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Meta-analysis

Efficacy and safety of monoclonal antibodies in neuromyelitis optica spectrum disorders: A survival meta-analysis of randomized controlled trials

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ABSTRACT

Background: Monoclonal antibodies such as rituximab (RTX), eculizumab, inebilizumab, satralizumab, and tocilizumab have been found to be effective therapies for neuromyelitis optica spectrum disease (NMOSD) in several clinical randomized controlled trials.

Objective: The purpose of this meta-analysis of randomized controlled trials was to assess the efficacy and safety of monoclonal antibodies in the treatment of NMOSD.

Methods: We searched the following databases for relevant English language literature from the establishment of the database to June 2021: PubMed, Embase, Cohorane Library, the Central Register of Controlled Trials (CENTRAL), and Web of Science. Randomized controlled trials of monoclonal antibodies were the targets of the review.

Results: We included seven trials containing 775 patients (485 in the monoclonal antibody group and 290 in the control group). Patients in the monoclonal group (HR 0.24, 95% CI: 0.14 to 0.40, $P < 0.00001$), as well as patients with seropositive AQP4-IgG (HR 0.18, 95% CI: 0.11 to 0.29, $P < 0.00001$), both had a higher free recurrence rate than that in the control group. In the first year (HR 0.25, 95% CI: 0.09 to 0.71, $P = 0.009$) and the second year (HR 0.32, 95% CI: 0.13 to 0.81, $P = 0.02$), no relapses were documented. The average changes of the expanded disability status scale (EDSS) score decreased by 0.29 (95% CI: −0.09 to 0.51, $P = 0.005$). Upper respiratory tract infection (OR 1.52, 95% CI: 0.76 to 3.04, $P = 0.24$), urinary tract infection(OR 0.79, 95% CI: 0.51 to 1.21, $P = 0.27$), and headache (OR 1.30, 95% CI: 0.78 to 2.17, $P = 0.31$) were three most frequent adverse reactions.

Conclusions: Monoclonal antibodies are particularly effective treatments in avoiding recurrence for NMOSD patients, according to this meta-analysis. The associated adverse responses are not significantly different from those seen with traditional immunosuppressants.

1. Introduction

1.1. Description of the condition

Neuromyelitis optica spectrum disease (NMOSD) is an inflammatory disease of the central nervous system that mainly involves the optic nerve and spinal cord.[1–3] Aquaporin-4 (AQP4) is a water channel protein expressed in the vascular astrocytes. When AQP4-IgG binds to the protein, it induces an inflammatory response by complementing the cellular mechanisms, causing astrocytic axon demyelination.[4–6] AQP4-IgG has lately been regarded as one of the most specific diagnostic markers of NMOSD since 80% of patients have this pathogenic autoantibody.[4,7] NMOSD is characterized by recurrent, severe neurological damage in patients, and if they are not given timely treatment, it will cause irreversible severe damage. Nevertheless, a curative treatment for NMOSD does not exist to date, the primary target of treatment is to alleviate symptoms and prevent patients from relapsing to reduce neurological impairment and disability worsening.[8,9] Because of the high morbidity

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associated with NMOSD relapse, early initiation of immunosuppressive therapy is recommended in AQP4-IgG seropositive patients from the first attack, and stopping immunosuppression is associated with an increased risk of disease recurrence.[10]

1.2. Description of the intervention

When patients are suffering an acute attack, corticosteroids, intravenous immunoglobulin (IVIG), or apheresis therapies (such as plasma exchange (PE) therapy and immunoadsorption) are recommended.[4,11–14] When the disease has progressed to the chronic stage, we frequently consider utilizing traditional immunosuppressive drugs, such as azathioprine (AZA) and mycophenolate mofetil (MMF).[11,15] Several randomized controlled trials (RCT) have recently revealed that monoclonal antibodies such as rituximab (RTX), eculizumab, inebilizumab, satralizumab, and tocilizumab may be effective treatments for NMOSD.[16–22] Therefore, we plan to conclude the studies by assessing the efficacy and safety of monoclonal antibodies in the treatment of neuromyelitis optica spectrum disorders.

1.3. Motivation for the review

System review and meta-analysis are not only crucial in the advancement of medicine but are also widely employed in other sectors.[23–27] RTX has been shown to have a good effect in preventing the recurrence of NMOSD, several monoclonal antibody medicines have been tested in clinical trials. A few randomized controlled trials have surfaced in the last two years, all of which have validated the exceptional therapeutic impact of these medications on NMOSD patients. Four of these papers were included in a prior meta-analysis, which verified partial results.[28] However, there were three new articles published recently,[19,20,22] and they provide us with more evidence. The previous meta-analysis of outcome evaluation was based solely on the number of events included in the study, performing a point estimation at a certain point in time and calculating the relapse events between different groups. The relapse rate ratio, that is, the relative risk (RR), was also described. The ratio was measured to some extent, but not all elements were taken into account; it is hard to convey a comprehensive picture of this type of data, and such incomplete data may lead to an inappropriate conclusion. The outcome of the event and the timing of the outcome are both essential in survival data. The most appropriate effect indicator for meta-analysis of survival research is the hazard ratio (HR), although it is sometimes difficult to get because the original research was not directly disclosed. As a result, we attempt to intercept the survival rate and other data from the survival curve of the original study, and the information, including follow-up time and other data, is entered into Excel for conversion to HR and 95% CI data.

2. Methods

2.1. Study protocol

A protocol of this study has been registered in PROSPERO; our registration number is CRD42021225328.

2.2. Search strategy and information sources

Two researchers independently searched the following databases for relevant English language literature from the establishing the database to June 2021: PubMed, Embase, Cochrane Libray, the Central Register of Controlled Trials (CENTRAL), and Web of Science. We used the keywords‘Neuromyelitis Optica’, ‘NMO Spectrum Disorder’, ‘monoclonal drugs’, ‘immunosuppressive drug’, ‘rituximab’, ‘eculizumab’, ‘inebilizumab’, ‘satralizumab’, ‘tocilizumab’, and ‘randomized controlled trial’, etc. The electronic database search was supplemented by a manual search of the reference lists of included articles.

2.3. Criteria for inclusion

2.3.1. Type of study

Randomized controlled trials were included in this survival meta-analysis.

2.3.2. Type of participants

The study contained patients who were diagnosed with NMOSD according to the 2015 International Panel for Neuromyelitis Optica Diagnosis criteria or 2006 NMO diagnosis criteria,[1,29] all patients had been treated with monoclonal antibodies. Patients were excluded if they had evidence of other systemic severe diseases. Traditional immunosuppressive medicines (corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide) were allowed for the control patients, but we excluded them if they had accepted any monoclonal antibodies within three months of enrolling in the trial.

2.3.3. Type of intervention

Monoclonal antibodies, such as RTX, eculizumab, inebilizumab, satralizumab, and tocilizumab were used to treat exposures; the patient could also take traditional immunosuppressive drugs (corticosteroids, azathioprine, mycophenolate mofetil, cyclophosphamide, and so on) before or during the treatment. Patients who utilized multiple monoclonal antibodies during the trial were disqualified.

2.3.4. Outcomes

The primary outcome for the comparison of interventions was the rate of free relapse, the first year of free recurrence rate, and the second year of free recurrence rate. Secondary outcomes for comparison were:(1) mean change in EDSS; (2) the proportion of participants with adverse effects (including urinary tract infection, upper respiratory tract infection, and headache); (3) the proportion of participants with serious adverse effects (such as death, serious affecting, and so on).

2.4. Selection of studies and data extraction

Endnote x9.2 was used to manage the search results. Two reviewers read the titles and abstracts independently selected the articles that fulfilled the inclusion criteria, kept the uncertain studies, then read the full texts to decide whether they should be enrolled or excluded. Any differences would be resolved by a third reviewer.

The following data were extracted: title, author, year of publication, the country where the study was conducted, diagnostic criteria, original inclusion criteria, sample size, sex ratio, age of onset, disease course, intervention method, following time, the serological state of AQP4-IgG, rate of relapse-free patients, basic EDSS score and mean changes of EDSS score, adverse effects, and serious adverse effects.

2.5. Risk of bias (every study)

Two reviewers independently assessed the quality of the selected studies according to the Cochrane Collaboration's tool for randomized controlled trials. Items were examined in three categories: low risk of bias, unclear bias, and high risk of bias. The following characteristics were considered: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias sources.[30,31] The results from these questions were graphed and assessed using Review Manager 5.4.

2.6. Strategy for data synthesis

We calculated and analyzed the recurrence-free survival data using a random effect model that appeared as hazard ratio (HR) (95% confidence interval [CI]), the dichotomous outcomes such as adverse events appeared as odds ratio (OR) and the consecutive outcomes appeared as

mean difference (MD); all these were completed by Review Manager 5.4. Statistical heterogeneity (I^2) was defined as follows: I^2 <25% represented "low heterogeneity,"25% < I^2 < 50% meant "moderate heterogeneity," and I^2>50% denoted "substantial heterogeneity." Two sides were used to test, and $P < 0.05$ was deemed significant for all analyses.

2.7. Subgroup analysis and investigation of heterogeneity

Subgroup analyses were conducted to explore the free recurrence rate of AQP4-IgG-positive patients.

3. Results

3.1. Description of studies

We performed the electronic searches on June 1, 2021 and identified 574 records in Pubmed, Embase, Web of Science, and CENTRAL (Fig. 1). Two reviewers read the titles and abstracts of the 423 remaining articles after removing 151 duplicated records. After that, we retrieved 23 full trials and excluded 16 studies. Eventually, we included seven trials containing 775 patients (485 in the monoclonal antibody group and 290 in the control group). The characteristics of each study are presented in Table 1.

3.1.1. Type of participants

Patients in seven trials had all been diagnosed with NMOSD or NMO, and had at least one relapse throughout the study.[17] Patients in two studies were all AQP4-IgG seropositive.[18,19] The percentages of AQP4-IgG seropositive individuals in four other studies were 48.5% in Ref. [17], 41.7% in Ref. [16], 66.3% in Ref. [21], 67.4% in Ref. [20], and 87.3% in Ref. [22]

3.1.2. Type of intervention

The seven trials provided a variety of comparisons. Two trials separately compared RTX with AZA and placebo,[17,19] two trials compared satralizumab with placebo,[20,21] and three trials compared the effects of eculizumab, inebilizumab, and tocilizumab to placebo or AZA, respectively.[16,18,22]

3.1.3. Type of outcome

Free relapse was monitored and reported as the primary outcome in all trials. We used Engauge Digitizer software to intercept the results of the Kaplan-Meier curve and evaluated the non-recurrence rate of the first and second years after the application of monoclonal antibodies following the method introduced in the literature.[32] EDSS scores were reported from four trials and evaluated by mean difference. According to the results, adverse events and serious adverse events were reported in all trials: upper respiratory tract infection, urinary tract infection, and headache were the most common adverse symptoms exhibited in these treatments.[33]

3.2. Risk of bias in included studies

The "risk of bias" assessments for the included studies are summarized in Fig. 2. The majority of the domains we assessed were "low bias"; where we couldn't determine the risk of bias based on the available data,

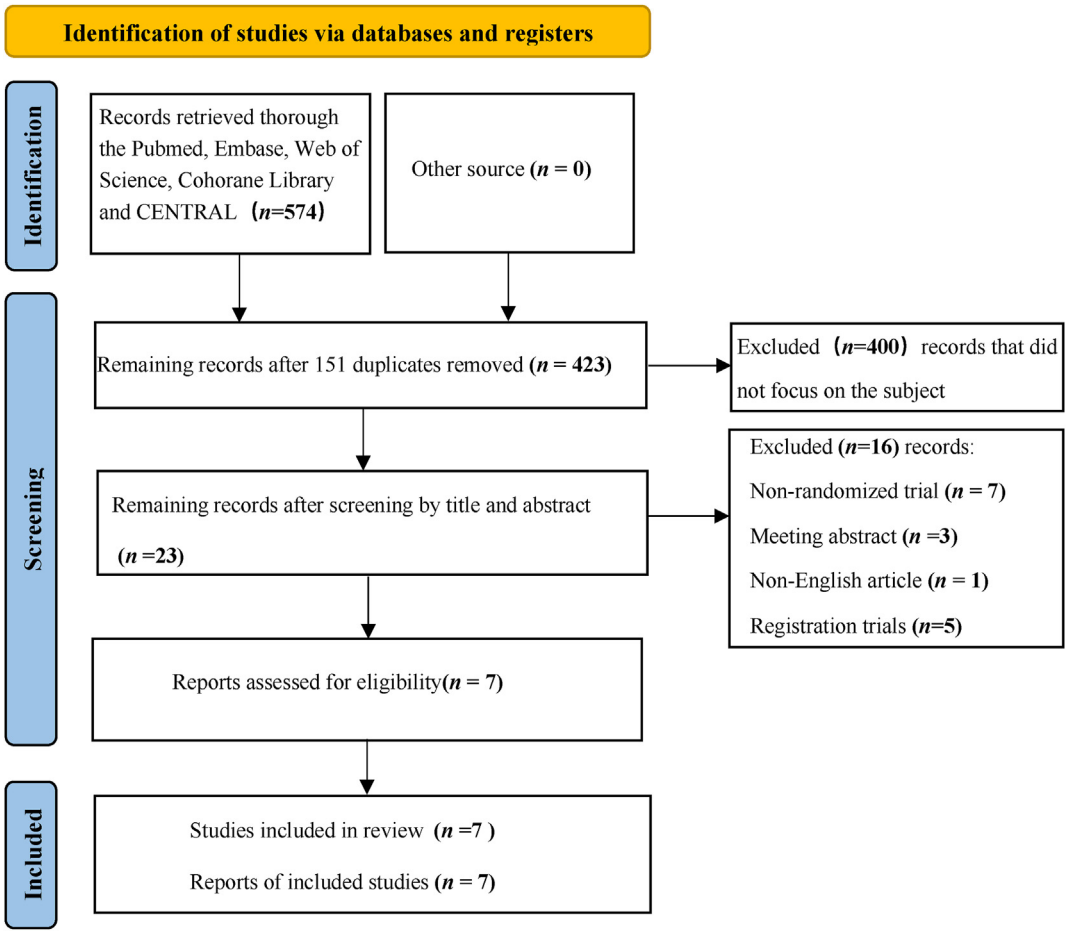

Fig. 1. Flow chart of the number of studies identified and selected for the meta-analysis.

Table 1
Characteristic of the included studies.

Include studies	Nikoo et al., 2017	Pittock,S. J.2019	Cree, B. A. C.2019	Yamamura, T.2019	Traboulsee, A.2020	Tahara, M.2020	Zhang, C.2020
Study design	Open-label randomized clinical trial	Randomized double-blind time-to-event trial	Multicentre double-blind, randomized placebo-controlled study	Randomized, double-blind, placebo-controlled trial	Double-blind, placebo-controlled parallel-group trial,	Multicentre, randomized double-blind placebo-controlled clinical trial	Open-label multicentre randomized phase 2 trial
Number randomized	35 in AZA group; 33 in RTX group	96 in eculizumab group; 47 in placebo group	174 in Inebilizumab group; 56 in placebo group	41 in Satralizumab group; 42 in placebo group	63 in Satralizumab group; 32 in placebo group	19 in RTX group; 19 in placebo group	59 in tocilizumab group; 59 in AZA group
AQP4 seropositive	20 (57.1%) in AZA group; 13 (39.4%) in RTX group	All AQP4-IgG seropositive	77(48%) in Inebilizumab; 19 (37%) in placebo	27 in Satralizumab; 28 in placebo	41 (65%) in Satralizumab; 23 (72%) in placebo	All AQP4-IgG-seropositive	50 (85%) in tocilizumab; 53 (90%) in AZA
Follow up	24 months	211weeks	197days	216weeks	216weeks	72weeks	90weeks
Country	Iran	American	American	Japan	Canada	Japan	China
Inclusion criteria	Diagnosis with NMOSD; Age between 18 and 50 years; EDSS between 0 and 7.0	At least 18 years; diagnosed NMOSD; AQP4-IgG seropositive status; A history of at least two relapses during the previous 12 months or three relapses during the previous 24 months; A score of 7.0 or less on the EDSS	Adults (≥18 years old) with a diagnosis of NMOSD; An EDSS score of 8.0 or less; A history of either at least one attack requiring rescue therapy (intravenous corticosteroids, intravenous immunoglobulin, plasma exchange, or a combination of these therapies) during the year before screening or at least two attacks requiring rescue therapy in the 2 years before screening	Adolescents or adults (12–74 years of age) diagnosed NMO/NMOSD; At least two relapses in the 2 years with at least one relapse occurring in the previous 12 months; EDSS score of 0–6.5 at screening	Adults (aged 18–74 years) diagnosed NMO/NMOSD; At least one documented attack in the 12 months before screening and a score of 6.5 or less on the EDSS	Patients aged 16–80 years who were diagnosed NMOSD with seropositive AQP4-IgG; A history of either optic neuritis or myelitis, receiving oral steroids; EDSS score 7.0 or less, and were neurologically stable.	Adults (≥18 years) with highly relapsing NMOSD; EDSS score of 7.5 or lower; A history of at least two clinical relapses during the previous 12 months or three relapses during the previous 24 months, with at least one relapse in the previous 12 months
Experimental	RTX	Eculizumab	Inebilizumab	Satralizumab	Satralizumab	RTX	Tocilizumab
Control	AZA	Placebo	Placebo	Placebo	Placebo	Placebo	AZA
Primary outcomes	ARR measured after 12 months of intervention	The first adjudicated relapse	Time from day 1 to the onset of an NMOSD attack, on or before day	The first protocol-defined relapse in the double-blind period in a time-to-event analysis	The time to the first protocol identified relapse in the double-blind period	ARR measured after 12 months of intervention	The first adjudicated relapse
Secondary outcomes	The EDSS was measured after 12 months	The adjudicated annualized relapse rate; Changes from baseline in scores on the EDSS; Modified Rankin scale; Hauser Ambulation Index; EQ-5D-3L visual analogue scale; EQ-5D-3L summary index	Worsening of EDSS score from baseline; Change from baseline in low contrast visual acuity bin ocular score; Cumulative total number of active MRI lesions; Number of NMOSD related inpatient hospitalisations	The change from baseline to week 24 in the visual analogue scale (VAS) score; The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) score; The 36item Short Form Health Survey; The EuroQol-5 Dimensions (EQ-5D) instrument; The modified Rankin scale; The Zarit Burden Interview; The EDSS score; visual acuity; The percentage of patients free from relapse	The change in the VAS pain score; FACIT score; Proportion of relapse-free patients; Annualized relapse rate; 36-item Short Form Health Survey; EuroQol-5 dimensions; Timed 25-foot walk speed; modified Rankin Scale; Zarit Burden Interview; EDSS; Visual acuity; Low-contrast visual acuity	The EDSS was measured after 12 months	The adjudicated annualized relapse rate; Changes from baseline in scores on the EDSS; Modified Rankin scale; Hauser Ambulation Index; EQ-5D-3L visual analogue scale; EQ-5D-3L summary index
Adverse events reported	RTX: Allergic reactions; AZA: Liver function; Gastrointestinal intolerance	Upper respiratory tract infection; Headache; Nasopharyngitis; Nausea; Diarrhoea; Urinary tract infection; Limb pain; Vomiting	Urinary tract infection; Arthralgia; Infusion-related reaction; Back pain; Headache; Nasopharyngitis; Diarrhoea; Upper respiratory tract infection; Depression; Oral herpes Pain in extremity; Pruritus; Vomiting	Nasopharyngitis; Upper respiratory tract infection; Headache; Urinary tract infection; Leukopenia; Injection-related reactions; Anemia; Hypercholesterolemia; Constipation; Pyrexia	Urinary tract infection; Upper respiratory tract infection; Injection-related reactions; Nausea; Rash; Headache; Pain in extremity; Nasopharyngitis; Arthralgia; Fatigue	Infusion reaction; Nasopharyngitis; Headache; Upper respiratory infection; Diarrhoea	Hepatotoxicity; Upper respiratory tract infection; Urinary tract infection; Anaemia; Leukopenia; Nausea; Fatigue

the risk was rated "unclear." Each domain of every article is summarized below. Based on the assessment of the quality of the trials, we judged the overall quality of evidence as high to moderate. Random sequence generation and allocation concealment were implemented in five of the seven included trials. Except for two studies,[17,22] blinding of participants and evaluators was used throughout the studies. Complete outcome data were reported from all tests. Only one article we analyzed was determined to show bias due to its incomplete reporting outcome[16]; no other conflict of interest were found in any articles.

3.3. Effect of intervention

The efficiency of this meta-analysis was primarily assessed using two outcome indicators: the rate of relapse-free and the mean change of EDSS score.

3.4. Free recurrence rate

As shown in Fig. 3A, patients in the monoclonal arm had a higher free recurrence rate than in control (HR 0.24, 95% CI: 0.14 to 0.40, $P < 0.00001$). We classified the result as "moderate heterogeneity; " therefore, we conducted a subgroup analysis of the results of the seven studies according to the status of serum AQP4-IgG. In AQP4-IgG seropositive patients, monoclonal effects seemed to be more valid in preventing relapse than the control (HR 0.18, 95% CI: 0.11 to 0.29, $P < 0.00001$; Fig. 3B). Four studies reported the first year of the no-relapse rate (HR 0.25, 95% CI: 0.09 to 0.71, $P = 0.009$; Fig. 3C); data on the second year (HR 0.32, 95% CI: 0.13 to 0.81, $P = 0.02$; Fig. 3D) were extracted from three studies.

3.5. EDSS score change

In the monoclonal groups, the mean EDSS score decreased significantly by 0.29 (95% CI: −0.09 to 0.51, $P = 0.005$; Fig. 3E).

3.6. Adverse events

There was no difference in the probability of adverse events occurring between the monoclonal and control group (OR 0.89, 95% CI: 0.49 to 1.59, $P = 0.68$; Fig. 4A). Among the included studies, the three most frequent adverse reactions were upper respiratory tract infection (OR 1.52, 95% CI: 0.76 to 3.04, $P = 0.24$; Fig. 4B), urinary tract infection (OR 0.79, 95% CI: 0.51 to 1.21, $P = 0.27$; Fig. 4C), and headache (OR 1.30, 95% CI: 0.78 to 2.17, $P = 0.31$; Fig. 4D). Similarly, there was no distinction between the occurrence of severe adverse events in the monoclonal groups and the control groups (OR 0.66, 95% CI: 0.41 to 1.06, $P = 0.08$; Fig. 4E).

4. Discussion

Seven RCTs with 775 randomized individuals were included in this review of monoclonal antibodies for NMOSD. Half of these studies were followed up for more than one year. These monoclonal antibodies appeared to be significantly more effective than control in preventing NMOSD relapses in the first two years. The total recurrence rate of patients treated with monoclonal antibodies was lowered, according to the findings, which is consistent with earlier research.[28,34–36] Furthermore, we analyzed the outcomes of the two-year follow-up period and discovered that the experimental group's recurrence rate was much lower. Previous studies and case reports have demonstrated that pregnancy patients usually had a poor prognosis due to the activity and pathogenesis of the disease.[37–39] Monoclonal antibodies may be an alternate treatment for pregnant patients with NMOSD. RTX administered before conception may prevent the mother from relapsing without exposing the fetus to potentially harmful effects.[40,41] Experts have recommended that receive RTX treatment until conception, and if necessary,

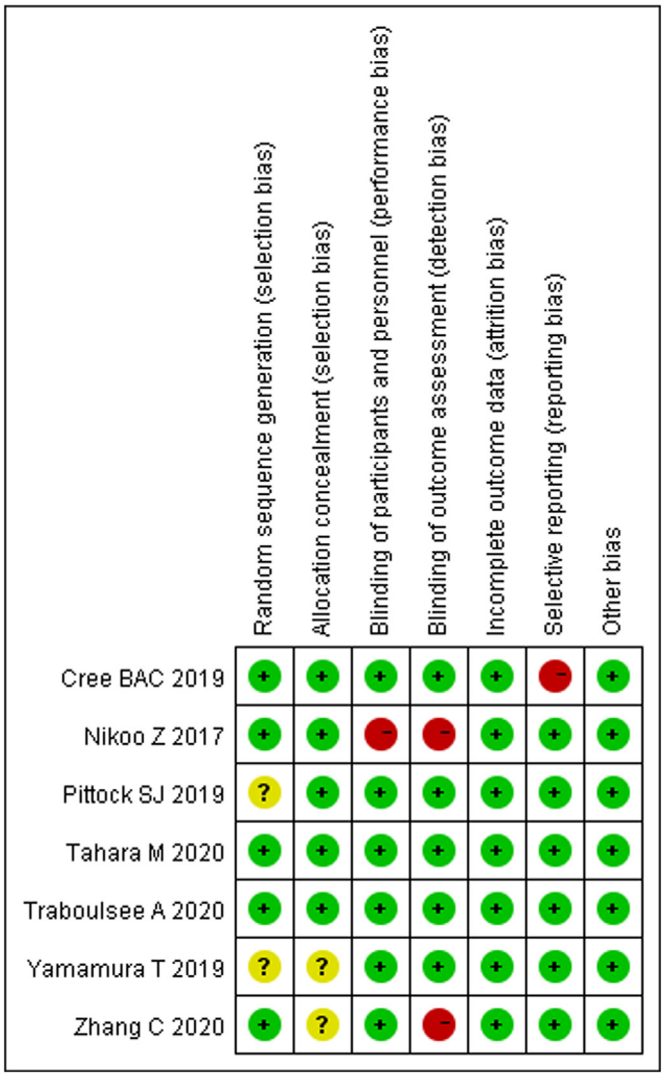

Fig. 2. Risk of bias summary.

during pregnancy as well.[6,41,42] A Japanese cohort study of pregnant women with rheumatoid arthritis reported that rates of spontaneous abortion, congenital abnormalities, and other pregnancy outcomes in the tocilizumab arm were not different from those seen in the general population.[43] Furthermore, experts support that tocilizumab and eculizumab can be considered if patients experience a very severe course of the disease.[6,8,44] The effects of inebilzumab and satralizumab on pregnancy are currently unknown, and we need to look for more evidence in the future.

A previously published network meta-analysis compared the efficacy of current immunosuppressive agents and monoclonal antibodies, and RTX was deemed to be more effective.[11] However, due to the recent introduction of new types of monoclonal antibodies and restricted research capability, the sample size was insufficient to draw a comprehensive conclusion.[17] As some studies have found that AQP4-IgG positive individuals respond well to satralizumab, eculizumab, and inebilizumab monotherapy.[35,45–47] IL-6 promotes the differentiation of naive T cells into inflammatory T-helper-17 cells, increases the permeability of the blood-brain barrier, and regulates the expression of complement C3. Targeting the IL-6 signaling pathway inhibits both the humoral immune response as well as the T-cell pathway and dysfunction of the BBB, providing comprehensive treatment for the different NMOSD manifestations. Satralizumab is a subcutaneously administered, humanized monoclonal antibody that binds to membrane-bound and soluble IL-6

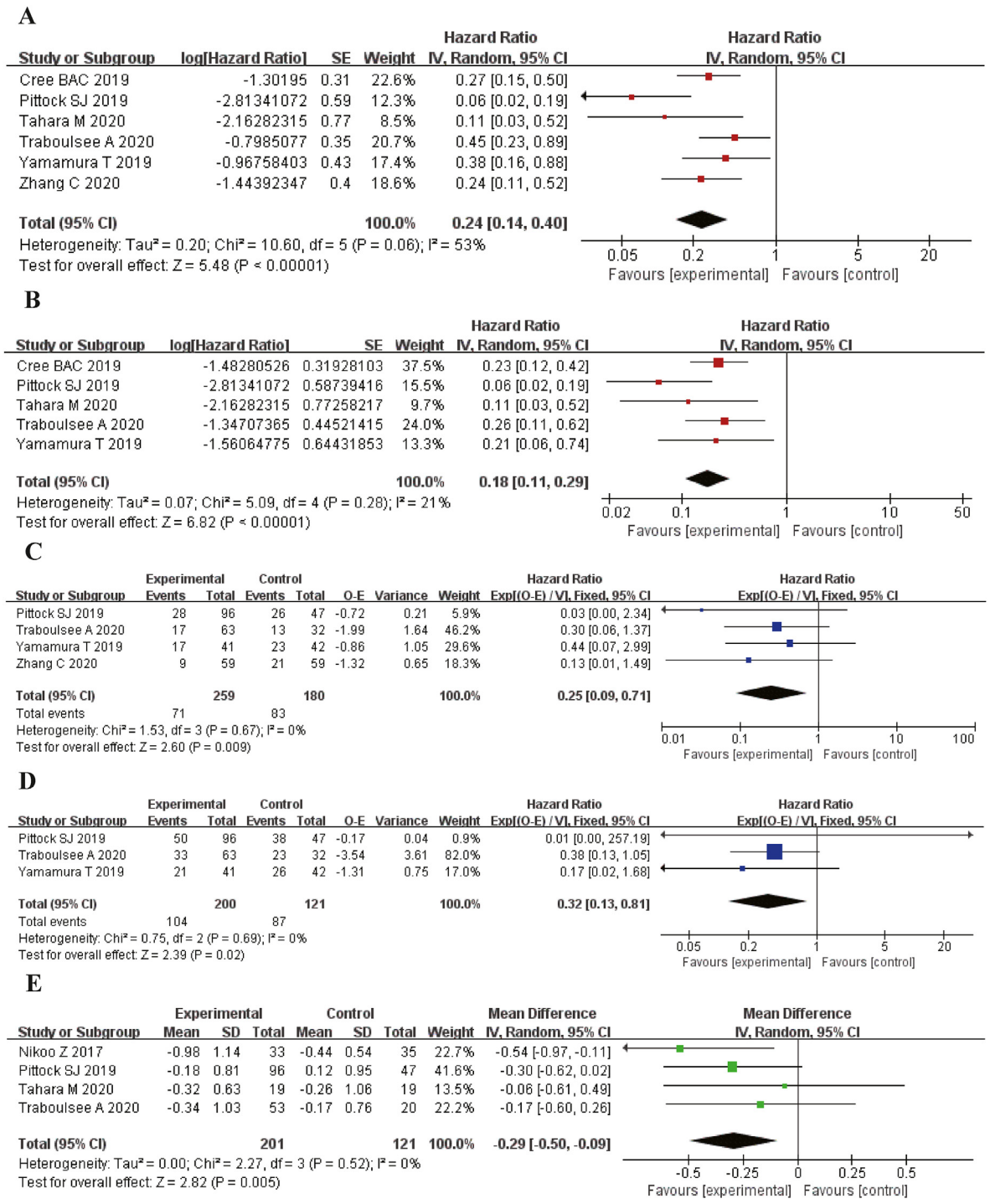

Fig. 3. The monoclonal effect of preventing recurrence, the forest plot indicates the estimated hazard ratio (95% confidence interval): A. in all patients; B. in AQP4-IgG seropositive patients; C. the first-year of no relapse rate; D. the second-year of no relapse rate; E. the mean change of EDSS score.

receptors, preventing IL-6 from binding and inhibiting the IL-6 signaling pathways involved in inflammation.[20] Eculizumab is a long-acting humanized monoclonal antibody targeted against complement C5, it inhibits the cleavage of C5 into C5a and C5b and hence inhibits the deployment of the terminal complement system including the formation of membrane attack complex.[35,46] Inebilizumab targets and depletes CD19-expressing B cells through antibody-dependent cell-mediated cytotoxicity.[46,47] In addition, we believe that numerous other factors, including those that frequency, severity, AQP4-IgG antibody status, and age, influence the disease's recurrence, based on available information.[45,48–50] Of note, differentiating symptoms between a true relapse and a pseudorelapse is a diagnostic challenge even for expert clinicians. Of the patients who presented with true relapses, 75% had positive AQP4-IgG serostatus, however, 60% of pseudorelapse patients had positive serostatus similarly. A previous study identified that vision loss in NMOSD is strongly suggestive of a true relapse vs a pseudorelapse, meanwhile, pseudorelapses localized to the spinal cord in patients with previous myelitis presented similarly to true relapses and could only be

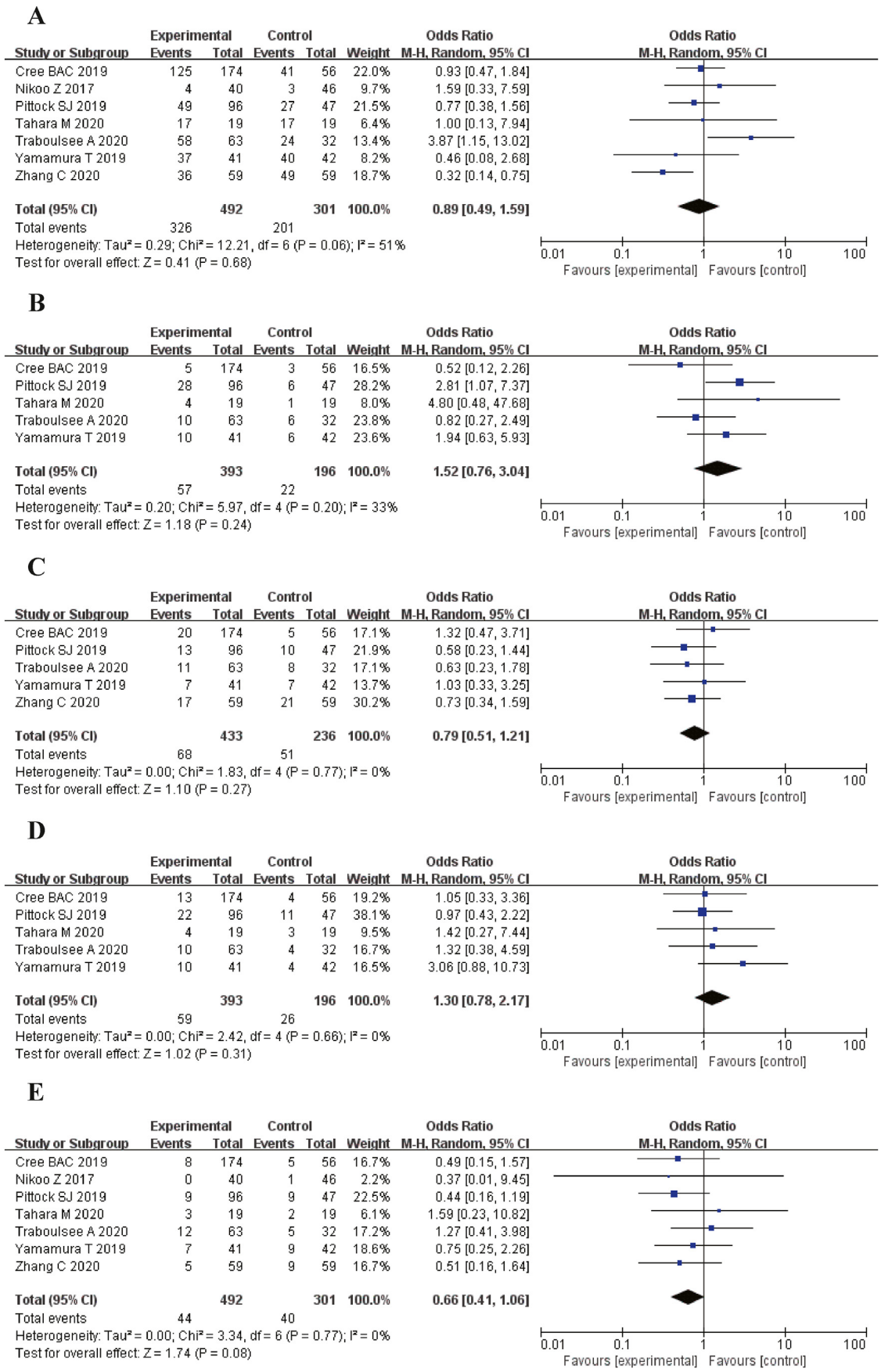

Fig. 4. The forest plot indicates the estimated odds ratio (95% confidence interval) of adverse events: A. the total adverse events; B. the upper respiratory tract infection; C. the urinary tract infection rate; D. headache; E. serious adverse events.

ruled out by a negative MRI.[51–53] To avoid and manage worsening conditions in the chronic phase, a correct assessment of the disease status and the adoption of appropriate treatment strategies are required.[8,35,36,54] This meta-analysis found that seropositivity for AQP4-IgG in NMOSD patients could effectively prevent recurrence when treated with monoclonal antibodies, although more research with more samples is needed.

The mean EDSS score change reported by four trials showed the result: monoclonal antibodies were correlated with a remarkable decrease in EDSS scores. Other non-RCT studies that were not included in the meta-analysis also found that monoclonal antibodies have a similar effect on reducing EDSS score.[34,35,54–56] However, the guidelines of the European Medicines Agency (EMA) suggest that an average change of EDSS score from baseline is not an adequate efficacy parameter. Instead, they recommend defining treatment success or treatment failure as either reaching a certain EDSS score or a sustained change of insufficient volume.[57] But due to the lack of raw data, we could not follow this method of analysis.

In comparison to standard immunosuppressants, there was no statistical difference in the safety of monoclonal antibodies for NMOSD. Upper respiratory tract infection, urinary tract infection, and headache were the most common side events reported in both the monoclonal antibodies and control groups. We hypothesize that the reason may be that patients in the control group did not restrict the use of other traditional immunosuppressants, and the adverse effects of immunosuppressants may be roughly similar to those of the experimental group. The possibility of numerous adverse events should be considered during therapy, and precautions should be made to avoid them. Because inebilizumab can cause hypogammaglobulinemia, it's vital to check immunoglobulin levels before and during treatment[58,59]; In patients with hepatitis B and active or untreated latent tuberculosis, satralizumab and RTX are contraindicated[19,21,58,60]; Meningococcal sepsis has been a severe adverse event in eculizumab-treated patients, and we believe that meningococcal vaccine should be given to patients at the commencement of treatment.[18,55]

5. Limitation

We limited our literature search and screening to studies written in English; as a result, the experimental results of certain non-English articles may have been overlooked. In addition, in the process of extracting data, we used the Engauge Digitizer software, although we have done our best to be accurate, it inevitably caused a bit of error in the calculation of two-year relapse-free survival by using the manual screenshot. Furthermore, there are few clinical studies on novel monoclonal antibody medications, a network meta-analysis to compare which works best is not possible.

6. Conclusions

Monoclonal antibodies are particularly effective treatments in avoiding recurrence for NMOSD patients, according to this meta-analysis. The associated adverse responses are not significantly different from those seen with traditional immunosuppressants.

Study approval

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by XX, LX, and LW. The first draft of the manuscript was written by XX and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declaration of completing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

AQP4	aquaporin-4
AZA	azathioprine
BBB	blood-brain barrier
EDSS	expanded disability status scale
HR	hazard ratio
IVIG	intravenous immunoglobulin
MMF	mycophenolate mofetil
MD	mean difference
NMOSD	neuromyelitis optica spectrum disorders
OR	odds ratio
RCT	randomized controlled trials
RTX	rituximab

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