Ther Adv Neurol Disord
2021, Vol. 14: 1–17
DOI: 10.1177/17562864211056710

Adverse events of rituximab in neuromyelitis optica spectrum disorder: a systematic review and meta-analysis

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Abstract

Background: The adverse events (AEs) of rituximab (RTX) for neuromyelitis optica spectrum disorder (NMOSD) are incompletely understood.

Aim: To collate information on the reported the AEs of RTX in NMOSD and assess the quality of evidence.

Methods: PubMed, EMBASE, Web of Science, Cochrane Library, Wanfang Data, CBM, CNKI, VIP, clinicaltrials.gov, and so on were searched for studies with control groups as well as for case series that had assessed the RTX-associated AEs. The incidence of AEs and the comparison of AE risks among different therapies were pooled. The GRADE was developed for evidence quality.

Results: A total of 3566 records were identified. Finally, 36 studies (4 RCTs, 6 crochet studies, 2 NRCTs, and 24 case series), including 1542 patients (1299 females and 139 males), were included for final analyses. Rates of patients with any AEs, any serious AEs (SAEs), infusion-related AEs, any infection, respiratory infection, urinary infection, and death were 28.57%, 5.66%, 27.01%, 17.36%, 4.76%, 4.76%, and 0.17%, respectively. The results from subgroup analysis showed that AE rates were most likely not associated with covariates such as duration of illness and study designs. Very low-quality evidence suggested that the risk ratios (RR) of any AEs (0.84, 95% CI = 00.42–1.69, $p = 0.62$) and any infections (1.24 95% CI = 0.18–8.61) of RTX were similar to that of azathioprine, and the RR of any AEs of RXT was akin to that of mycophenolate mofetil (0.66, 95% CI = 0.32–1.35 $p = 0.26$). Evidence of low to high quality showed the lower RR of RTX in other AEs, but not in infusion-related AEs. Strategies to handle AEs focused on symptomatic treatments.

Conclusions: RTX is mostly safer than other immunosuppressants in NMOSD: the incidence of RTX-associated AEs was not high, and when present, the AEs were usually mild or moderate and could be well controlled. Given its efficacy and safety, RTX could be recommended as a first-line treatment for NMOSD.

Keywords: neuromyelitis optica spectrum disorder (NMOSD), adverse events (AEs), rituximab (RTX), systematic review, meta-analysis

Received: 26 June 2021; revised manuscript accepted: 10 October 2021.

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Introduction

Neuromyelitis optica spectrum disorder (NMOSD, previously known as Devic's disease or neuromyelitis optica (NMO)), resenting most often with optic neuritis and transverse myelitis, is a rare antibody-mediated central nervous system disease with a typically relapsing course.[1,2] The estimated prevalence of NMOSD is approximately 0.5 to 10 people per 100,000 population, and is higher among the women and in Africans, East Asians,

and Latin Americans.[1,3,4] Astrocyte aquaporin 4 (AQP4) is the most widely expressed water channel protein in the central nervous system.[5] The IgG autoantibody binding to AQP4 (AQP4-IgG), which is seen in most NMOSD patients, can bind to the extracellular domain of AQP4, activate complement that leads to complement-mediated destruction of astrocytes, induce internalization of the water channel, and mediate antibody-dependent cell cytotoxicity.[6–8] The treatments of NMOSD, which usually include steroids and immunosuppressants, such as mycophenolate mofetil (MMF), azathioprine (AZA), and methotrexate,[9,10] are not always effective in all patients for their worrisome AEs.[11]

As the first mouse/human monoclonal antibody (mAb) binding to CD20,[12,13] rituximab (RTX), which was accepted to treat NMO in 2005,[14] is increasingly used in NMOSD because of its therapies targeting antibody-producing B cells and the pathogenic role of AQP4-IgG in NMOSD.[11] Although the safety profile of RTX has been defined after two decades of its application, and many studies have been focused on its safety for NMOSD,[11,15,16] yet few studies have done comprehensive and systematic analyses on the rates of specific adverse events (AEs) of RTX or on its safety compared with other treatments. In parallel, latest randomized controlled trials (RCTs)[15,16] need to be included in the studies to enhance the level of evidence. Thus, to address these knowledge shortfalls, we conducted this systematic review and meta-analysis to evaluate the rates of AEs associated with RTX and the risks of AEs compared with other NMOSD treatments.

Methods

This study has been registered on INPLASY with registration number Inplasy protocol 202150034. Our research was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[17]

Data sources and search strategies

Four bibliographic databases, PubMed, Cochrane Library, EMBASE, and Web of Science (WOS), as well as four Chinese databases, Wanfang data, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI), and China Science and Technology Journal database (VIP), were searched. The search time spanned from the construction of the databases to 21 November 2020, with no regional or language restrictions. Articles in languages other than in English or Chinese were translated with the help of the Google Translator and DeepL. A combination of Medical Subject Headings (MeSH) and free text terms was used. In order to perform a complete search for AEs, our search terms also included other related diseases, such as Myelin oligodendrocyte glycoprotein antibody disorders (MOGAD) and Chronic Relapsing Inflammatory Optic Neuropathy, and so on, as studies of these diseases might involve AEs of NMOSD. Search strategies included 'Rituximab', 'Rituximab CD20 Antibody', 'Rituxan', 'Neuromyelitis Optica', 'Devic* Disease', and so on. The PubMed search strategy was provided in the protocol and Supplementary Appendix. Other sites, which were searched for additional results, included Clinical Trials.gov.; the National Institute for Health and Care Excellence (NICE); National Guideline Clearinghouse (NGC); GIN (the guidelines international network); Cumulative Index to Nursing & Allied Health Literature (CINAHL); World Health Organization (WHO) and Medlive. Reference lists for all topic-related reviews, reports, and meta-analyses were further searched.

Criteria for the selection of studies

We included all RCTs, non-randomized controlled trials (NRCTs), cohort studies, case-control studies (considered as studies with control groups), and case series with subjects that (1) met 2015, 2006, or 1999 NMO/NMOSD diagnostic consensus criteria,[2,18,19] with no restriction of age, race, sex, or nationality; (2) were treated by any dose of RTX with or without glucocorticoid therapy and other standard-care treatments; (3) were under any other treatments (including placebo) in the control groups (if any). Key exclusion criteria included studies (1) without reporting AE; (2) with other comorbidities or sample size less than 5; (3) published as conference abstracts without full text, as well as book chapters and dissertations; (4) on RTX biosimilars. We included the study with the latest and most comprehensive data when multiple articles covered the same study population.

Study selection and data extraction

ENDNOTE X9 and Microsoft Office Excel were developed to manage search records, and extract

data, respectively. Pre-tests were also performed to ensure high inter-rater reliability among evaluators. The work was undertaken independently by two investigators, and discrepancies were resolved through discussion. If not, a third assessor would help to resolve the arguments.[20,21] Two investigators reviewed the titles and abstracts of all records and identified studies potentially eligible for inclusion, which received a full-text evaluation if meeting our inclusion criteria. The following data of each study were extracted: first author's name; year of publication; study designs; sample size; diagnostic criteria; mean/median age; races; gender; disease duration; follow-up period; treatments and concomitant medications of interventions/comparisons; AE-associated populations; particular populations (e.g. elderly, children, and pregnant women); AE types; RTX dose; AQP4/Myelin oligodendrocyte glycoprotein (MOG)-IgG serostatus, and so on. Contact the authors for further information when the study reports are unavailable or data lack.

Methodological quality assessment and definition of outcomes

Numerous quality assessment instruments were utilized to evaluate the methodological quality of included studies, including the Cochrane risk of bias assessment tool (Cochrane-ROB, version 6)[22] for RCTs; Newcastle-Ottawa Scale (NOS)[23] for cohort and case-control studies; Joanna Briggs Institute (JBI)[24] for case series studies, and methodological index for non-randomized studies (MINORS)[25] for NRCTs. Under the guidance of methodological experts (Kehu Yang and Lili Wei), the studies, which were considered as ones with low risks of bias when the high bias items of Cochrane-ROB were no more than 5 and the NOS, JBI, and MINORS scores were respectively greater than or equal to 6, 5, and 12, were included in the final analyses. The primary outcomes were the rates of patients with at least one any AE to the total number of observations, and the risks of the number of patients experiencing at least one any AE between RTX and other different therapies. We define any AE as the total AE reported by the authors, which usually means any undesirable occurrence that happened during the use of RTX for NMOSD. The secondary outcomes were similar to the primary outcomes, which referred to the rates of patients with at least one serious adverse event (SAE) to the total number of participants, and the risks of the number of patients with at least one SAE between RTX and other different treatments. SAEs are defined as SAEs reported by the authors, mainly referring to AEs causing death, interruption or discontinuation of the therapy, hypotension (blood pressure $< 90/60$ mmHg), prolongation of hospitalization (subject to the reports), and requiring a blood transfusion (The information reported by the authors was not always so detailed that the common terminology criteria for adverse events (CTCAE) was not applicable). Other notable outcomes included the rates of patients with at least one of following AEs to the total number of participants, and the risks of the number of participants experiencing at least one of following AEs between RTX and other different treatments: infection, death associated with RTX use (i.e. author-reported deaths that might be associated with the use of RTX, such as death following severe infection or shock which related to RTX use), drug withdrawal or change due to AEs, infusion-related AEs, neoplasms, organ impairments (e.g. liver or kidney impairments), hematologic complications (e.g. blood immune cells and immunoglobulins decline), and so on. All of the outcomes were prespecified.

Statistical analysis and evidence quality

Continuous data are summarized by the mean ± SD or median (range or interquartile range). Categorical data are reported as numbers and percentages. Given that a large majority of the articles did not explicitly report the time during which the adverse events occurred, the number of people experiencing the specific AE and the total number of observations, rather than the number of AEs, were used for the statistical analysis. Considering that most of the studies might not satisfy the normal distribution, we transformed the data via the transformation method of 'odds data' and modified an offset of 0.5 for all 0 cells. The specific transformation method is as follows: $\log(\mathrm{OR}) = \ln(\mathrm{odds}) = \ln(\mathrm{X}/(n-\mathrm{X}))$, $\mathrm{SE}(\mathrm{P}) = \mathrm{SE}(\ln(\mathrm{odds})) = \sqrt{1/\mathrm{X} + 1/(n-\mathrm{X})}$. In this calculation, 'log (OR)' means the logarithmic value of the incidence of patients with at least one of the AEs in each study, 'SE' represents the standard error, 'X' represents the number of patients with at least one of the AEs and 'n' means the total number of observed populations. The 'log (OR)' and 'SE' values are used to summarize the pooled 'odds ratio' (OR) and its 95% confidence intervals (CIs). After the summary, the following transformation was required to obtain the

final incidence of patients with at least one of the AEs and its 95% CIs: $P = OR/(1+OR)$, $LL = LL_{OR}/(1+LL_e), UL = UL_{OR}/(1+UL_{OR})$. In this transformation, 'P' means the transformed final incidence, 'LL' means the transformed final lower limit of the 95% CI, 'LL_{OR}' means the lower limit of the 95% CIs before transformation, 'UL' means the transformed final upper limit of the 95% CIs, and 'UL_{OR}' means the upper limit of the 95% CIs before transformation. It should be noted that we performed a post hoc analysis to correct incidence of patients experiencing death associated with using RTX, as 95.24% of the studies reported 0 death-event, and so many modifications of 0.5 for 0 cells could significantly increase the incidence (this situation did not occur in the transformation of other outcomes, which hardly contain 0 cells). Therefore, the total number of patients experiencing death associated with using RTX divided by the total number of observations was used to conduct the post hoc analysis. The risks of the number of patients experiencing at least one AE in various therapies were compared by using data from studies with control groups. In studies involving multiple arms, the differences between the RTX arm and other arms were compared, respectively. As the outcome was relatively uncommon when comparing each outcome in different treatments, we used odds ratio (OR) and its 95% CIs of case-control studies as an estimate for risk ratio (RR) and its 95% CIs to combine the effect estimate with RR from RCTs, NRCTs and cohort studies.[26] RR or OR suggested a higher risk of AEs in the RTX group than in the control group when the value exceeded 1. Heterogeneity was quantified by using the chi-square-based-Q-statistics test and I2 test ($P > 0.10$ and $I2 < 50\%$ indicated acceptable heterogeneity, with the $N - 1$ degrees of freedom). We selected the random effects model in advance due to expected heterogeneity in study designs. The leave-one-out approach was executed to complete the sensitivity analyses when there was significant statistical heterogeneity, and studies with a clear source of heterogeneity (e.g. clinical, or statistical heterogeneity) were excluded. To explore the sources of heterogeneity and the potential therapeutic implications, we performed the prespecified subgroup analyses based on characteristic stratifications, such as NMOSD definition (1999, 2006 or 2015),[2,18,19] RTX dose (>500 mg/dose or ⩽ 500 mg/dose), disease definition (0–3, 4–6, 7–9, 10–12, years), AQP4/MOG-IgG serostatus (positive or negative), patient characteristic (race, age, sex, etc.), follow-up period (>2 years or ⩽ 2 years), study design (retrospective or prospective), and so on. All *p* values were two-sided with a significance level of 0.05. Results of sensitivity and subgroup analyses were non-significant, unless otherwise mentioned. The publication bias of outcomes including at least 10 studies was tested graphically via funnel plots.[27]

We evaluated was the quality of evidence for the risks of the number of patients experiencing at least one AE in various therapies rather than the rates of it for lacking comparable true values of these therapies. The quality of evidence was assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) methods[28] via GRADEpro GDT website, which categorized the quality of evidence as follows: high; moderate; low and very low quality. Data were synthesized and analyzed by using Review Manager (version 5.4.1; Cochrane Collaboration) and Microsoft Office Excel.

Results

Search results and methodological quality of included studies

Initially, a total of 3555 study records form databases (PubMed: 268; Cochrane: 43; EMBASE: 1679; WOS: 874; Wanfang data: 66; CBM: 30; CNKI: 576; VIP: 19), and 11 additional records from Clinical Trials.gov., were identified. There were 2203 references left after deleting duplications from various databases. After reviewing the titles and abstracts, 1810 papers were excluded due to case reports (n = 276), without RTX treatment (n = 889), without NMOSD (n = 378), with other comorbidities (n = 79), fundamental studies (n = 34), clinical guidelines (n = 11), duplicates (n = 26) and reviews (n = 117). 393 references were re-evaluated for full texts, and 316 of them were excluded for without NMOSD (n = 179), without RTX treatment (n = 29), duplicates (n = 16), case reports (n = 13), conference abstracts (n = 26), reviews (n = 24), data unavailable (n = 12), full article unavailable (n = 17), without clear definition of NMOSD (n = 6), and with immunosuppressants (n = 4). 67 eligible publications were contributed to the quantitative analysis, 36 of which (all 4 RCTs, 6 out of 10 cohort studies, 2 out of 3 NRCTs, 24 out of 47 case series, but no case-control studies) showed a

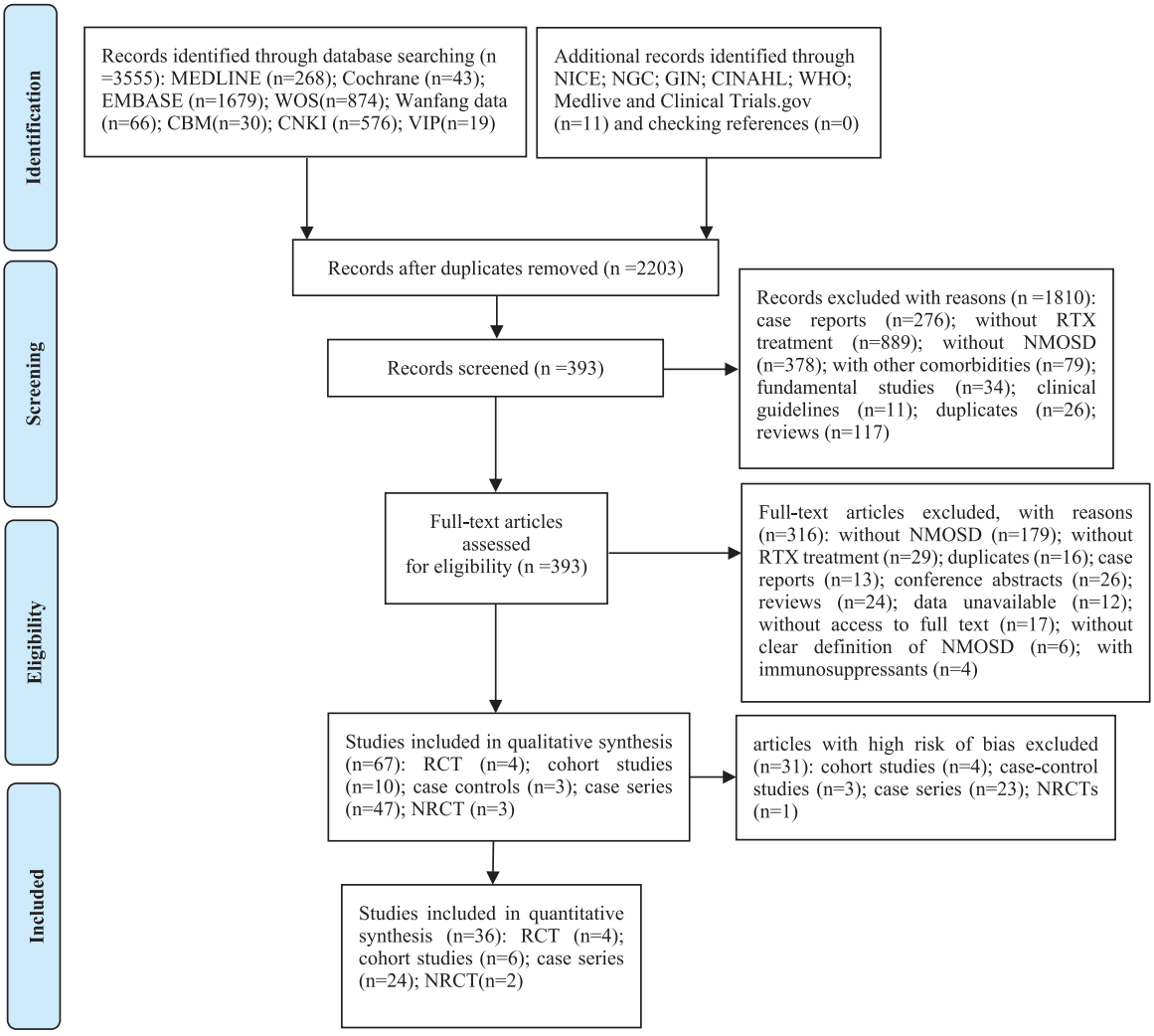

Figure 1. PRISMA 2009 flow diagram.

low risk of bias and were included in the statistical analysis. The authors' judgment on each risk of bias item for all studies is detailed in Supplementary Table 1–5 and Supplementary Figures 2–3. The PRISMA flow diagram of study selection is presented in Figure 1.

Characteristics of included studies and patients. The included 36 articles were published between 2005 and 2020 involving mostly retrospective studies (52.78%) and case series or cohort studies (83.33%). A total of 1542 patients (1299 females and 139 males, with non-reported genders of 104 patients) were enrolled with from 5 to 100 patients per study. Most studies have reported patients with an 18- to 65-year-old mean or median age, 2015 or 2006 NMOSD definition, > 2-year disease duration, > 500 mg single infusions RTX alone, > 50% AOP4 positive, while few studies have reported the information on particular populations or ethnicities. Most patients received four infusions per week of RTX at 375 mg/m^2 (>500 mg/dose). The demographic and clinical features for the enrolled patients are registered in Table 1 and Supplementary Tables 6–7.

Estimates for the rates of patients with at least one AEs. Based on the sensitivity analysis of AE rates through the leave-one-out approach, three studies[29–31] with significant heterogeneity were excluded from pooling the rates of patients with at least one any AEs. The potential sources might be the small sample size (<10 persons), the short number of AQP4 positive patients (<50%), and unclear follow-up periods or duration of treatment because over 2 months were needed if CD20

Table 1. Summary of characteristics of included studies and patients.

Study characteristics	# Studies	# Patients (Male/Female)
Total (prospective/retrospective/not clear)	36 (15/19/2)	1542 (139/1299)[a]
Mean or median, years		
⩽ 18	2	24 (4/20)
18–65	34	1518 (135/1279)[a]
> 65	0	0
NMOSD definition		
1999	1	8 (1/7)
2006	20[c]	684 (88/492)[a]
2015	20[c]	926 (136/790)
Disease duration, years		
> 2	27	1236 (96/1041)[b]
⩽ 2	2	75 (10/60)[b]
Not clear	7	231 (33/198)
RTX dose, mg/dose		
> 500	19	771 (102/669)
⩽ 500	7	480 (22/354)[a]
Not clear	10	291(15/276)
Number of AOP4 positive patients		
> 50% total sample size (number of AOP4 positive, Male/Female)	24	1123 (843, 79/940)[a]
⩽ 50% total sample size (number of AOP4 positive, Male/Female)	4	204 (57, 27/177)
Not clear	8	215 (33/182)
Pregnant women	0	0 (N/A)
Studies reporting race	9	369 (72/292)[b]
Asian (%)[d]	6	231 (62.60%)
Caucasian (%)[d]	3	45 (12.20%)
Mulatto (%)[d]	3	19 (5.15%)
Black people (%)[d]	3	36 (9.76%)
Others (%)[d]	4	38 (10.30%)
Studies reporting refractory and/or recurrent NMOSD	18	536 (68/463)[b]

N/A, not applicable; NMOSD, neuromyelitis optica spectrum disorder; No., numbers; RTX, rituximab.
Data from studies with more than two arms were combined. Only the reported data were counted. The total counts of males and females might less than the total number because of non-report. Percentages might not total 100 because of rounding.
[a]Two studies reported no data on male and female.
[b]One study reported no data on male or female.
[c]Five studies utilized both 2006 and 2015 diagnostic criteria.
[d]The percentage came from studies in which race was reported. The details of each involved study were displayed in Supplementary Table 6–7.

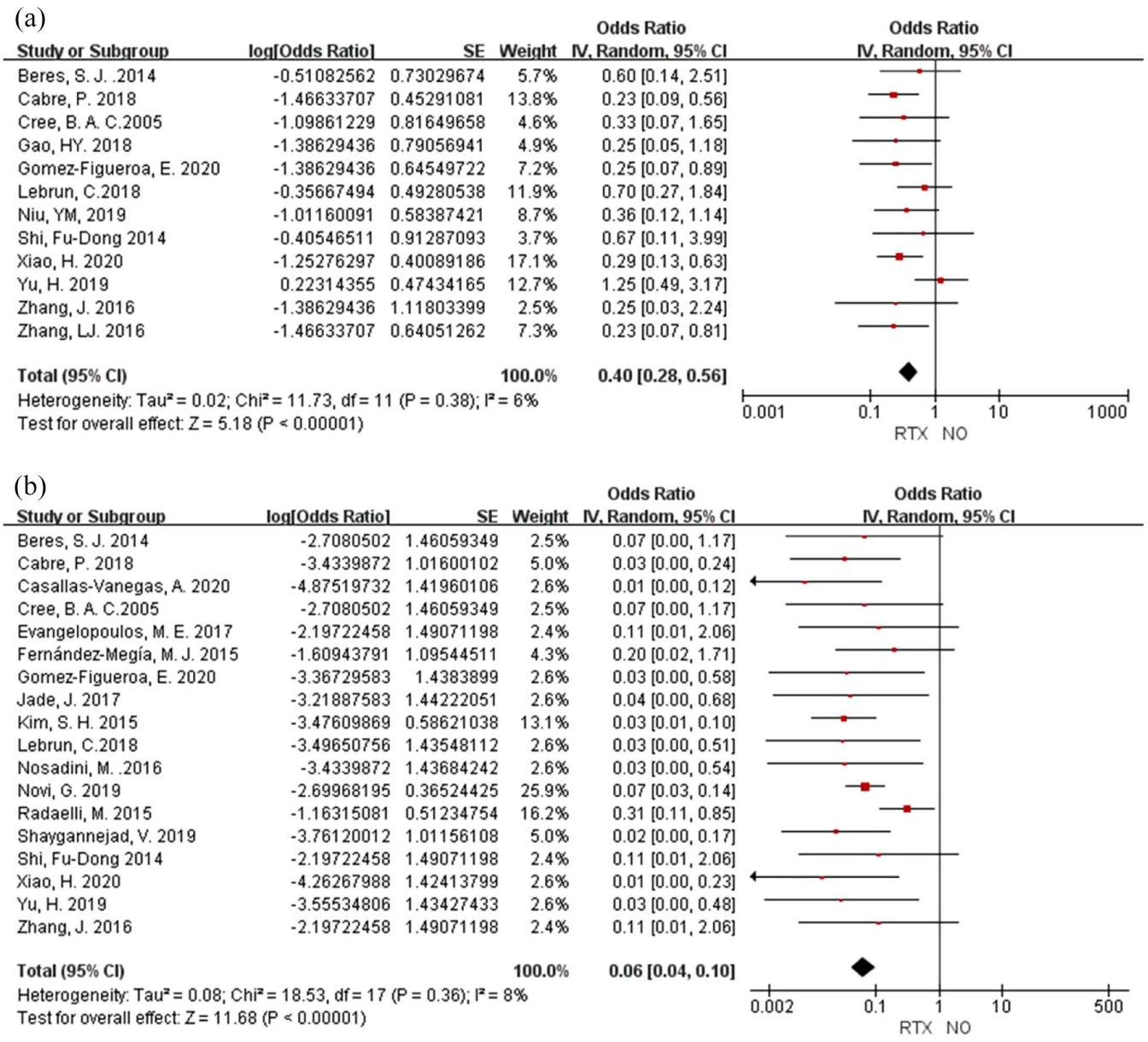

Figure 2. The forest plot for the rates of patients with at least one any AE or any SAE. (a) The forest plot for estimate rates of patients with at least one any AE. (b) The forest plot for estimate rates of patients with at least one any SAE. Any AEs are defined as the total AE reported by the authors, which usually means any undesirable occurrences that happened during the use of RTX for NMOSD. SAEs are defined as SAEs reported by the authors, mainly referring to AEs causing death, interruption or discontinuation of the therapy, hypotension (blood pressure $<$90/60 mmHg), prolongation of hospitalization (subject to the reports), requiring a blood transfusion. Of note, since some studies did not report any AEs, the number of studies reporting any AEs might be smaller than the number of studies reporting other AEs, such as any SAEs. Data in the forest plot were converted through the transformation method of 'odds data' and modified an offset of 0.5 for all 0 cells via EXCEL. The specific transformation is as follows: $\log(\mathrm{OR}) = \ln(\mathrm{odds}) = \ln(\mathrm{X}/(n-\mathrm{X}))$, $\mathrm{SE} = \mathrm{SE}(\ln(\mathrm{odds})) = \sqrt{1/\mathrm{X} + 1/(n-\mathrm{X})}$. In this calculation, 'log (OR)' means the logarithmic value of the incidence of AEs in each study, 'SE' means the standard error, 'X' means the number of patients with at least one of the AEs and 'n' means the total number of observed populations. The 'log (OR)' and 'SE' values are used to summarize the pooled 'OR' and its 95% CIs, and the log (OR), SE, OR and the 95% CIs are all displayed in the figure. After the summary, the following final transformation was required to obtain the final AE rates and its 95% CIs: P = OR/(1 + OR), LL = LL_{OR}/(1 + LL_{OR}), UL = UL_{OR}/(1 + UL_{OR}). In this transformation, 'P' means the transformed final rate of AEs, 'LL' means the transformed final lower limit of the 95% CI, 'LL_{OR}' means the lower limit of the 95% CIs before transformation, 'UL' means the transformed final upper limit of the 95% CIs, and 'UL_{OR}' means the upper limit of the 95% CIs before transformation. After the final transformation, the pooled rates of any AEs and any SAEs were 28.57% (95% CI = 21.88–35.90) and 5.66% (95% CI = 3.85–9.09), respectively.
AEs, adverse events; CIs, confidence intervals; OR, odds ratio; SE, standard error.

Table 2. Summary of estimate rates of AEs by types of events in case series.

Outcomes	No. of studies	P% (95% CI)	$\chi 2$	I2 (%)	P (Z)
Any AEs	12	28.57 (21.88–35.90)	11.73	6	< 0.00001
Any SAEs	18	5.66 (3.85–9.09)	18.53	8	< 0.00001
Infusion-related AEs[a]	18	27.01 (21.88–32.43)	21.32	20	< 0.00001
Any infection	8	17.36 (9.91–28.06)	14.19	51	< 0.00001
Respiratory infection	6	4.76 (2.91–9.91)	5.58	10	< 0.00001
Urinary infection	5	4.76 (2.91–10.71)	2.64	0	< 0.00001
Death associated with RTX use[b]	21	0.17	N/A	N/A	N/A
Drug withdrawal or change due to AEs	10	4.76 (1.96–9.09)	6.06	0	< 0.00001
Skin or mucous related AEs[c]	6	12.28 (6.54–21.88)	6.73	26	< 0.00001
Cardiovascular AEs[d]	5	10.71 (5.66–18.70)	1.73	0	< 0.00001
IgM decline[e]	3	22.48 (16.67–29.08)	0.03	0	< 0.00001
IgA decline[e, f]	2	12.28 (0.99–57.26)	12.96	92	0.009
IgG decline[e]	4	14.53 (6.54–29.58)	8.51	65	0.04
Herpes zoster	6	5.66 (2.91–9.91)	3.24	0	< 0.00001

AEs, adverse events; CI, confidence interval; N/A, not applicable; No., numbers; RTX, rituximab; SAEs, serious adverse events.
The AE rates and its 95% were the final ones after the final transformation, the method of which had already been detailed in the 'Statistical analysis' and Figure 2. Of note, since some studies did not report any AEs, the number of studies reporting any AEs might be smaller than the number of studies reporting other AEs, such as any SAEs and infusion-related AEs. Any AEs are defined as the total AE reported by the authors, which usually means any undesirable occurrences that happened during the use of RTX for NMOSD. SAEs are defined as SAEs reported by the authors, mainly referring to AEs causing death, interruption or discontinuation of the therapy, hypotension (blood pressure < 90/60 mmHg), prolongation of hospitalization (subject to the reports), and requiring a blood transfusion.
[a]Infusion-related AEs included fever, chills, urticaria, pruritus, angioedema, flushing, headache, and so on.
[b]The rates shown in the table were the corrected rates after post hoc analysis, the total number of patients experiencing death associated with using RTX divided by the total number of observations was used to conduct the post hoc analysis. The corrected rate was 0.17% (1 in 589 patients), and the pre-corrected incidence was 2.91% (95% CI = 1.96–4.76), $\chi^2 = 11.6$, $I^2 = 0\%$, P (Z) < 0.00001.
[c]Skin or mucous related AEs included rashes, itching, skin infections, and so on.
[d]Cardiovascular AEs included cardiovascular infections, atrial fibrillation, deep vein thrombosis, hypertension, angioedema, thrombocytopenia, and so on.
[e]No time-related outcomes were reported.
[f]The results were with significant heterogeneity.

lymphocyte clearance achieved immunosuppressive effects.[16] Overall, 12, and 18 case series reported the number of patients with at least one any AEs, or any SAEs, respectively. The pooled rates of patients with at least one any AEs, or any SAEs were 28.57% (95% CI = 21.88%-35.90%), and 5.66% (95% CI = 3.85%-9.09%), respectively (Figure 2 and Table 2). Other outcomes of interest included the rates of participants with at least one infusion-related AEs (27.01%, 95% CI = 21.88–32.43), any infection (17.36%, 95% CI = 9.91–28.06), respiratory infection (4.76%, 95% CI = 2.91–9.91), and urinary infection (4.76%, 95% CI = 2.91–10.71). Considering that the number of RTX-related deaths reported in 95.24% articles which reported death was 0, we corrected the incidence of it. The per-correction rate of participants with RTX-related deaths

was 2.91% (95% CI = 1.96–4.76), and the corrected rate was 0.17% (1 in 589 patients) (Table 2). Of noteworthy, the results on IgM, IgA, and IgG decline should be interpreted with caution as some studies did not report the time of the events. Some of the included studies reported these AEs with unfortunately unidentified number of the cases. Notably, among all included patients there were reporting four patients with serious infusion-related AEs, five patients with serious infection AEs, four participants with gastrointestinal upset AEs, eight participants with blood immune cells decline (two studies reported leukopenia, including five patients with persistent leukopenia (range: $2.6–3.6 \times 10^9$/L) and two patients experiencing transient leukopenia, and one study reporting one patient with delayed neutropenia), and two participants with malignant tumors. However, the incidence of these AEs was not pooled due to the extensive heterogeneity between studies.

Risks of the number of patients experiencing at least one AEs between RTX and other treatments. As no case-control studies were included, we grouped the RR of the number of patients experiencing at least one AEs from four RCTs, six cohort studies, and two NRCTs. Owing to the heterogeneity, only the data from the RTX vs AZA and RTX vs MMF studies were calculated. Pooled analyses showed that the risks of the number of patients with at least one any AEs (0.84, 95% CI = 0.42–1.69, $p = 0.62$), gastrointestinal upset (0.37, 95% CI = 0.08–1.81, $p = 0.22$) and any infections (1.24, 95% CI = 0.18–8.61, $p = 0.83$) for RTX were similar to those of AZA (Figure 3 and Table 3). The risks for RTX of the number of patients with at least one any SAEs (0.30, 95% CI = 0.13–0.68, $p = 0.004$), liver or kidney impairments (0.19, 95% CI = 0.06–0.60, $p = 0.005$), drug withdrawal or change due to AEs (0.30, 95% CI = 0.13–0.70, $p = 0.005$) and hematologic complications (0.13, 95% CI = 0.03–0.48, $p = 0.002$) were statistically lower than those for AZA; conversely, the risk for the number of patients with at least one infusion-related AEs was significantly higher in the RTX group (9.23, 95% CI = 2.15–39.59, $p = 0.003$) (Figure 3 and Table 3). The risks of the number of patients with at least one any AEs (0.66, 95% CI = 0.32–1.35, $p = 0.26$), any SAEs (0.38, 95% CI = 0.20–0.75, $p = 0.005$), drug withdrawal or change due to AEs (0.28, 95% CI = 0.12–0.67, $p = 0.004$), infusion-related AEs (9.41, 95% CI = 1.18–75.24, $p = 0.03$) for RTX vs MMF, were comparable to those for RTX vs AZA (Figure 3 and Table 3). In the non-pooled analyses, two studies[32,33] reported the AEs for RTX vs Cyclophosphamide (CTX), of which lower rates of the participants with any AEs (25% vs 80%) and higher rates of infusion-related AEs (8% vs 0%) in the RTX group were reported. These results were comparable to those of RTX vs AZA or MMF groups. Interestingly, two studies[34,35] investigated various doses of RTX. One showed that there were no significant differences for risks of the number of patients with at least one AE between the 375 mg/m^2 group and the 1000 mg group, while the other suggested that the 300 mg group suffered more liver or kidney impairments and immunoglobulin lowering events compared to the 100 mg group.

Subgroup analysis. The prespecified subgroup analyses of the RR comparisons between RTX and other treatments were limited because of lacking reporting on characteristic stratification. Thus, the subgroup analyses were performed only in the section for rates of patients with at least one AEs. Due to the unavailability of several characteristic stratifications in the case series, we developed the subgroup analysis based on disease definition (2006, 2015, 2006 or/and 2015), RTX dose (>500 mg/dose or ⩽ 500 mg/dose), disease duration (0–3, 4–6, or 10–12, years, no study reported the disease duration of 7–9 years) and study design (retrospective or prospective) in the following outcomes: rates of patients with any AEs, any SAEs, infusion-related AEs, any infection, respiratory infection, urinary infection and skin or mucous related AEs. It was found that the patients with 2006 NMOSD definition had the highest rates of participants with infusion-related AEs (31.51%, 95% CI = 25.37–38.65), followed by those with 2015 definition (26.47%, 95% CI = 17.36–38.27), and those with 2006 or/and 2015 definition (11.50%, 95% CI = 5.66–23.08), p for subgroup differences = 0.03. Likewise, it was found that the patients with 2006 NMOSD definition had numerically the highest rates of participants with any AEs (41.86%, 95% CI = 29.58–55.56), followed by those with 2015 definition (24.81%, 95% CI = 12.28–43.18), and those with 2006 or/and 2015 definition (18.70%, 95% CI = 10.71–31.51). p for subgroup differences = 0.07. Interestingly, we also found that higher doses of RTX (>500 mg/dose) (13.79%, 95% CI = 7.41–24.24 vs 30.56%, 95% CI = 19.35–44.75, $p = 0.04$) were associated with lower rates of the participants with infection. There were no significant differences between other subgroups (Table 4).

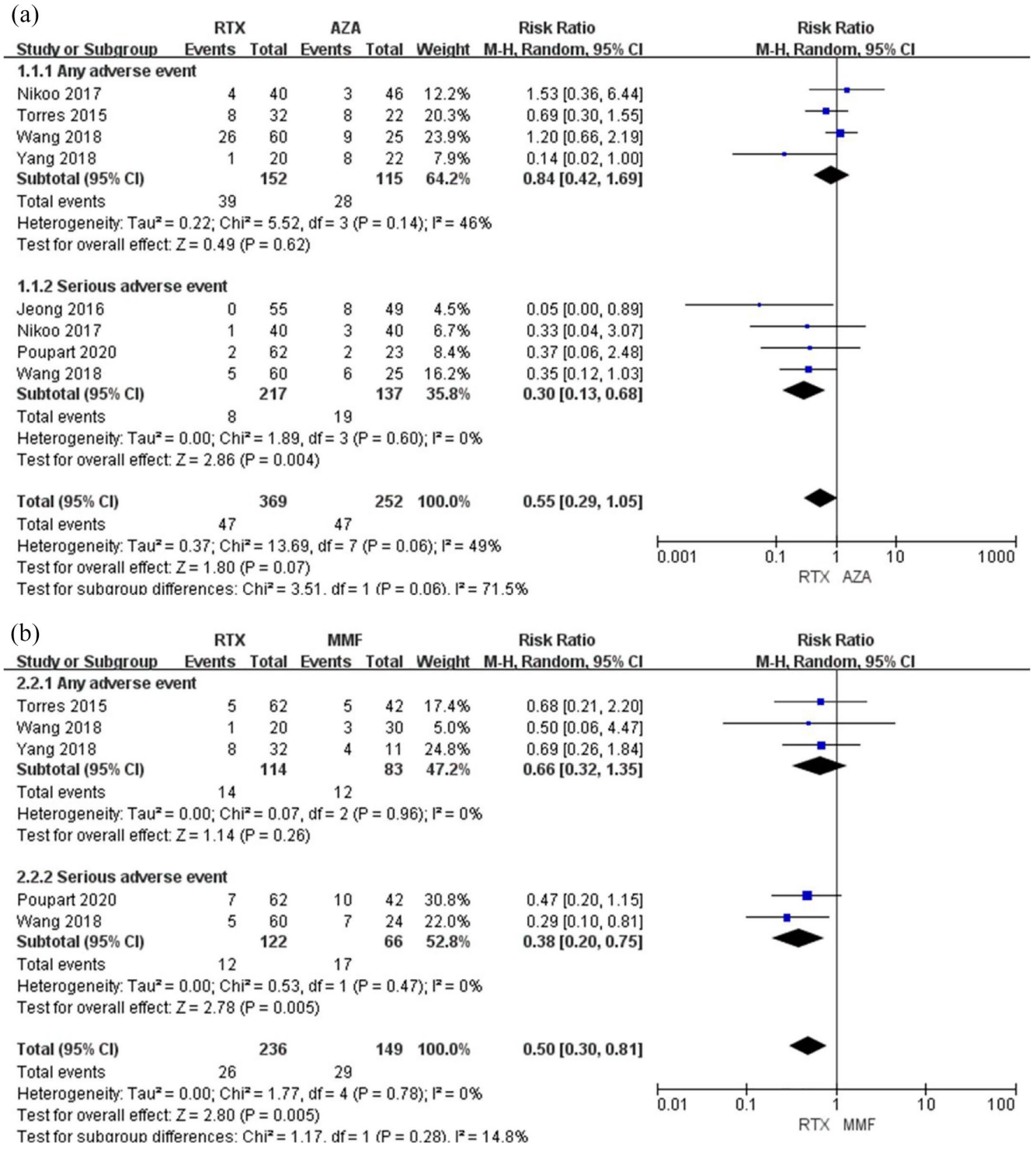

Figure 3. The risk ratio (RR) of the number of patients experiencing at least one any AE or SAE in NMOSD for RTX vs AZA and RTX vs MMF. (a) The risk ratio (RR) of the number of patients experiencing at least one any AE and SAE in NMOSD for RTX vs AZA. (b) The risk ratio (RR) of the number of patients experiencing at least one any AE and SAE in NMOSD for RTX vs MMF. Any AEs are defined as the total AE reported by the authors, which usually means any undesirable occurrences that happened during the use of RTX for NMOSD. SAEs are defined as SAEs reported by the authors, mainly referring to AEs causing death, interruption or discontinuation of the therapy, hypotension (blood pressure $<90/60$ mmHg), prolongation of hospitalization (subject to the reports), and requiring a blood transfusion.

AEs, adverse events; AZA, azathioprine; MMF, mycophenolate mofetil; RTX, rituximab; SAEs, serious adverse events.

Table 3. Comparison on AEs between RTX-based group versus non-RTX group.

Outcomes	No. of studies	RR (95% CI)	χ^2	I^2 (%)	df	P(df)	Z	P(Z)	Quality of evidence
RTX vs AZA									
Any AEs	4	0.84 (0.42–1.69)	5.52	46	3	0.14	0.49	0.62	very low
Any SAEs	4	0.30 (0.13–0.68)	1.89	0	3	0.6	2.86	0.004[a]	moderate
Liver or kidney impairment[b]	5	0.19 (0.06–0.60)	2	0	4	0.74	2.83	0.005[a]	high
Gastrointestinal upset[c]	3	0.37 (0.08–1.81)	0.23	0	2	0.89	1.23	0.22	low
Infusion-related AEs[d]	4	9.23 (2.15–39.59)	0.68	0	3	0.88	2.99	0.003[a]	moderate
Drug withdrawal or change due to AEs	4	0.30 (0.13–0.70)	1.92	0	3	0.59	2.81	0.005[a]	moderate
Hematologic complications[e]	4	0.13 (0.03–0.48)	0.72	0	3	0.87	3.04	0.002[a]	high
Any infections	2	1.24 (0.18–8.61)	1.49	33	1	0.22	0.22	0.83	very low
RTX vs MMF									
Any AEs	3	0.66 (0.32–1.35)	0.07	0	2	0.96	1.14	0.26	very low
Any SAEs	2	0.38 (0.20–0.75)	0.53	0	1	0.47	2.78	0.005[a]	moderate
Infusion-related AEs	2	9.41 (1.18–75.24)	0.45	0	1	0.50	2.11	0.03[a]	moderate
Drug withdrawal or change due to AEs	2	0.28 (0.12–0.67)	0	0	1	0.96	2.85	0.004[a]	moderate

AE, adverse events; AZA, azathioprine; CI, confidence interval; df, degrees of freedom; MMF, mycophenolate mofetil; No., numbers; RR, risk ratio; RTX, rituximab.
Any AEs are defined as the total AE reported by the authors, which usually means any undesirable occurrences that happened during the use of RTX for NMOSD. SAEs are defined as SAEs reported by the authors, mainly referring to AEs causing death, interruption or discontinuation of the therapy, hypotension (blood pressure $<$90/60 mmHg), prolongation of hospitalization (subject to the reports), and requiring a blood transfusion. Of note, since some studies did not report any AEs, the number of studies reporting any AEs might be smaller than the number of studies reporting other AEs, such as any SAEs and infusion-related AEs.
[a]Statistically significant.
[b]Liver or kidney impairments mainly included abnormality of laboratory indicators such as transaminase and creatinine.
[c]Gastrointestinal upset included nausea, vomiting, diarrhea, and so on.
[d]Infusion-related AEs included fever, chills, urticaria, pruritus, angioedema, flushing, headache, and so on.
[e]Hematologic complications included blood immune cells, immunoglobulins decline, and so on.

Prevention or treatments of AEs. A total of 23 publications (18 case series, 2 RCTs, 2 cohort studies, and 1 NRCT) reported the strategies for AEs, with 5 on preventive measures and 18 on therapeutic measures. Preventive measures, including the use of non-steroidal anti-inflammatory drugs (NSAIDs) (acetaminophen, etc.), antihistamines (iproniazid, diphenhydramine, dimethindene, chlorpheniramine, etc.), and glucocorticoids (cortisone, dexamethasone, prednisolone, hydrocortisone, etc.), mainly focused on infusion-related AEs. Therapeutic measures concentrated on infusion-related AEs, infections, liver, or kidney impairments. In addition to the use of the above drugs, treatments for infusion-related AEs also included a decrease in the rate of infusion and a reduction in the dose of the drug. Infection was controlled with antibiotics and related vaccines. Liver function was stabilized through hepatoprotective drugs. If unacceptable AEs appeared, RTX would be withdrawn. Overall, AEs of RTX for NMOSD were so mild or moderate that could be prevented or treated by

Table 4. Subgroup analysis of estimate rates of AEs by types of events by study characteristics in case series.

Outcomes		Any AEs	Any SAEs	Infusion-related AEs	Any infection	Respiratory infection	Urinary infection	Skin or mucous related AEs
Total incidence		28.57% (21.88–35.90), 6	5.66% (3.85–9.09), 8	27.01% (21.88–32.43), 20	17.36% (9.91–28.06), 51	4.76% (2.91–9.91), 10	4.76% (2.91–10.71), 0	12.28 (6.54–21.88), 26
Definition	2006	41.86% (29.58–55.56), 0[a]	9.09% (2.91–21.88), 50	31.51% (25.37–38.65), 0[b]	25.93% (13.79–42.86), 36	3.85% (0.99–16.67), 44	N/A	18.70% (6.54–44.75), NA
	2015	24.81% (12.28–43.18), 67[a]	4.76% (2.91–8.26), 0	26.47% (17.36–38.27), 42[b]	9.91% (4.76–18.70), 28	6.54% (2.91–15.59), 15	5.66% (1.96–13.79), 14	6.54% (2.91–14.53), 0
	2006 or/and 2015	18.70% (10.71–31.51), 0[a]	13.79% (3.85–42.20), 0	11.50% (5.66–23.08), 0[b]	37.11% (6.54–83.22), 85	13.79% (0.99–75.06), 86[c]	3.85% (0.99–15.25), 0	17.36% (6.54–38.27), 0
Dose, mg	>500	30.07% (20.63–41.86), 38	7.41% (3.85–12.28), 20	26.47% (21.26–32.89), 27	13.79% (7.41–24.24), 14[b]	N/A	N/A	12.28% (7.41–21.26), 0
	$\leqslant 500$	31.51% (19.35–46.81), 26	3.85% (0.99–13.79), 0	28.06% (19.35–39.76), 0	30.56% (19.35–44.75), 0[b]	N/A	N/A	6.54% (0.99–42.53), 60
Disease duration, years	0–3	35.06% (20.63–52.38), 30	4.76% (0.99–15.97), 0	35.06% (23.08–49.49), 0	12.28% (3.85–33.77), 0	12.28% (1.96–13.79), N/A	5.66% (1.96–13.79), 14	19.35% (7.41–41.18), 0
	4–6	28.57% (14.53–47.64), 61	5.66% (2.91–13.04), 45	30.07% (23.08–37.89), 29	27.01% (15.25–35.48), 49	6.54% (2.91–15.97), 15	5.66% (1.96–13.04), 14	3.85% (0.99–15.25), 0
	10–12	60% (29.58–84.18), N/A	2.91% (0.99–9.09), N/A	25.93% (18.03–35.48), N/A	60% (29.58–84.18), N/A[c]	3.85% (0.99–16.67), 44	N/A	9.91% (0.991–46.81), N/A
Study types	Retrospective	31.03% (22.48–41.52), 16	4.76% (2.91–8.26), 0	28.06% (23.66–33.33), 0	9.09% (5.66–13.79), 0	4.76% (1.96–11.50), 32	5.66% (1.96–13.79), 14	12.28% (6.54–23.08), 0
	Prospective	22.48% (10.71–40.83), 8	5.66% (1.96–20.63), 59	18.03% (8.26–37.50), 38	24.81% (13.79–39.76), 56	2.91% (0.99–7.41), N/A	5.66% (0.99–19.35), 0	7.41% (0.99–39.02), 69

AE, adverse events; N/A, not applicable; SAEs, serious adverse events.
The data in each cell represented the estimate rates, 95%
CI and I^2, respectively.
[a]There were numerically significant differences in the parameters from different groups.
[b]There were statistically significant differences in the parameters from different groups.
[c]With considerable heterogeneity.

symptomatic strategies, and the prognosis of AEs was excellent in general.

Potential publication bias and GRADE profile evidence. Visual inspection of funnel plots revealed an obvious symmetry in the rates of patients with at least one any AE, in contrast to those with any SAEs, infusion-related AEs, or drug withdrawal or change due to AEs, in which there might be potential publication bias (Supplementary Figure 3–6). No outcome for RTX vs MMF but two outcomes for RTX vs AZA (liver or kidney impairments, and hematologic complications) demonstrated the high quality of evidence. It was worth noting that the quality of evidence for the outcomes of any AEs in these two groups were both very low, as well as the outcome of any infections in RTX vs AZA group. Overall, high or moderate quality evidence accounted for 66.67% of all assessed outcomes, and the quality of evidence for specific outcomes was detailed in Table 3 and Supplementary Tables 8–9.

Discussion

Our study specifically assessed the AEs of RTX for NMOSD with two primary findings as follows. First, the rates of patients with at least one AE were not so high or serious that could be well prevented or controlled by strategies. Second, the risks of the number of patients experiencing at least one AE (except for infusion-related AEs) for RTX were lower than those for other standard therapies such as AZA or MMF. Both findings provided substantial evidence supporting RTX as a safe intervention option for NMOSD, although the between-study heterogeneity might limit the findings. Our results, that RTX was safe and imposed no extra burden on NMOSD patients, could primarily be applied to AOP4 positive NMOSD adult patients with a 2015 or/and 2006 NMOSD definition considering the basic characteristics of the included population.

In accordance with earlier studies,[18,36,37] the pooled rates demonstrated that infusion-related AEs, and infections were common, which might spring from the release of cytokines and/or other chemical mediators,[36] and the decreased immunoglobulin levels,[37] respectively. However, the rates of patients with infusion-related AEs and any infections were numerically higher,[11,37] and the infections mainly occurred in pulmonary and urinary, but did not present as herpetic rashes or tuberculosis reactivation when compared with the previous studies.[37,38] Meanwhile, the rates of participants with RTX-related deaths before correction were numerically higher in this study,[11,37,39,40] especially when compared to the N-MOmentum study for inebilizumab[41] which reported two deaths with one clearly due to ongoing disease process rather than treatment. If we included the remaining death as a treatment effect the death rate was 0.5%. This might result from the overestimations caused by the modification of 0.5 for 0 cells in 95.24% included studies. However, the corrected rate (0.17%) was in line with the result from the N-MOmentum study. We therefore believed that the true rate of RTX-related death in NMOSD was closer to 0.17%. Notably, in comparison with our study, more any AEs, any SAEs, infusion-related AEs, as well as less AE-related death and skin or mucous related AEs were numerically likely to occur in the latest, double-blind, placebo-control RCT,[16] probably due to the small sample size (38 patients) and short follow-up time (72 weeks). Findings from studies with control groups mainly indicated lower risks of AEs (except for infusion-related AEs) for RTX compared to those for AZA, MMF or CTX. Likewise, one study had found better safety of RTX than other first-line treatments (e.g. glucocorticoid and plasma exchange (PLEX)).[40] There were no significant differences between results from subgroups; however, the 2006 definition of NMOSD was numerically and significantly associated with higher rates of any AEs and infusion-related AEs, respectively. A probable explanation for this was that the new diagnostic criteria introduced the concept of NMOSD, which expanded the patients who might have improved tolerance to these AEs. Interestingly, patients with higher doses of RTX (>500 mg/dose) had lower overall infection risks, which might relate to the antibiotics or vaccines used for infection prophylaxis in advance. Overall, our results could demonstrate that, at least in part, the rates of patients with RTX-related AEs were not high and might not be related to covariates such as duration of illness and study designs; and RTX mostly had a better safety profile than other first-line treatments. However, infusion-related AEs must be focused for its high incidence. Given the rigorous, systematic, and quantitative analyses of this study, we insisted that our findings could effectively reflect the actual safety of RTX for NMOSD. Nevertheless, due to the heterogeneity and some lacking tests on correlation, our results must be considered as purely exploratory and the reasons

behind them need to be interpreted with caution and validated by further studies.

It is worth noting that there have been around 20 biosimilars of RTX but none of them has indicated perfect agreement with RTX,[42] which poses new challenges in evaluating the safety equivalence of these biosimilars to RTX. To date, a total of five RCTs have reported four novel monoclonal antibodies safe for NMOSD: the PREVENT study for eculizumab (targets complement protein C5),[43] the N-MOmentum study for inebilizumab (targets CD19-positive B cells),[41] the SAkuraSky[44] and SAkuraStar[45] studies for satralizumab (targets the interleukin 6 receptor) and TANGO study[46] for tocilizumab (targets the interleukin 6 receptor). Aligned with RTX, these medications were developed based on the pathophysiology of NMOSD, three of which (eculizumab, inebilizumab, and satralizumab) have been approved by the FDA to treat NMOSD. The pooled studies[47–49] found that there were no significant AE or SAE differences among these monoclonal antibodies (including RTX), no AE increased when comparing with placebo or AZA, and few deaths occurred. In other major immune-related diseases, most AEs of RTX were mild or moderate,[50–52] so that they could be solved by symptomatic treatments such as reducing the drug infusion rates, providing minor supportive treatments (e.g. steroid and antihistamine),[39] which was consistent with our findings in RTX for NMOSD. Nevertheless, it had been reported higher risks of progressive multifocal leukoencephalopathy (PML, 1/25000)[53] and hepatitis *B* (HBV) reactivation[54–56] of RTX for diseases such as rheumatoid arthritis. To our knowledge, no cases of PML or HBV reactivation of RTX for NMOSD have been observed, but given the global prevalence of hepatitis B, especially in developing regions,[57] HBV screening appeared to be necessary to prevent this SAE. Consequently, combined with preceding studies, our research could deduce that the AE profiles of RTX for NMOSD were aligned with other monoclonal antibodies or most other immune-related diseases, which was basically the same as the known safety profile of RTX.[38]

Several limitations of the present study are recognized. First, similar to other meta-analyses on drug safety,[58] some factors might limit our interpretations of the data: the overestimations of observational studies on results (accounting for the majority of included ones); the uses of AEs as the primary definition (with a risk of more events unrelated to RTX use); the competing risks from complications; and the heterogeneity among studies; yet these are owing to the current situation of this field. Second, most of the included follow-up periods for prospective studies ranged from approximately 1–2 years, resulting in insufficient detailed data on the duration of the AE responses. As a result, the long-term safety of RTX in NMOSD needs to be discussed. Finally, our findings mainly focus on RTX and NMOSD, which might reduce the reliability and generalizability to other demyelinating diseases and treatments (e.g. MS and RTX biosimilars), meaning caution must be needed when promoting these findings. Additional studies, especially RCTs with a large sample size and long-term monitoring, are required to assess the long-term safety of RTX for NMOSD. In order to benefit patients, there should be more efforts in identifying the optimal dose of RTX and the timing of drug use, evaluating the risk factors at the patient-level and discerning the populations with the highest risks of AEs.

Conclusion

Data from case series studies have revealed 28.57% rates of any AEs or 5.66% rates of SAEs for the treatments of NMOSD with RTX. Other AEs were mainly infusion-related AEs (27.01%) and infections (17.36%). The AE rates were most likely not associated with covariates such as duration of illness or study designs. Very-low-quality evidence indicated that RTX was a safe drug as AZA in terms of any AEs and any infections, and also implicated that RTX was a safe drug as MMF regarding any AE. Low to high quality evidence showed better safety of RTX in SAEs, infusion-related AEs, and drug withdrawal or change due to AEs and so on, but not in infusion-related AEs. Strategies to handle AEs focused on symptomatic treatments. Overall, we might infer that the AEs of RTX for NMOSD, which are mild or moderate, have non-high incidences with mostly lower risks comparing to other traditional immunosuppressants, and thus could be prevented or treated well. Consequently, considering the efficacy and safety of RTX, it could be advised as a first-line treatment for NMOSD.

Author contributions

Hao Wang: Conceptualization; Data curation; Methodology; Software; Visualization; Writing-original draft; Writing-review & editing.

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This study was supported by the tenth batch of provincial science and technology programs (innovation base and talent program) projects in 2020 of Science and Technology Department of Gansu Province. (Item No. *20JR10FA669*)

Ethical approval

Our study did not require an ethical board approval because this study is a systematic review and the data used are published and do not violate ethical standards.

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Supplemental material

Supplemental material for this article is available online.

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