98.49). Reported AEs for MMF varied among the included studies, and none were severe. The effectiveness of MMF was ranked the third; statistical differences were only observed when compared with CTX in lowering EDSS score, which might be related to the biases inherent to retrospective study designs or short-term follow-up.

CyA is a metabolite of the fungus *Tolypocladium inflatum*. CyA can inhibit calcineurin and curb the activation of T cells, and it is also approved to prevent rejection of organ transplants and treat a growing number of autoimmune diseases (Bach, 1999; Beauchesne et al., 2007). The study by Kageyama was the first to demonstrate the effectiveness of

Table 2
Estimated differences in the efficacy of interventions for reduction of the annualized relapse rate in neuromyelitis optica spectrum disorders.

	Standardized mean difference (traditional pairwise meta-analysis)				
Standardized mean difference (network meta-analysis)	**Rituximab**	—	0 (−0.57, 0.57)	**−0.91 (−1.78, −0.038)**	—
	−0.18 (−1.97, 1.63)	**Cyclosporine A**	—	−0.57 (−1.65, 0.52)	—
	−0.70 (−1.62, 0.26)	−0.53 (−2.05, 0.99)	**Mycophenolate mofetil**	0.0070 (−0.20, 0.21)	−0.27 (−0.71, 0.17)
	−0.86 (−1.60, −0.11)	−0.69 (−2.39, 1.01)	−0.15 (−0.89, 0.57)	**Azathioprine**	−0.15 (−0.50, 0.21)
	−0.98 (−2.31, 0.40)	−0.79 (−2.71, 1.12)	−0.27 (−1.45, 0.91)	−0.12 (−1.29, 1.08)	**Cyclophosphamide**

Median values of standardized mean differences with 95% confidence intervals (column vs. row) in the efficacy of interventions (orange, lower left of table), and standardized mean differences with 95% confidence intervals using the metan command (blue, upper right of table). Values < 0 favor the intervention in the column. Interventions are ordered in accordance with efficacy ranking. Numbers in bold (darker shaded) show statistically significant results.

Table 3
Estimated hazard ratios of adverse events for the included interventions.

Hazard ratios (network meta-analysis)	Hazard ratios (traditional pairwise meta-analysis)			
	Mycophenolate mofetil	2.00 (0.21, 19.23)	**0.22 (0.11, 0.44)**	**0.11 (0.03, 0.50)**
	1.31 (0.15, 9.67)	**Rituximab**	0.34 (0.08, 1.41)	—
	4.47 (0.94, 20.33)	3.48 (0.71, 18.71)	**Azathioprine**	0.59 (0.33, 1.07)
	7.82 (0.74, 98.49)	6.09 (0.42, 110.50)	1.73 (0.18, 20.85)	**Cyclophosphamide**

Meidan values of hazard ratios with 95% confidence intervals (column vs. row) for safety of the interventions (orange, lower left of table), and hazard ratios with 95% confidence intervals using the metan command (blue, upper right of table). Values >1 favor the intervention in the column. Interventions are ordered in accordance with safety ranking. Numbers in bold (darker shaded) show statistically significant results.

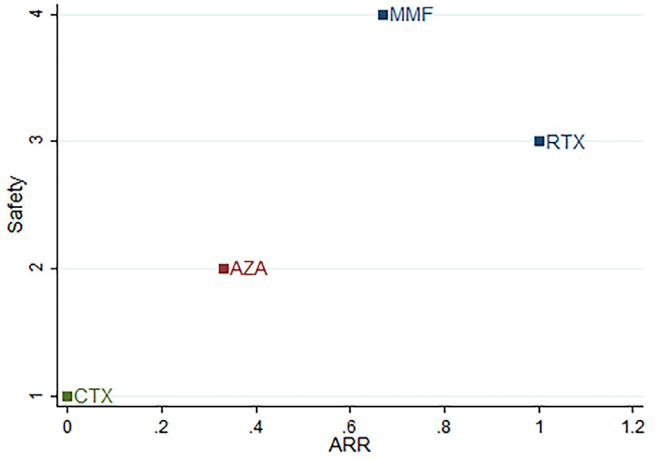

Fig. 3. Combined results for reduction of the annualized relapse rate and grade of tolerability of included interventions. Data of AEs for CyA were not accessible. The figure displays combined results for the remaining four drugs. AZA: azathioprine; MMF: mycophenolate mofetil; CTX: cyclophosphamide; RTX: rituximab.

Table 4
Risk of bias assessment for observational studies.

Author, Year	Selection				Comparability	Outcome			Total score
	1	2	3	4	1	1	2	3	
Kageyama et al., 2013	☆	☆	☆	☆	☆☆	☆	☆	–	8
Chen et al., 2016	☆	☆	☆	☆	☆	☆	☆	☆	8
Xu et al., 2016	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhang et al., 2017	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yang et al., 2018	☆	☆	☆	☆	☆☆	☆	☆	☆	9

Risk of bias assessed using the Newcastle–Ottawa Scale. A higher overall score indicates lower risk of bias. A score of 5 or lower (out of 9) corresponds to a high risk of bias.

CyA in NMOSD. In that study, although specific data of AEs were not mentioned, no serious AEs were reported. Furthermore, when used in other autoimmune diseases, most reported AEs were mild, reversible, and diminished with dose reduction or withdrawal of CyA (Conti et al., 2000; Ogawa et al., 2010). Taken together, this evidence indicates that low-dose CyA could be safe in patients with NMOSD. Our findings showed that CyA was the second most efficacious drug in lowering both the ARR and EDSS score. We suggest that low-dose CyA (140–150 mg/day as in Kageyama's study) can be used as an alternative therapy for patients with NMOSD refractory to RTX or MMF.

Belonging to the purine analog family, AZA can slow the proliferation of lymphocytes (Borisow et al., 2018). We observed significant differences only in traditional pairwise meta-analysis, in a comparison of AZA with CTX for lowering the EDSS score (−0.56; 95% CI: −0.92, −0.20). The HR for AEs of AZA was ranked third and was superior to CTX (1.73; 95% CI: 0.18, 20.85). Most adverse events in the included studies involved bone marrow suppression, gastrointestinal disturbances, elevated liver enzymes, and mild hair loss. Although AZA, MMF, and RTX are all recommended as first-line preventive therapies for NMOSD, the effectiveness and tolerability of AZA were inferior to the other agents in this NMA, which is in accordance with the results of several studies (Jeong et al., 2016; Torres et al., 2015). To be fully effective, AZA should be supplemented with oral prednisone for 3–6 months during the initial period. We suggest that AZA be used as a second-line preventive drug for NMOSD rather than first-line treatment.

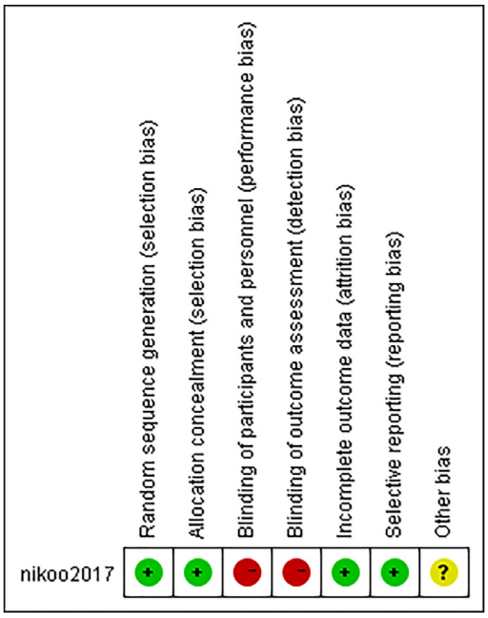

Fig. 4. Summary of risk of bias according to the authors' judgment of each bias risk item in each included study. A plus sign represents risk of bias present, a minus sign represents risk of bias absent, and question mark sign represents risk of bias uncertain.

CTX is a well-known medication used in chemotherapy. As an alkylating agent, it has antimitotic and antireplicative effects (Ahlmann and Hempel, 2016). CTX has been used as a second-line preventive drug in NMOSD. Our results showed that both its effectiveness and tolerability were the lowest among the five included drugs. In another study, the effectiveness and tolerability of CTX were also reported to be inferior to those of RTX, MMF, and AZA (Torres et al., al.,2015), which strongly indicates that CTX might not be a good option for treating NMOSD.

To date, our study is the first NMA comparing multiple drugs in the preventive treatment of NMOSD. Traditionally, NMAs have only incorporated data from RCTs because these trials can balance confounding factors by means of randomization. Lately, an increasing number of NMAs have combined RCTs with observational studies

(Efthimiou et al., 2017; Hajibandeh et al., 2016; Mendoza et al., 2014; Verde and Ohmann, 2015). RCTs for NMOSD are scarce; we were able to identify only one RCT. No evidence of heterogeneity was found in an integral inconsistency test for the primary outcome. Furthermore, the results of our direct and network meta-analyses were in accordance, and the pooled estimates were robust. The present combination of an RCT and observational studies proved to be valid and valuable with respect to the preventive treatment of NMOSD. The quality of evaluation and individual differences among patients may account for the heterogeneity in EDSS scores.

There were several limitations present in the published evidence as well as in the NMA process. First, the number of included studies and closed loops per comparison were few, which might lower reliability of the findings. The results of direct and indirect comparisons in the NMA model were based on relative treatment effects. Second, a definite therapeutic response could not be accurately evaluated because not all immunosuppressants were used as monotherapy. Third, some data of the outcome measures were not listed individually; therefore, we used estimated values. AEs were counted but severe AEs were not distinguished, leading to the possibility that tolerability was improperly calculated. Moreover, several promising new agents, like inebilizumab, tocilizumab and satralizumab, were not included owing to a paucity of comparative studies. Additional clinical trials conducted in real-world settings are needed in order to accurately assess the effectiveness and tolerability of preventive drugs for NMOSD.

In conclusion, this NMA provided a comprehensive summary of effectiveness and tolerability of preventive treatment for NMOSD, which might provide a reference for the optimal treatment. The results suggested RTX and MMF are superior to AZA, low-dose CyA may be alternative treatment for refractory NMOSD patients, CTX should not be a common preventive treatment for NMOSD.

Declaration of competing interest

The authors declare that they have no competing interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.msard.2019.08.009.

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