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Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD ：a protocol for systematic review and meta-analysis.

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Abstract

Introduction Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory and heterogeneous astrocyte disorder of the central nervous system (CNS) with the characteristic of higher incidence in women and Asian. Most patients with NMOSD have a course of recurrence and remission, which are prone to cause paralysis and blindness. A number of studies have confirmed the efficacy and promising prospect of mycophenolate mofetil (MMF) in the treatment of NMOSD. However, there are controversial about its therapeutic effect and safety. The purpose of this study is to conduct a systematic review and meta-analysis to assess the efficacy and safety of MMF in treating NMOSD.

Methods and analysis This systematic review will include all comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study. A relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang

Database, China Science and Technology Journal database (VIP) and CBM. We will also search registers of clinical trials, potential gray literature, and conference abstracts. There are no limits on language and publication status. The reporting quality and risk of bias will be assessed by two researchers independently. Expanded disability status scales (EDSS), annualized relapse rate (ARR)will be evaluated as the primary outcome. The secondary outcomes will include the frequency and extent of adverse events (AEs), best-corrected visual acuity (BCVA), relapse-free rate and time to the next attack. Meta-analysis will be performed using RevMan5.3 software provided by the Cochrane Collaboration and Stata 12.0.

Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and will be shared on social media platforms.

PROSPERO registration number： PROSPERO CRD42020164179.

Strengths and limitations of this study:

► This study is the first to conduct an exhaustive literature search to identify studies aimed to assess the effectiveness and safety of MMF in treating NMOSD.

► One limitation of this study is that differences in patients, interventions and primary outcomes may mean that meta-analysis cannot be conducted, and narrative and meta-analytical syntheses are planned.

► Although we will include studies published in any language, translation difficulties may arise, which will result in the exclusion of these studies.

► The analysis of different sources of heterogeneity and the assessment of risk of bias of the included studies is a key point for extracting and synthesising evidence-based conclusions.

Keywords: mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol, systematic review, meta-analysis.

1. Introduction

Neuromyelitis optica (NMO), also known as Devic disease, is currently considered to be a rare autoimmune astrocyte disease of the central nervous system mediated by

autoantibodies, dominated by humoral immunity and involving multiple immune cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical clinical manifestations.[1] NMO has been recognized as a subtype of multiple sclerosis (MS) for more than 100 years since it was first described and reported.[2] Until 2004, the discovery and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) made significant progress in pathogenesis, diagnosis and treatment of NMO.[3 4] The concept of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the widespread clinical use of specific AQP4-IgG,[4] which mainly referred to the limited NMO of positive AQP4-IgG. However, with the gradual improvement of the specificity of AQP4-IgG clinical testing, the shortcomings of the diagnostic criteria of NMO in 2006 and NMOSD in 2007 became prominent. In 2015, the international NMO diagnostic team proposed a new international diagnostic standard for NMOSD.[5] NMOSD includes NMO, ON, longitudinally extensive transverse myelitis and other typical demyelinating brain syndrome.[5] Up to now, there is no solid data on the incidence and prevalence of NMOSD in the world. According to the existing epidemiological data of small samples, middle-aged and young women are the high incidence of this disease, with the onset age ranging from 32 to 41 years old, and the incidence of female is about 10 times that of male.[5] The incidence and prevalence vary from region to region, with the incidence and prevalence being about 0.05-0.40 and 0.52-4.40/100,000, respectively.[6] The areas with a large Asian population are the region with high incidence of NMOSD.[7-9] Most patients with NMOSD have a course of recurrence and remission, including ON, myelitis and lesions in special parts of the brain, which are prone to cause paralysis and blindness.[5] NMOSD has become one of the most common causes of non-traumatic disability and blindness in young and middle-aged people, bringing heavy burdens on the life, work and study of patients, as well as the society and economy of various countries.[10] Relevant clinical data show that after an average of 5 years of NMO, about 1/4 of the patients will be unable to walk independently, about 10% will be wheelchair-dependent, and more than half of the patients will develop severe visual impairment in at least one eye.[11] In particular, ON associated with NMO (NMO-ON) has poor recovery of visual impairment even after

conventional treatment. They often develop into severe bilateral visual impairment in the long term, leaving behind varying degrees of optic atrophy, which is different from MS.[12 13]

Currently, there are no uniform guidelines for the clinical management of NMOSD. The class of drugs in treating NMOSD is collectively referred to as disease modifying drugs,[14] and the treatment is divided into two stages: acute phase and remission phase. The former is based on corticosteroids to reduce the severity of acute attacks. Treatment options include intravenous corticosteroids (IVCSs), plasma exchange (PLEX) and immunoglobulin. Immunosuppressive agents are often used in the latter to prevent recurrence and reduce the progression of neurological disability.[15] Common drugs include mycophenolate mofetil (MMF), azathioprine (AZA), tacrolimus, cyclosporine, and monoclonal antibodies, etc.[15] Although AZA and rituximab are suggested as first-line treatments based on observational studies and expert opinion from the published guidelines for NMOSD recommending,[16] there are still AEs such as disease recurrence and myelosuppression, which lead to drug withdrawal in patients with MMF.[17] In recent years, rituximab has also been reports of infusion reactions, infection, and even death,[18-20] and its clinical application has been limited by factors such as high price.[18 21] Therefore, we urgently need to find new immunoregulatory drugs for the treatment of NMOSD. The application of MMF in NMOSD is still in the exploration stage and is recommended as second-line treatments,[16] but a number of studies have confirmed the efficacy and promising prospect of MMF in the treatment of NMOSD,[21-24] and only a few adverse events (AEs) have been reported.[21 22] Further studies also suggested that MMF was more effective and caused fewer AEs than AZA.[25 26]

Although MMF is increasingly used in NMOSD, its therapeutic effect and safety are still controversial. There are no systematic reviews and meta-analysis yet that evaluated the effects of MMF against other therapies in patients with NMOSD. It is therefore timely to perform a systematic review and meta-analysis to assess the efficacy and safety of MMF on current research for its potential use in clinical practice in treating NMOSD.

2. Methods

This protocol has been registered on PROSPERO (registration number: CRD 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE),[27] the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines. [28 29]

2.1 Inclusion criteria for study selection

2.1.1 Types of studies

All comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study, covering at least two interventions, will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative studies, animal trials, laboratory studies and studies only involving one intervention.

2.1.2 Types of patients

Patients diagnosed as having NMOSD will be included in the study.[5 30] There will be no restrictions based on other conditions, such as age at onset, sex, ethnicity, educational or economic status, number of relapses prior to treatment, previous treatment, duration of illness, disease severity, and baseline expanded disability status scales (EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or to any other active drugs will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be excluded. The control interventions will include AZA, tacrolimus, cyclosporine, and monoclonal antibody drugs, placebo, etc.

2.1.4 Types of outcome measures

2.1.4.1 *Primary outcomes*

(1) EDSS: Disability progression was defined as an increase of at least 1 point above the pre-treatment score if baseline score < 5.5, and of at least a half point if baseline score > 5.5, of the Kurtzke EDSS. Outcome measured was the mean change in the EDSS from before and after MMF treatment.[31 32]

(2) Annualized relapse rate (ARR): A relapse is defined as neurologic symptoms lasting for > 24 h, which occur at least 30 days after the onset of a preceding event. ARR is computed as a function of the number of relapse over the number of days (years) in observation. Post-treatment ARR were compared to pre-treatment ARR. [33]

2.1.4.2 Secondary outcomes

(1) The frequency and extent of Adverse events (AEs): Any symptomatic events which had a possible, probable or definite causal relationship with MMF treatment were defined as AEs during the treatment and follow-up periods.

(2) Relapse-free rate: the absence of relapse during the observation period of the study reported as percentage per study.[32]

(3) Best-corrected visual acuity (BCVA): measured according to a validated measure such as the ETDRS chart, Snellen chart or a similar tool, other measures of visual acuity would be considered if outcomes could be justified and validated in relation to accepted relevant standard measures. Outcome measured was the mean change in the BCVA from before and after MMF treatment.[34]

(4) Time to the next attack.

(5) Relapse-free rates.

2.1.4.3 Security index

The safety was assessed by the occurrence of AEs. Any unexpected events that occurred during the studies will be recorded on an adverse event report form, including: [35]

(1) General physical examination (temperature, pulse, respiration, blood pressure).

(2) Routine examination of blood, urine and stool.

(3) Liver and kidney function examination.

(4) Gastrointestinal discomfort.

(5) Hair loss or Alopecia.

(6) Allergic or Anaphylactoid reactions.

(7) Drug discontinued due to drug-related AEs.

(8) Possible AEs and related detection indicators.

2.2 Search methods for the identification of studies

2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the the following electronic databases from their inception to December 31, 2019: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP)and CBM. Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows: Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, "mofetil, mycophenolate", cellcept, myfortic, RS61443). The search strategy for PubMed is listed in Table 1, which including all search terms, and other searches will be conducted based on these results. This will be appropriately adapted for search in the other databases. There are no limits on language and publication status.

2.2.2 Searching other resources

we will also search PROSPERO, the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica spectrum disorders. Relevant journals and conference processes will be manual searched. We will also review papers and bibliographies included in the trials.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any obviously irrelevant articles. Studies only related to human subjects will be included. Any disagreements will be resolved by discussion between the 2 authors and an arbiter (MJ). The study selection procedure is presented in a PRISMA flow chart (Fig. 1).

2.3.2 Data extraction and management

Based on the inclusion criteria, a standard data collection form will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and

duplicate entries removed. Two authors (MYH and ZQL) will extract the data of interest from the eligible study and enter the following information in the data extraction sheet: The basic characteristics of each study (study design or methods , author, title, source/journal, time of publication, country, hospital setting); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type, duration, frequency and dosage of MMF, randomization, allocation concealment, blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes, and follow up); If funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer (MJ) will make a decision.

2.3.3 Assessment of risk of bias

Two authors (Yang Chen and LQN) will independently evaluate the risk and bias using the Cochrane risk of bias (ROB) assessment tool for RCTs.[36] Methodological quality assessment of the included observational studies will be performed using the Newcastle–Ottawa Scale (NOS).[37] The RevMan software program (V.5.3) will record the selected details of each study.[38]

2.3.4 Measures of treatment effect

The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze dichotomous data and measure the treatment effect. A weighted mean difference (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze continuous outcomes.

2.3.5 Unit of analysis issue

We will only extract the 1st experimental period data of crossover trials to avoid carryover effects. Meanwhile, considering that there are multiple intervention groups in trials, we will combine all analogous groups into a single pairwise comparison to prevent a unit of analysis issue.

2.3.6 Management of missing data

Reviewer (YLQ) will contact the appropriate author of the included trials for clarification or more details via email and telephone if necessary. The missing data will

be deleted, if there is no response from the author. In this case, this will be addressed in the discussion. Qualitative analysis would be used if relevant data was not available.

2.3.7 Assessment of heterogeneity and data synthesis

We will use the complete case data as the analysis data. Heterogeneity will be tested with a standard Chisquare test.[39] In order to quantify the impact of the statistical heterogeneity on the systematic review, the I^2 value will be applied to calculate and present the heterogeneity degree. When $P>0.1$, $I^2<50\%$, it is considered that there is no heterogeneity between the trials, and the fixed effect model will be used, otherwise, the random effect model will be adopted. All statistical analyses will be performed using RevMan5.3 software provided by the Cochrane Collaboration. Using the software to obtain forest plots and test the heterogeneity between the included studies. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) will be use to assess the meta-analysis findings and determine the quality of evidence. Narrative comprehensive synthesis will be adopted, if meta-analysis is not possible due to lack of clinical studies or heterogeneity.

2.3.8 Assessment of reporting biases

When 10 or more studies are included in a meta-analysis, we will assess funnel plot asymmetry for reporting biases and small study effects using Egger's method.[40] For Egger's test, P value of greater than 0.05 was determined as no considerable publication bias or small-study effects in studies. As funnel plot asymmetry does not necessarily suggest reporting bias, we will try to distinguish possible reasons for the asymmetry, including poor methodological quality and true heterogeneity of studies.

2.3.9 Subgroup analysis

When heterogeneity is detected, a subgroup analysis will be conducted to judge the source of heterogeneity. The criteria for a subgroup analysis are as follows:

(1) Age.

(2) Type of MMF.

(3) Research type.

(4) Participation population.

(5) Type of control interventions.

(6) Intervention dosage, frequency and duration.

(7) AQP4-IgG serological status.

2.3.10 Sensitivity analysis

In the case of sufficient trials data, the ROB tool will be used to assess methodological quality. Sensitivity analysis will be performed to assess the robustness of aggregate estimates and to detect whether any single study accounts for a significant proportion of heterogeneity by removing the included studies one by one from the summary analysis. If low-quality articles are deleted, a second meta-analysis will be performed. The results and effect size of the two meta-analyses will be compared and discussed. [41]

2.4 Patient and public involvement Patients and/or the public will not participate in the study. However, once our findings are disseminated by scientific publications, they are shared through social networks, so that our conclusions can influence the behavior of neuro-ophthalmologist and health policy makers.

3 Discussion

NMOSD is an inflammatory and heterogeneous astrocyte disorder of the CNS with the characteristic of higher incidence in women and Asian, concerned because of its high pathogenicity, high risk of recurrence and poor prognosis.[1] Most patients with NMOSD have a course of recurrence and remission, which are prone to cause paralysis and blindness,[5] bringing heavy burdens on the life, work and study of patients, as well as the society and economy of various countries. At present, the treatment of NMOSD is divided into two stages: acute phase (IVCSs, PLEX, and immunoglobulin) and remission phase (MMF, AZA, tacrolimus, cyclosporine, monoclonal antibodies, etc.).[15] AEs associated with AZA were seemingly frequent and may contribute to patient nonadherence to prescribed medication.[16 17] In recent years, rituximab has been recommended to prevent recurrence of NMOSD, but there have also been reports of infusion reactions, infection, and even death,[18-20] and its clinical application has been limited by factors such as high price.[18 21] Therefore, we urgently need to find new immunoregulatory drugs for the treatment of NMOSD.

A number of studies have confirmed the efficacy and promising prospect of MMF in the treatment of NMOSD,[21-24] and only a few adverse events (AEs) have been reported.

[21 22] Further studies also suggested that MMF was more effective and caused fewer AEs than AZA. [25 26] However, there are controversial about its therapeutic effect and safety. The primary objective of this systematic review is to evaluate the clinical efficacy and safety of MMF in the treatment of NMO. We will conduct qualitative and quantitative analysis of the overall data included in each study.The presented evidences were collected from RCTs and observational studies with different evidence strengths to provide more comprehensive analysis. Therefore, the heterogeneity of the methodology will be a major limitation in this systematic review, which may lead to some results not being analyzed.We expect that this systematic review will benefit patients with NMOSD, clinicians, healthcare managers and policy-makers.

Author contributions

MYH conceived and designed the protocol, and MYH drafted the protocol manuscript. MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL planned the data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of all included studies. MYH, ZQL, LQN, Yang Chen, HM, YC, ZJW, YLQ and MJ critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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SUPPLEMENTARY MATERIAL

Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR

	Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	((((("Randomized Controlled Trial" [Publication Type]) OR RCT[Title/Abstract])) OR (("Cohort Studies"[Mesh]) OR ((cohort study[Title/Abstract]) OR "studies, cohort"[Title/Abstract]))) OR ((((Case-Referrent Studies[Title/Abstract]) OR Case-Base Studies[Title/Abstract])) OR (("Case-Control Studies"[Mesh]) OR Case-Comparison Studies[Title/Abstract]))
#4	#1 and #2 and #3

Figure1. The PRISMA flow chart of the selection process.

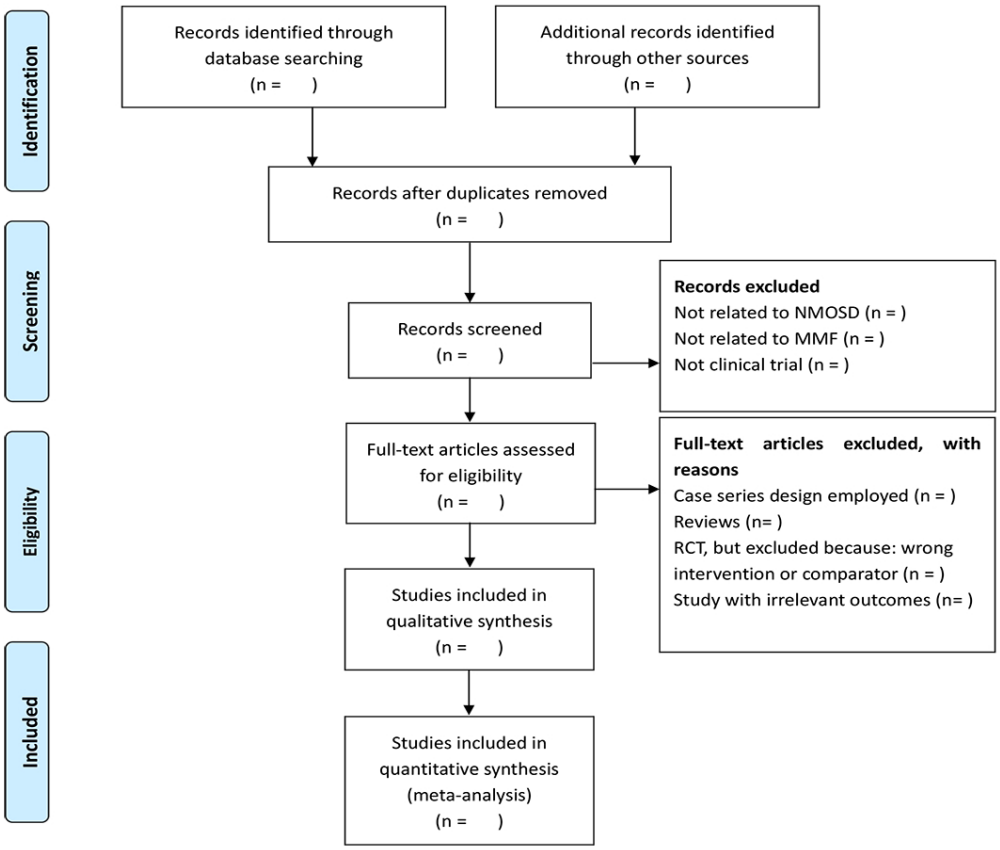

Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page1,11,12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 1
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page 1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what	Page 2,3,4

		is already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5,6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7,8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7,8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page7,8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7,8
Study records -	#11c	Describe planned method of extracting data from reports	Page 7,8,9

data collection process		(such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page5,6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9,10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	Page 9

		type of summary planned	
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8,9
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 9

BMJ Open

Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

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Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD ：a protocol for systematic review and meta-analysis.

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Abstract

Introduction Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory and heterogeneous astrocyte disorder of the central nervous system (CNS) with the characteristic of higher incidence in women and Asian. Most patients with NMOSD have a course of recurrence and remission that is prone to cause paralysis and blindness. Several studies have confirmed the efficacy and promising prospect of mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect and safety are controversial. This research aims to perform a systematic review and meta-analysis to evaluate MMF's effectiveness and safety in treating NMOSD.

Methods and analysis This systematic review will cover all comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study. A relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). We will also search registers of clinical trials, potential gray literature, and abstracts from conferences. There are no limits on language and publication status. The reporting quality and risk of bias will be assessed by two researchers independently. Expanded disability status scales (EDSS), annualized relapse rate (ARR)will be evaluated as the primary outcome. The secondary

outcomes will consist of the frequency and severity of adverse events (AEs), best-corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-analysis will be performed using RevMan5.3 software provided by the Cochrane Collaboration and Stata 12.0.

Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and will be shared on social media platforms.

PROSPERO registration number： PROSPERO CRD42020164179.

Strengths and limitations of this study:

► This study will carry out an exhaustive literature search to identify studies aimed at evaluating the efficacy and safety of MMF in treating NMOSD.

► One limitation of this study is that differences in patients, interventions and primary outcomes may mean that meta-analysis cannot be performed and there are plans for narrative and meta- analytical syntheses.

► Although we will include studies published in any language, translation difficulties may arise, which will result in the exclusion of these studies.

► The analysis of various sources of heterogeneity and the assessment of risk of bias of the included studies is a critical point for extracting and synthesizing evidence-based conclusions.

Keywords: mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol, systematic review, meta-analysis.

1. Introduction

Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced by autoantibodies, dominated by humoral immunity and involving numerous immune cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical clinical manifestations.[1] NMO has been known as a subtype of multiple sclerosis (MS) for over 100 years since it was first described and reported.[2] Until 2004, the discovery and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made

substantial progress in pathogenesis, diagnosis, and treatment of NMO.[3 4] The notion of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the wide clinical use of specific AQP4-IgG,[4] which mainly referred to the minimal AQP4-IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in 2006 and NMOSD in 2007 became prominent with the incremental improvement of the specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.[5] NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other common cerebral demyelinating syndromes.[5] There are so far no reliable statistics on the worldwide incidence and prevalence of NMOSD. According to the current epidemiological evidence of small samples, the high incidence of this disease is among middle-aged and young women, with the onset age varying from 32 to 41 years old, and the incidence in females is about 10 times that of males.[5] The incidence and prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to region.[6] A populous region of Asia is the region with a high incidence of NMOSD.[7-9] Most NMOSD patients have a recurrence and remission including ON, myelitis, and lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.[5] NMOSD has become one of the most common causes of non-traumatic disability and blindness in young and middle-aged individuals, putting heavy burdens on the life, work and study, as well as the society and economy of various countries.[10] Clinical studies indicate that approximately 1/4 of patients will not be able to walk independently after an average of 5 years of NMO, approximately 10% will be wheelchair-dependent, and more than half of patients will have serious vision loss in at least one eye.[11] In particular, ON associated with NMO (NMO-ON) possesses poor recovery even after traditional therapy, which often progresses into significant bilateral visual loss in the long term, leaving behind varying degrees of optic atrophy, which is different from MS.[12 13]

Currently, there are no standardized guidelines for the clinical management of NMOSD. The class of NMOSD drugs is commonly referred to as disease-modifying drugs,[14] and the treatment is split into two stages: the acute phase and the period of remission. The

former is based on corticosteroids to reduce the severity and frequency of acute attacks that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the process of recovery to avoid recurrence and to mitigate the progression of neurological impairment.[15 16] Although AZA and rituximab are recommended as first-line therapies obtained from clinical trials and expert opinion from the published guidelines for NMOSD,[16] there are still adverse events (AEs) such as disease recurrence and myelosuppression that result in drug withdrawal or replacement of patients with NMOSD.[17] Rituximab has also been reported in recent years as infusion reactions, infection, and even death, [18-20] and its clinical application has been constrained by such factors as high price.[18 21] Therefore, a better immunosuppressant for the treatment of NMOSD is urgently needed. The application of MMF in NMOSD is still under investigation and is recommended as second-line treatments,[16] but some studies have verified MMF's efficacy and promising potential,[21-24] and only a few AEs were published.[21 22] Especially, additional studies have also indicated that MMF was more effective and triggered less AEs than AZA.[25 26] In patients experiencing AEs or poor response to AZA, MMF is recommended as an alternative therapy.[16]

Although MMF is increasingly employed in NMOSD, there is still controversy about its related harms and benefits. At present, only low evidence exists concerning comparative treatment efficacy of MMF with other drugs. Based on current clinical trials, it is therefore timely to perform a systematic review and meta-analysis to elucidate the efficacy and safety of MMF in treating NMOSD.

2. Methods

This protocol has been registered on PROSPERO (registration number: CRD 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE),[27] the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines. [28 29]

2.1 Inclusion criteria for study selection

2.1.1 Types of studies

All comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study, covering at least two interventions, will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative studies, animal trials, laboratory studies and studies only involving one intervention.

2.1.2 Types of patients

Patients diagnosed as having NMOSD will be included in this study.[5 30] There will be no restrictions based on other conditions, such as age at onset, sex, ethnicity, educational or economic status, number of pre-treatment relapses, previous treatment, duration of illness, disease severity, and baseline expanded disability status scales (EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

2.1.4 Types of outcome measures

2.1.4.1 *Primary outcomes*

(1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.[31 32]

(2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR. [33]

2.1.4.2 Secondary outcomes

(1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.

(2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.[32]

(3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.[34]

(4) Time to the next attack.

2.1.4.3 Security index

The safety was assessed by the occurrence of AEs. Any unexpected events that occurred during the studies will be recorded on an AEs report form, including: [35]

(1) General physical examination (temperature, pulse, respiration, blood pressure).

(2) Routine examination of blood, urine and stool.

(3) Liver and kidney function examination.

(4) Gastrointestinal discomfort.

(5) Hair loss or Alopecia.

(6) Allergic or Anaphylactoid reactions.

(7) Drug discontinued due to drug-related AEs.

(8) Possible AEs and related detection indicators.

2.2 Search methods for the identification of studies

2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the following electronic databases from their inception to June 31, 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows:

Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, "mofetil, mycophenolate", cellcept, myfortic, RS61443). The search strategy for PubMed is described in Table 1, which will include all search terms, and other searches will be carried out based on those results. This will be suitably adapted to search in the other databases. There are no limits on language and publication status.

2.2.2 Searching other resources

we will also search PROSPERO, the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica spectrum disorders. Manual searches will be conducted for related journals and conference processes. We will also review papers and bibliographies included in the trials.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any irrelevant articles. Studies only related to human subjects are to be included. Any discord will be resolved by discussion between the two authors and an arbiter (MJ). The selection procedure for the study is shown in a PRISMA flow chart (Fig. 1).

2.3.2 Data extraction and management

Based on the inclusion criteria, a standard form of data collection will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and duplicate entries removed. Two authors (MYH and ZQL) will extract the data of interest from the eligible study and enter the data extraction sheet as follows: The basic characteristics of each study (study design or methods, author, title, source/journal, time of publication, country, hospital setting); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type, duration, frequency and dosage of MMF, randomization, allocation concealment,

blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes, and follow up); If funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer (MJ) will make a decision.

2.3.3 Assessment of risk of bias

Two authors (Yang Chen and LQN) will independently estimate the risk and bias using the Cochrane risk of bias (ROB) assessment tool for RCTs.[36] Methodological quality evaluation of the included observational studies will be carried out using the Newcastle–Ottawa Scale (NOS).[37] The RevMan software program (V.5.3) will document the selected details of each study.[38]

2.3.4 Measures of treatment effect

The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze dichotomous data and calculate the treatment effect. A weighted mean difference (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze continuous outcomes.

2.3.5 Unit of analysis issue

We will only extract the 1st experimental period data of crossover trials to avoid carryover effects. In the meantime, given that there are multiple intervention groups in trials, we will combine all analogous groups into a single pairwise comparison to avoid the issue of a unit of analysis.

2.3.6 Management of missing data

Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials for clarification or more details via email and telephone if necessary. The missing data will be deleted, if there is no response from the author. That will be addressed in the discussion in this case. If quantitative data were not available, then the qualitative analysis should be used.

2.3.7 Assessment of heterogeneity and data synthesis

We will use all of the case data for the analysis data. Heterogeneity will be tested with a standard Chisquare test.[39] To quantify the impact of the statistical heterogeneity on

the systematic review, the I^2 value will be applied to calculate and present the heterogeneity degree. If P>0.1, I^2<50%, it is considered that there is no heterogeneity between the trials, and the model of fixed effect will be used, otherwise, the model of random effect will be adopted. All statistical analyzes will be performed using the RevMan5.3 software provided by the Cochrane Collaboration. Using the software to obtain forest plots and test the heterogeneity between the included studies. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) will be used to assess the meta-analysis findings and determine the quality of evidence. Where meta-analysis is not feasible due to lack of clinical trials or heterogeneity, systematic narrative synthesis is adopted.

2.3.8 Assessment of reporting biases

When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot asymmetry for reporting biases and small-study effects using Egger's method.[40] For Egger's test, P value of greater than 0.05 was determined as no significant publishing bias or small-study effects in studies. As funnel plot asymmetry does not necessarily suggest reporting bias, we will attempt to recognize potential causes for the asymmetry, including poor methodological quality and true heterogeneity of studies.

2.3.9 Subgroup analysis

Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the source of heterogeneity. The criteria for a subgroup analysis are as follows:

(1) Age.

(2) Type of MMF.

(3) Research type.

(4) Participation population.

(5) Type of control interventions.

(6) Intervention dosage, frequency and duration.

(7) AQP4-IgG serological status.

2.3.10 Sensitivity analysis

The ROB tool will be used to estimate methodological quality in the case of sufficient data from trials. Sensitivity analysis will be performed to determine the robustness of

aggregate estimates and to detect whether any single study accounts for a substantial proportion of heterogeneity by eliminating the included studies from the summary review one by one. If low-quality articles are deleted, then a second meta-analysis will be carried out. Comparison and discussion of the results and effect size of the two meta-analyses will be held. [41]

2.4 Patient and public involvement Patients and/or the public will not participate in the study. However, once scientific publications disseminate our findings, they are circulated across social networks so that our conclusions will affect the actions of neuro-ophthalmologists and health policymakers.

3 Discussion

Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research as AQP4-IgG were first identified. Patients with NMOSD should receive standardized and personalized immunotherapy as soon as possible, as any further acute episodes may result in severe and often irreversible disability. The challenges in discovering new and better drugs for NMO are the rareness of the disease and the unfavorable prognosis in many cases, which make clinical studies with placebo groups difficult.[16] Many studies have confirmed the efficacy and promising prospect of MMF in the treatment of NMOSD,[21-24] and only a few AEs were reported. [21 22] Additional studies have also indicated that MMF was more effective and triggered less AEs than AZA.[25 26] However, its therapeutic effect and safety remain controversial. The primary aim of this systematic review is to determine MMF's clinical effectiveness and safety in treating NMOSD. The overall data used in each analysis will be evaluated qualitatively and quantitatively. To provide a more detailed review, the evidence provided was obtained from RCTs and observational studies with different evidence strengths. Hence, the methodology's variability would be a significant weakness of this systematic analysis, which may result in certain results not being evaluated. We expect that this systematic review will benefit patients with NMOSD, physicians, health care administrators and policy-makers.

Author contributions

MYH conceived and designed the protocol, and MYH drafted the protocol manuscript. MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and MJ critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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Project administration: Ming Jin.

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Validation: Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

Visualization: Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

Writing – original draft: Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

Writing – review & editing: Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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Competing interests: None declared.

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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	#1 and #2

Figure1. The PRISMA flow chart of the selection process.

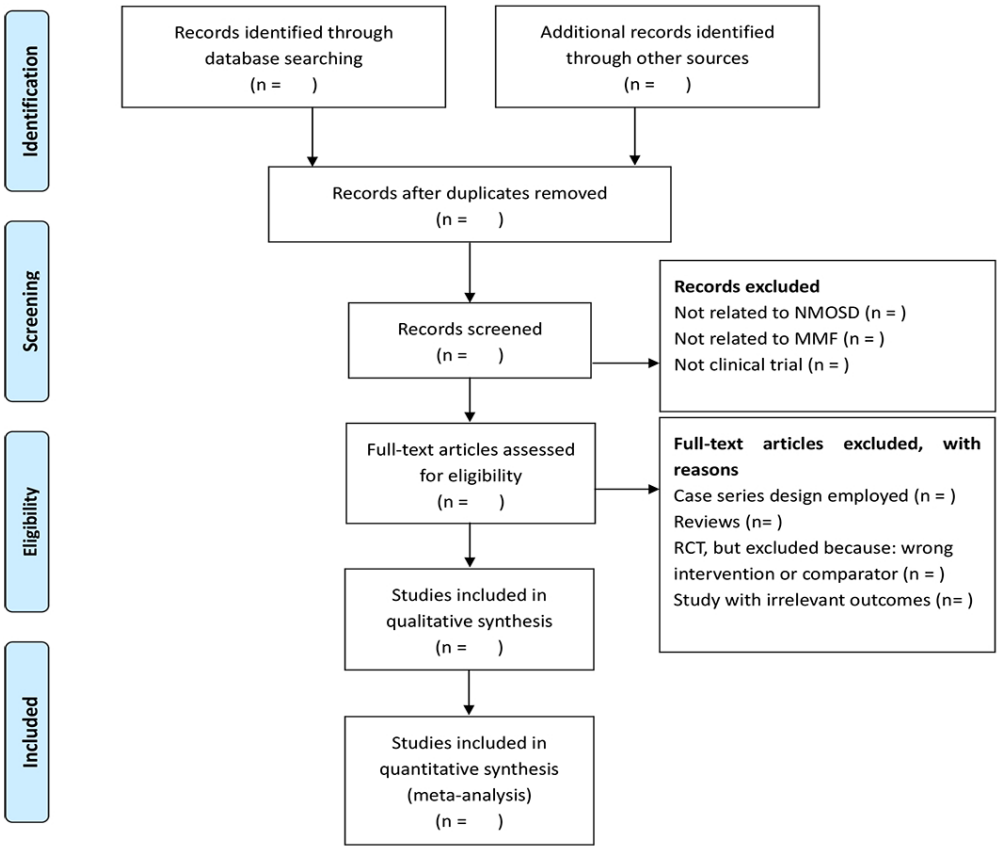

Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page1,11
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 1
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page 1
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 1
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what is	Page

		already known	2,3,4
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5,6
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7,8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7,8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page7,8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7,8
Study records - data collection	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate),	Page 7,8,9

process		any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page5,6
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 7,8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9,10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Page 9
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	Page 8,9

		publication bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 9

BMJ Open

Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD : a protocol for systematic review and meta-analysis.

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Safety and Efficacy of Mycophenolate Mofetil in Treating NMOSD ：a protocol for systematic review and meta-analysis.

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Abstract

Introduction Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory and heterogeneous astrocyte disorder of the central nervous system (CNS) with the characteristic of higher incidence in women and Asian people. Most patients with NMOSD have a course of recurrence and remission that is prone to cause paralysis and blindness. Several studies have confirmed the efficacy and promising prospect of mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect and safety are controversial. Although there has been two published literature that is relevant to the topic of this study, both of them have certain defects, and they can only provide answers about the efficacy or safety of MMF in the treatment of NMOSD from partial perspectives or conclusions. This research aims to perform a direct and comprehensive systematic review and meta-analysis to evaluate MMF's effectiveness and safety in treating NMOSD.

Methods and analysis This systematic review will cover all comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study. A relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). We will also search registers of clinical trials,

potential gray literature, and abstracts from conferences. There are no limits on language and publication status. The reporting quality and risk of bias will be assessed by two researchers independently. Expanded disability status scales (EDSS), annualized relapse rate (ARR)will be evaluated as the primary outcome. The secondary outcomes will consist of the frequency and severity of adverse events (AEs), best-corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-analysis will be performed using RevMan5.3 software provided by the Cochrane Collaboration and Stata 12.0.

Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and will be shared on social media platforms.

PROSPERO registration number： PROSPERO CRD42020164179.

Strengths and limitations of this study:

► This study will carry out an exhaustive literature search to identify studies aimed at evaluating the efficacy and safety of MMF in treating NMOSD.

► One limitation of this study is that differences in patients, interventions and primary outcomes may mean that meta-analysis cannot be performed and there are plans for narrative and meta- analytical syntheses.

► Although we will include studies published in any language, translation difficulties may arise, which will result in the exclusion of these studies.

► The analysis of various sources of heterogeneity and the assessment of risk of bias of the included studies is a critical point for extracting and synthesizing evidence-based conclusions.

Keywords: mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol, systematic review, meta-analysis.

1. Introduction

Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced by autoantibodies, dominated by humoral immunity and involving numerous immune

cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical clinical manifestations.[1] NMO has been known as a subtype of multiple sclerosis (MS) for over 100 years since it was first described and reported.[2] Until 2004, the discovery and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made substantial progress in pathogenesis, diagnosis, and treatment of NMO.[3 4] The notion of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the wide clinical use of specific AQP4-IgG,[4] which mainly referred to the minimal AQP4-IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in 2006 and NMOSD in 2007 became prominent with the incremental improvement of the specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.[5] NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other common cerebral demyelinating syndromes.[5] There are so far no reliable statistics on the worldwide incidence and prevalence of NMOSD. According to the current epidemiological evidence of small samples, the high incidence of this disease is among middle-aged and young women, with the onset age varying from 32 to 41 years old, and the incidence in females is about 10 times that of males.[5] The incidence and prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to region.[6] A populous region of Asia is the region with a high incidence of NMOSD.[7-9] Most NMOSD patients have a recurrence and remission including ON, myelitis, and lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.[5] NMOSD has become one of the most common causes of non-traumatic disability and blindness in young and middle-aged individuals, putting heavy burdens on the life, work and study, as well as the society and economy of various countries.[10] Clinical studies indicate that approximately 1/4 of patients will not be able to walk independently after an average of 5 years of NMO, approximately 10% will be wheelchair-dependent, and more than half of patients will have serious vision loss in at least one eye.[11] In particular, ON associated with NMO (NMO-ON) possesses poor recovery even after traditional therapy, which often progresses into significant bilateral visual loss in the long term, leaving behind varying degrees of optic atrophy, which is

different from MS.[12 13]

Currently, there are no standardized guidelines for the clinical management of NMOSD. The class of NMOSD drugs is commonly referred to as disease-modifying drugs,[14] and the treatment is split into two stages: the acute phase and the period of remission. The former is based on corticosteroids to reduce the severity and frequency of acute attacks that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the process of recovery to avoid recurrence and to mitigate the progression of neurological impairment.[15 16] Although AZA and rituximab are recommended as first-line therapies obtained from clinical trials and expert opinion from the published guidelines for NMOSD,[16] there are still adverse events (AEs) such as disease recurrence and myelosuppression that results in drug withdrawal or replacement of these drugs in patients with NMOSD.[17] Other AEs for Rituximab have also been reported in recent years such as infusion reactions, infection, and even death, [18-20] and its clinical application has been constrained by such factors as high price.[18 21] Therefore, a better immunosuppressant for the treatment of NMOSD is urgently needed. The application of MMF in NMOSD is still under investigation and is recommended as second-line treatments,[16] but some studies have verified MMF's efficacy and promising potential,[21-24] and only a few AEs were published.[21 22] Especially, additional studies have also indicated that MMF was more effective and triggered less AEs than AZA.[25 26] In patients experiencing AEs or poor response to AZA, MMF is recommended as an alternative therapy.[16]

Although MMF is increasingly employed in NMOSD, there is still controversy about its related harms and benefits. At present, there are mainly two published articles that are relevant to the topic and purpose of our research.[27 28] Nevertheless, these two studies have some imperfections in the direct evaluation of the efficacy and safety of MMF in the treatment of NMOSD patients. For example, the Espiritu and Pasco paper did not quantitatively evaluate the efficacy of MMF in the treatment of NMOSD and did not

compare the AEs of MMF with other drugs in the treatment of NMOSD. Additionally, Huang et al. 's research was a network meta-analysis and the literature related to MMF in this paper was three observational studies that made the number of included studies and closed loops per comparison were few, which might lower the reliability of the findings. In our study, the database we searched includes not only the English database but also the Chinese database. The retrieval time is limited to June 2020, and we will add 3 retrospective studies involving 471 patients with NMOSD,[29-31] which makes the retrieval literature more comprehensive. At the same time, the conclusions of the previously published literature about the clinical effect of MMF were inconsistent. Poupart argued that RTX was clinically better tolerated than MMF.[30] But Huang et al argued that MMF had the best drug tolerance and was superior to RTX.[31] We expect our research to help solve this problem as well.

2. Methods

This protocol has been registered on PROSPERO (registration number: CRD 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE),[32] the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines. [33 34]

2.1 Inclusion criteria for study selection

2.1.1 Types of studies

All comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study, covering at least two interventions, will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative studies, animal trials, laboratory studies and studies only involving one intervention.

2.1.2 Types of patients

Patients diagnosed as having NMOSD will be included in this study.[5 35] There will be no restrictions based on other conditions, such as age at onset, sex, ethnicity, educational or economic status, number of pre-treatment relapses, previous treatment, duration of illness, disease severity, and baseline expanded disability status scales

(EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

2.1.4 Types of outcome measures

2.1.4.1 *Primary outcomes*

(1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.[36 37]

(2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR. [38]

2.1.4.2 Secondary outcomes

(1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.

(2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.[35]

(3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.[39]

(4) Time to the next attack.

2.1.4.3 Security index

The safety was assessed by the occurrence of AEs. Any unexpected events that occurred during the studies will be recorded on an AEs report form, including: [28]

(1) General physical examination (temperature, pulse, respiration, blood pressure).

(2) Routine examination of blood, urine and stool.

(3) Liver and kidney function examination.

(4) Gastrointestinal discomfort.

(5) Hair loss or Alopecia.

(6) Allergic or Anaphylactoid reactions.

(7) Drug discontinued due to drug-related AEs.

(8) Possible AEs and related detection indicators.

2.2 Search methods for the identification of studies

2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the following electronic databases from their inception to June 31, 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows: Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, "mofetil, mycophenolate", cellcept, myfortic, RS61443). The search strategy for PubMed is described in Table 1, which will include all search terms, and other searches will be carried out based on those results. This will be suitably adapted to search in the other databases. There are no limits on language and publication status.

2.2.2 Searching other resources

we will also search PROSPERO, the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica spectrum disorders. Manual searches will be conducted for related journals and

conference processes. We will also review papers and bibliographies included in the trials.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any irrelevant articles. Studies only related to human subjects are to be included. Any discord will be resolved by discussion between the two authors and an arbiter (MJ). The selection procedure for the study is shown in a PRISMA flow chart (Fig. 1).

2.3.2 Data extraction and management

Based on the inclusion criteria, a standard form of data collection will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and duplicate entries removed. Two authors (MYH and ZQL) will extract the data of interest from the eligible study and enter the data extraction sheet as follows: The basic characteristics of each study (study design or methods, author, title, source/journal, time of publication, country, hospital setting); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type, duration, frequency and dosage of MMF, randomization, allocation concealment, blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes, and follow up); If funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer (MJ) will make a decision.

2.3.3 Assessment of risk of bias

Two authors (Yang Chen and LQN) will independently estimate the risk and bias using the Cochrane risk of bias (ROB) assessment tool for RCTs.[40] Methodological quality evaluation of the included observational studies will be carried out using the Newcastle–Ottawa Scale (NOS).[41] The RevMan software program (V.5.3) will document the selected details of each study.[42]

2.3.4 Measures of treatment effect

The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze dichotomous data and calculate the treatment effect. A weighted mean difference (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze continuous outcomes.

2.3.5 Unit of analysis issue

We will only extract the 1st experimental period data of crossover trials to avoid carryover effects. In the meantime, given that there are multiple intervention groups in trials, we will combine all analogous groups into a single pairwise comparison to avoid a unit of analysis issue.

2.3.6 Management of missing data

Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials for clarification or more details via email and telephone if necessary. The missing data will be deleted, if there is no response from the author. That will be addressed in the discussion in this case. If quantitative data were not available, then the qualitative analysis should be used.

2.3.7 Assessment of heterogeneity and data synthesis

We will use all of the case data for the analysis data. Heterogeneity will be tested with a standard Chisquare test.[43] To quantify the impact of the statistical heterogeneity on the systematic review, the I^2 value will be applied to calculate and present the heterogeneity degree. If $P>0.1$, $I^2<50\%$, it is considered that there is no heterogeneity between the trials, and the model of fixed effect will be used, otherwise, the model of random effect will be adopted. All statistical analyzes will be performed using the RevMan5.3 software provided by the Cochrane Collaboration. Using the software to obtain forest plots and test the heterogeneity between the included studies. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) will be used to assess the meta-analysis findings and determine the quality of evidence. Where meta-analysis may not be not feasible due to lack of clinical trials or heterogeneity, systematic narrative synthesis will be adopted.

2.3.8 Assessment of reporting biases

When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot

asymmetry for reporting biases and small-study effects using Egger's method.[44] For Egger's test, P value of greater than 0.05 was determined as no significant publishing bias or small-study effects in studies. As funnel plot asymmetry does not necessarily suggest reporting bias, we will attempt to recognize potential causes for the asymmetry, including poor methodological quality and true heterogeneity of studies.

2.3.9 Subgroup analysis

Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the source of heterogeneity. The criteria for a subgroup analysis are as follows:

(1) Age.

(2) Type of MMF.

(3) Research type.

(4) Participation population.

(5) Type of control interventions.

(6) Intervention dosage, frequency and duration.

(7) AQP4-IgG serological status.

2.3.10 Sensitivity analysis

The ROB tool will be used to estimate methodological quality in the case of sufficient data from trials. Sensitivity analysis will be performed to determine the robustness of aggregate estimates and to detect whether any single study accounts for a substantial proportion of heterogeneity by eliminating the included studies from the summary review one by one. If low-quality articles are deleted, then a second meta-analysis will be carried out. Comparison and discussion of the results and effect size of the two meta-analyses will be held. [45]

2.4 Patient and public involvement Patients and/or the public will not participate in the study. However, once scientific publications disseminate our findings, they are circulated across social networks so that our conclusions will affect the actions of neuro-ophthalmologists and health policymakers.

3 Discussion

Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research as AQP4-IgG were first identified. Patients with NMOSD should receive standardized

and personalized immunotherapy as soon as possible, as any further acute episodes may result in severe and often irreversible disability. The challenges in discovering new and better drugs for NMO are the rareness of the disease and the unfavorable prognosis in many cases, which make clinical studies with placebo groups difficult.[16] Many studies have confirmed the efficacy and promising prospect of MMF in the treatment of NMOSD,[21-24] and only a few AEs were reported. [21 22] Additional studies have also indicated that MMF was more effective and triggered less AEs than AZA.[25 26] However, its therapeutic effect and safety remain controversial. Although there has been two published literature that is relevant to the topic of this study,[27 28] both of them have certain defects, and they can only provide answers about the efficacy or safety of MMF in the treatment of NMOSD from partial perspectives or conclusions. If our paper is completed, it will be a currently searchable protocol for a traditional meta-and systematic review that directly and synthetically evaluates the efficacy and safety of MMF in the treatment of NMOSD. One of the strengths of this protocol will use a comprehensive search strategy of published literature. The overall data used in each analysis will be evaluated qualitatively and quantitatively. The sources of heterogeneity and different subgroups of the articles will be analyzed to comprehensively evaluate the efficacy and safety of MMF in the treatment of NMOSD, and to increase the credibility of the article content and conclusions. We expect that this systematic review will benefit patients with NMOSD, physicians, health care administrators and policy-makers.

Author contributions

MYH conceived and designed the protocol, and MYH drafted the protocol manuscript. MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and MJ critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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Software: Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong.

Supervision: Meng-Yu Han, Zhi-Jun Wang, Ming Jin.

Validation: Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

Visualization: Huan Meng, Yang Chen, Ya-li Qin, Ming Jin.

Writing – original draft: Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

Writing – review & editing: Meng-Yu Han, Zi-Qiang Liu, Lu-Qi Nong, Ming Jin.

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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders [Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])

#3	#1 and #2

Figure1. The PRISMA flow chart of the selection process.

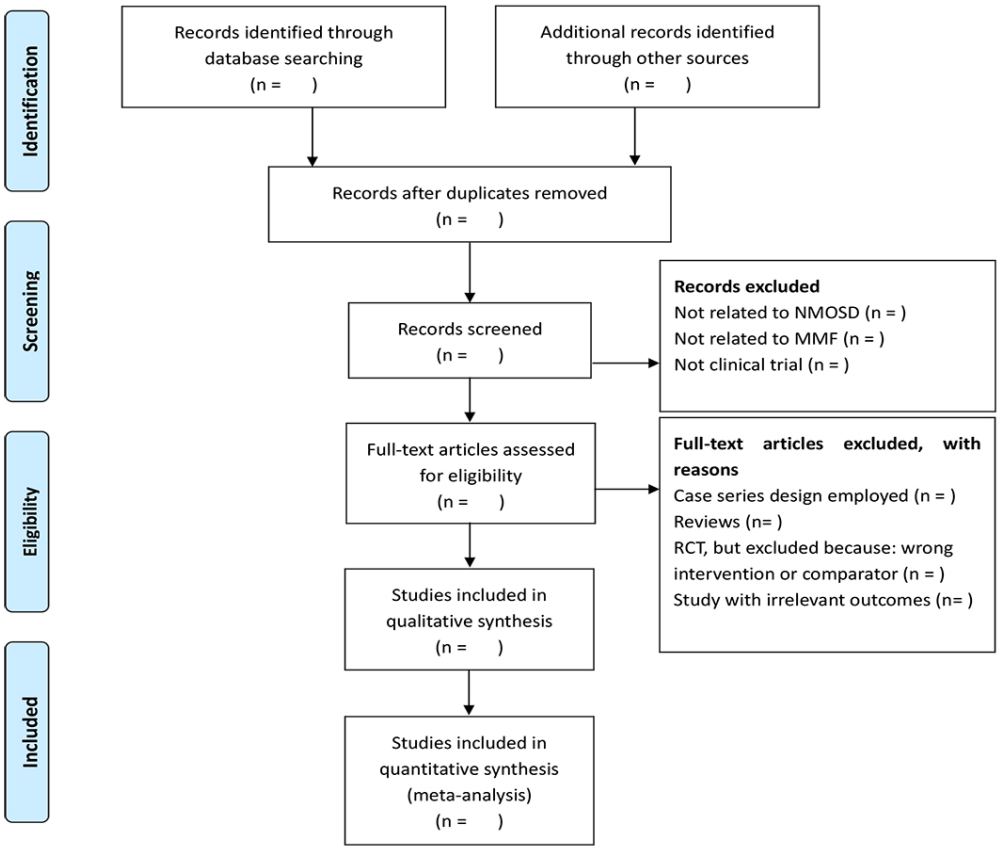

Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page1,11,12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 12
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page 12
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 12
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what	Page 2,3,4,5

		is already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5,6,7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7,8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7,8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 8
Study records -	#11c	Describe planned method of extracting data from reports	Page 8,9

data collection process		(such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6,7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9,10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	Page 9

		type of summary planned	
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8,9,10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 9

BMJ Open

Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica Spectrum Disorders : a protocol for systematic review and meta-analysis.

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Secondary Subject Heading:	Neurology, Evidence based practice
Keywords:	OPHTHALMOLOGY, NEUROLOGY, IMMUNOLOGY, Neuro-ophthalmology < NEUROLOGY

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Safety and Efficacy of Mycophenolate Mofetil in Treating Neuromyelitis Optica Spectrum Disorders ：a protocol for systematic review and meta-analysis.

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Abstract

Introduction Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory and heterogeneous astrocyte disorder of the central nervous system (CNS) with the characteristic of higher incidence in women and Asian people. Most patients with NMOSD have a course of recurrence and remission that is prone to cause paralysis and blindness. Several studies have confirmed the efficacy and promising prospect of mycophenolate mofetil (MMF) in the treatment of NMOSD. Yet its therapeutic effect and safety are controversial. Although there has been two published literature that is relevant to the topic of this study, both of them have certain defects, and they can only provide answers about the efficacy or safety of MMF in the treatment of NMOSD from partial perspectives or conclusions. This research aims to perform a direct and comprehensive systematic review and meta-analysis to evaluate MMF's effectiveness and safety in treating NMOSD.

Methods and analysis This systematic review will cover all comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study. A relevant literature search will be conducted in PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM) from their inception to June 31, 2020. We will

also search registers of clinical trials, potential gray literature, and abstracts from conferences. There are no limits on language and publication status. The reporting quality and risk of bias will be assessed by two researchers independently. Expanded disability status scales (EDSS), annualized relapse rate (ARR)will be evaluated as the primary outcome. The secondary outcomes will consist of the frequency and severity of adverse events (AEs), best-corrected visual acuity (BCVA), relapse-free rate and time to the next attack. A meta-analysis will be performed using RevMan5.3 software provided by the Cochrane Collaboration and Stata 12.0.

Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-reviewed journal, presented at conferences and will be shared on social media platforms.

PROSPERO registration number： PROSPERO CRD42020164179.

Strengths and limitations of this study:

► This study will carry out an exhaustive literature search to identify studies aimed at evaluating the efficacy and safety of MMF in treating NMOSD.

► One limitation of this study is that differences in patients, interventions and primary outcomes may mean that meta-analysis cannot be performed and there are plans for narrative and meta- analytical syntheses.

► Although we will include studies published in any language, translation difficulties may arise, which will result in the exclusion of these studies.

► The analysis of various sources of heterogeneity and the assessment of risk of bias of the included studies is a critical point for extracting and synthesizing evidence-based conclusions.

Keywords: mycophenolate mofetil, neuromyelitis optica spectrum disorders, protocol, systematic review, meta-analysis.

1. Introduction

Neuromyelitis Optica (NMO), also known as Devic disease, is generally considered to be a rare autoimmune astrocyte disorder of the central nervous system (CNS), induced by autoantibodies, dominated by humoral immunity and involving numerous immune

cells and factors, with optic neuritis(ON) and acute transverse myelitis as typical clinical manifestations.[1] NMO has been known as a subtype of multiple sclerosis (MS) for over 100 years since it was first described and reported.[2] Until 2004, the discovery and confirmation of anti-aquaporin-4 immunoglobulin G (AQP4-IgG) had made substantial progress in pathogenesis, diagnosis, and treatment of NMO.[3 4] The notion of neuromyelitis optica spectrum disorders (NMOSD) was first proposed based on the wide clinical use of specific AQP4-IgG,[4] which mainly referred to the minimal AQP4-IgG positive NMO. However, the deficiencies of the diagnostic criteria of NMO in 2006 and NMOSD in 2007 became prominent with the incremental improvement of the specificity of clinical AQP4-IgG tests. In 2015, a groundbreaking international diagnostic protocol for NMOSD was put forward by the global NMO diagnostic team.[5] NMOSD consists of NMO, ON, longitudinally extensive transverse myelitis and other common cerebral demyelinating syndromes.[5] There are so far no reliable statistics on the worldwide incidence and prevalence of NMOSD. According to the current epidemiological evidence of small samples, the high incidence of this disease is among middle-aged and young women, with the onset age varying from 32 to 41 years old, and the incidence in females is about 10 times that of males.[5] The incidence and prevalence of approximately 0.05-0.40 and 0.52-4.40/100,000 vary from region to region.[6] A populous region of Asia is the region with a high incidence of NMOSD.[7-9] Most NMOSD patients have a recurrence and remission including ON, myelitis, and lesions in special parts of the brain that are vulnerable to cause paralysis and blindness.[5] NMOSD has become one of the most common causes of non-traumatic disability and blindness in young and middle-aged individuals, putting heavy burdens on the life, work and study, as well as the society and economy of various countries.[10] Clinical studies indicate that approximately 1/4 of patients will not be able to walk independently after an average of 5 years of NMO, approximately 10% will be wheelchair-dependent, and more than half of patients will have serious vision loss in at least one eye.[11] In particular, ON associated with NMO (NMO-ON) possesses poor recovery even after traditional therapy, which often progresses into significant bilateral visual loss in the long term, leaving behind varying degrees of optic atrophy, which is

different from MS.[12 13]

Currently, there are no standardized guidelines for the clinical management of NMOSD. The class of NMOSD drugs is commonly referred to as disease-modifying drugs,[14] and the treatment is split into two stages: the acute phase and the period of remission. The former is based on corticosteroids to reduce the severity and frequency of acute attacks that include intravenous corticosteroids (IVCSs), plasma exchange (PLEX), and immunoglobulin. Immunosuppressive agents, including mycophenolate mofetil (MMF), azathioprine (AZA), cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, are frequently used during the process of recovery to avoid recurrence and to mitigate the progression of neurological impairment.[15 16] Although AZA and rituximab are recommended as first-line therapies obtained from clinical trials and expert opinion from the published guidelines for NMOSD,[16] there are still adverse events (AEs) such as disease recurrence and myelosuppression that results in drug withdrawal or replacement of these drugs in patients with NMOSD.[17] Other AEs for Rituximab have also been reported in recent years such as infusion reactions, infection, and even death, [18-20] and its clinical application has been constrained by such factors as high price.[18 21] Therefore, a better immunosuppressant for the treatment of NMOSD is urgently needed. The application of MMF in NMOSD is still under investigation and is recommended as second-line treatments,[16] but some studies have verified MMF's efficacy and promising potential,[21-24] and only a few AEs were published.[21 22] Especially, additional studies have also indicated that MMF was more effective and triggered less AEs than AZA.[25 26] In patients experiencing AEs or poor response to AZA, MMF is recommended as an alternative therapy.[16]

Although MMF is increasingly employed in NMOSD, there is still controversy about its related harms and benefits. At present, there are mainly two published articles that are relevant to the topic and purpose of our research.[27 28] Nevertheless, these two studies have some imperfections in the direct evaluation of the efficacy and safety of MMF in the treatment of NMOSD patients. For example, the Espiritu and Pasco paper did not quantitatively evaluate the efficacy of MMF in the treatment of NMOSD and did not

compare the AEs of MMF with other drugs in the treatment of NMOSD. Additionally, Huang et al. 's research was a network meta-analysis and the literature related to MMF in this paper was three observational studies that made the number of included studies and closed loops per comparison were few, which might lower the reliability of the findings. In our study, the database we searched includes not only the English database but also the Chinese database. The retrieval time is limited to June 2020, and we will add 3 retrospective studies involving 471 patients with NMOSD,[29-31] which makes the retrieval literature more comprehensive. At the same time, the conclusions of the previously published literature about the clinical effect of MMF were inconsistent. Poupart argued that RTX was clinically better tolerated than MMF.[30] But Huang et al argued that MMF had the best drug tolerance and was superior to RTX.[31] We expect our research to help solve this problem as well.

2. Methods

This protocol has been registered on PROSPERO (registration number: CRD 42020164179). Our protocol will follow the Meta-analysis of Observational Studies in Epidemiology (MOOSE),[32] the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol (PRISMA-P) statement guidelines. [33 34]

2.1 Inclusion criteria for study selection

2.1.1 Types of studies

All comparative researches, from randomized controlled trials (RCTs) to cohort studies, and case-control study, covering at least two interventions, will be included. The current clinical trial results will be objectively integrated, which is conducive to the evaluation of the efficacy and safety of MMF for NMOSD. We will exclude reviews, qualitative studies, animal trials, laboratory studies and studies only involving one intervention.

2.1.2 Types of patients

Patients diagnosed as having NMOSD will be included in this study.[5 35] There will be no restrictions based on other conditions, such as age at onset, sex, ethnicity, educational or economic status, number of pre-treatment relapses, previous treatment, duration of illness, disease severity, and baseline expanded disability status scales

(EDSS), AQP4-IgG serological status.

2.1.3 Types of interventions

Trials comparing MMF to placebo or any other active substances, including AZA, cyclophosphamide, methotrexate, mitoxantrone, tacrolimus, cyclosporine, and monoclonal antibodies, will be considered. Besides, the types, dosage, and frequency of MMF were not limited. Studies that MMF with combination therapy fail to objectively evaluate the efficacy and safety of MMF will be eliminated.

2.1.4 Types of outcome measures

2.1.4.1 *Primary outcomes*

(1) EDSS: Disability progression was characterized as an increase in the Kurtzke EDSS by at least 1 point above the pre-treatment score if baseline score < 5.5, and by at least half-point if baseline score > 5.5. Outcome measured was the mean changes of EDSS before and after MMF treatment.[36 37]

(2) Annualized relapse rate (ARR): Relapse is equivalent to a neurologic symptom lasting for > 24 h, which occurs at least 30 days after the onset of a preceding event. ARR is computed as the number of relapses divided by the time in years (days). Post-treatment ARR was contrasted with pre-treatment ARR. [38]

2.1.4.2 Secondary outcomes

(1) The frequency and extent of AEs: During treatment and follow-up periods, any symptomatic events which had a possible, probable or definite causal relationship to MMF treatment were defined as AEs.

(2) Relapse-free rate: The absence of relapse during the observation period of the study reported as percentage per study.[35]

(3) Best-corrected visual acuity (BCVA): BCVA was measured using a standardized test, such as the ETDRS chart, Snellen chart or similar method, and other visual acuity measures would be allowed if findings could be justified as well as validated concerning accepted relevant standard measures. Outcome measured was the mean change of BCVA from before and after MMF treatment.[39]

(4) Time to the next attack.

2.1.4.3 Security index

The safety was assessed by the occurrence of AEs. Any unexpected events that occurred during the studies will be recorded on an AEs report form, including: [28]

(1) General physical examination (temperature, pulse, respiration, blood pressure).

(2) Routine examination of blood, urine and stool.

(3) Liver and kidney function examination.

(4) Gastrointestinal discomfort.

(5) Hair loss or Alopecia.

(6) Allergic or Anaphylactoid reactions.

(7) Drug discontinued due to drug-related AEs.

(8) Possible AEs and related detection indicators.

2.2 Search methods for the identification of studies

2.2.1 Electronic searches

A relevant literature search by sensitive search strategies was conducted using the following electronic databases from their inception to June 31, 2020: PubMed, Web of Science, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal database (VIP) and Chinese Biomedical Literature database (CBM). Search methods of MeSH terms with free words were applied in English databases. The related terms are as follows: Participants (neuromyelitis optica, neuromyelitis optica spectrum disorders, Devic Neuromyelitis Optica, Devic's Neuromyelitis Optica, Devic's Syndrome, NMO spectrum disorders), Intervention (mycophenolic acid, mycophenolate mofetil, "mofetil, mycophenolate", cellcept, myfortic, RS61443). The search strategy for PubMed is described in Table 1, which will include all search terms, and other searches will be carried out based on those results. This will be suitably adapted to search in the other databases. There are no limits on language and publication status.

2.2.2 Searching other resources

we will also search PROSPERO, the International Clinical Trials Registry Platform (ICTRP), ClinicalTrials.gov, dissertations, and gray literature to identify systematic reviews or clinical trials related to mycophenolate mofetil and neuromyelitis optica spectrum disorders. Manual searches will be conducted for related journals and

conference processes. We will also review papers and bibliographies included in the trials.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two reviewers (MYH and ZQL) will independently browse the titles and abstracts of all of the retrieved records to distinguish and exclude any irrelevant articles. Studies only related to human subjects are to be included. Any discord will be resolved by discussion between the two authors and an arbiter (MJ). The selection procedure for the study is shown in a PRISMA flow chart (Fig. 1).

2.3.2 Data extraction and management

Based on the inclusion criteria, a standard form of data collection will be produced prior to data extraction. Search results will be entered into an EndNote X9 database and duplicate entries removed. Two authors (MYH and ZQL) will extract the data of interest from the eligible study and enter the data extraction sheet as follows: The basic characteristics of each study (study design or methods, author, title, source/journal, time of publication, country, hospital setting); participants characteristics (average age, gender, sample size, inclusion and exclusion criteria, baseline situation); Interventions (type, duration, frequency and dosage of MMF, randomization, allocation concealment, blinding methods); Comparators (AZA, tacrolimus, cyclosporine, monoclonal antibodies, and placebo, etc); Outcomes (measures, main outcomes, security indexes, and follow up); If funded, it will also be recorded. When the consensus on data extraction is not available through discussion, the third reviewer (MJ) will make a decision.

2.3.3 Assessment of risk of bias

Two authors (Yang Chen and LQN) will independently estimate the risk and bias using the Cochrane risk of bias (ROB) assessment tool for RCTs.[40] Methodological quality evaluation of the included observational studies will be carried out using the Newcastle–Ottawa Scale (NOS).[41] The RevMan software program (V.5.3) will document the selected details of each study.[42]

2.3.4 Measures of treatment effect

The risk ratio (RR) and 95% confidence interval (CI) will be used to analyze dichotomous data and calculate the treatment effect. A weighted mean difference (WMD) or a standard mean difference (SMD) with 95% CIs will be used to analyze continuous outcomes.

2.3.5 Unit of analysis issue

We will only extract the 1st experimental period data of crossover trials to avoid carryover effects. In the meantime, given that there are multiple intervention groups in trials, we will combine all analogous groups into a single pairwise comparison to avoid a unit of analysis issue.

2.3.6 Management of missing data

Reviewer (YLQ and You Chen) will contact the appropriate author of the included trials for clarification or more details via email and telephone if necessary. The missing data will be deleted, if there is no response from the author. That will be addressed in the discussion in this case. If quantitative data were not available, then the qualitative analysis should be used.

2.3.7 Assessment of heterogeneity and data synthesis

We will use all of the case data for the analysis data. Heterogeneity will be tested with a standard Chisquare test.[43] To quantify the impact of the statistical heterogeneity on the systematic review, the I^2 value will be applied to calculate and present the heterogeneity degree. If $P>0.1$, $I^2<50\%$, it is considered that there is no heterogeneity between the trials, and the model of fixed effect will be used, otherwise, the model of random effect will be adopted. All statistical analyzes will be performed using the RevMan5.3 software provided by the Cochrane Collaboration. Using the software to obtain forest plots and test the heterogeneity between the included studies. The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) will be used to assess the meta-analysis findings and determine the quality of evidence. Where meta-analysis may not be not feasible due to lack of clinical trials or heterogeneity, systematic narrative synthesis will be adopted.

2.3.8 Assessment of reporting biases

When 10 or more studies are included in a meta-analysis, we will evaluate funnel plot

asymmetry for reporting biases and small-study effects using Egger's method.[44] For Egger's test, P value of greater than 0.05 was determined as no significant publishing bias or small-study effects in studies. As funnel plot asymmetry does not necessarily suggest reporting bias, we will attempt to recognize potential causes for the asymmetry, including poor methodological quality and true heterogeneity of studies.

2.3.9 Subgroup analysis

Upon detection of heterogeneity, a subgroup analysis will be carried out to judge the source of heterogeneity. The criteria for a subgroup analysis are as follows:

(1) Age.

(2) Type of MMF.

(3) Research type.

(4) Participation population.

(5) Type of control interventions.

(6) Intervention dosage, frequency and duration.

(7) AQP4-IgG serological status.

2.3.10 Sensitivity analysis

The ROB tool will be used to estimate methodological quality in the case of sufficient data from trials. Sensitivity analysis will be performed to determine the robustness of aggregate estimates and to detect whether any single study accounts for a substantial proportion of heterogeneity by eliminating the included studies from the summary review one by one. If low-quality articles are deleted, then a second meta-analysis will be carried out. Comparison and discussion of the results and effect size of the two meta-analyses will be held. [45]

2.4 Patient and public involvement Patients and/or the public will not participate in the study. However, once scientific publications disseminate our findings, they are circulated across social networks so that our conclusions will affect the actions of neuro-ophthalmologists and health policymakers.

2.5 Ethics and dissemination Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The systematic review will be published in a peer-

reviewed journal, presented at conferences and will be shared on social media platforms.

3 Discussion

Pathogenesis, diagnosis and treatment of NMO are rapidly growing areas of research as AQP4-IgG were first identified. Patients with NMOSD should receive standardized and personalized immunotherapy as soon as possible, as any further acute episodes may result in severe and often irreversible disability. The challenges in discovering new and better drugs for NMO are the rareness of the disease and the unfavorable prognosis in many cases, which make clinical studies with placebo groups difficult.[16] Many studies have confirmed the efficacy and promising prospect of MMF in the treatment of NMOSD,[21-24] and only a few AEs were reported. [21 22] Additional studies have also indicated that MMF was more effective and triggered less AEs than AZA.[25 26] However, its therapeutic effect and safety remain controversial. Although there has been two published literature that is relevant to the topic of this study,[27 28] both of them have certain defects, and they can only provide answers about the efficacy or safety of MMF in the treatment of NMOSD from partial perspectives or conclusions. If our paper is completed, it will be a currently searchable protocol for a traditional meta-and systematic review that directly and synthetically evaluates the efficacy and safety of MMF in the treatment of NMOSD. One of the strengths of this protocol will use a comprehensive search strategy of published literature. The overall data used in each analysis will be evaluated qualitatively and quantitatively. The sources of heterogeneity and different subgroups of the articles will be analyzed to comprehensively evaluate the efficacy and safety of MMF in the treatment of NMOSD, and to increase the credibility of the article content and conclusions. We expect that this systematic review will benefit patients with NMOSD, physicians, health care administrators and policy-makers.

Author contributions

MYH conceived and designed the protocol, and MYH drafted the protocol manuscript. MYH developed the search strategy, with input from ZQL and LQN. MYH and ZQL

planned data extraction. MYH, Yang Chen and ZJW planned the quality appraisal of all included studies. MYH, ZQL, LQN, Yang Chen, HM, You Chen, ZJW, YLQ and MJ critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

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Table 1 Search strategy used in PubMed database.

Number	Search terms
#1	("Neuromyelitis Optica"[Mesh]) OR (((((neuromyelitis optica spectrum disorders [Title/Abstract]) OR Devic Neuromyelitis Optica [Title/Abstract]) OR Devic's Neuromyelitis Optica [Title/Abstract]) OR Devic's Syndrome [Title/Abstract]) OR NMO spectrum disorders

	[Title/Abstract])
#2	("Mycophenolic Acid"[Mesh]) OR (((((Mycophenolate Mofetil [Title/Abstract]) OR "Mofetil,Mycophenolate" [Title/Abstract]) OR Cellcept [Title/Abstract]) OR Myfortic [Title/Abstract]) OR RS61443 [Title/Abstract])
#3	#1 and #2

Figure1. The PRISMA flow chart of the selection process.

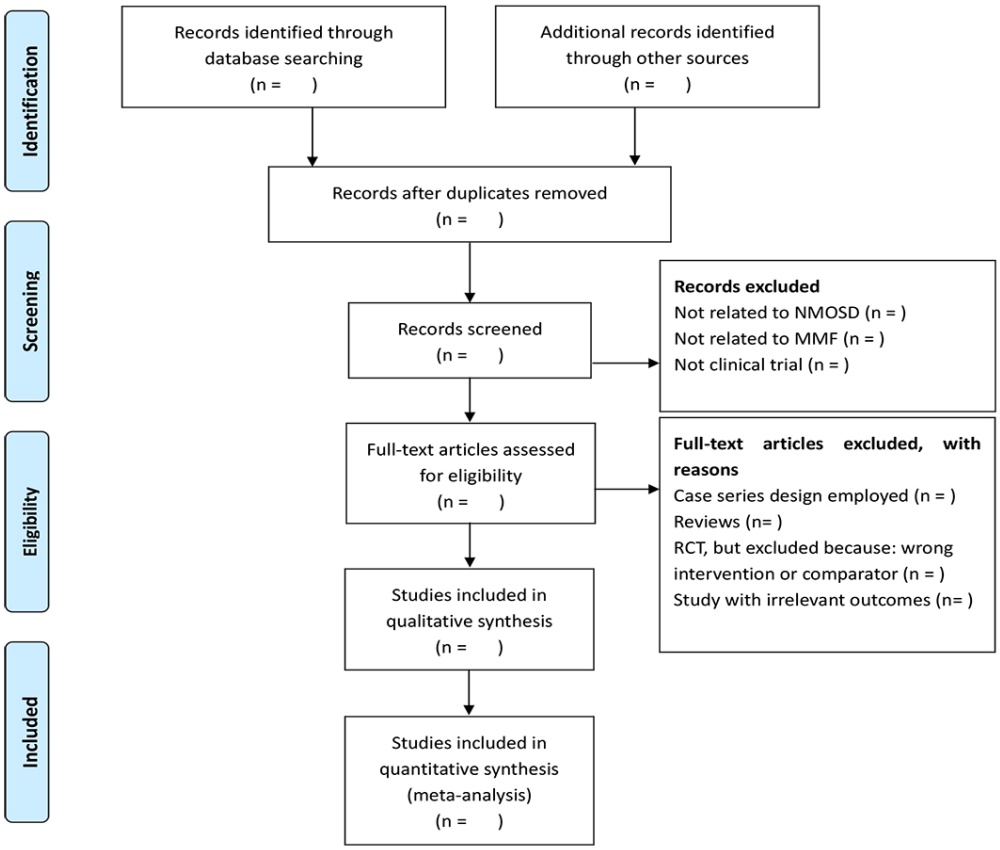

Figure1. The PRISMA flow chart of the selection process.

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	Page 1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	

Registration			
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Page 2
Authors			
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Page 1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	Page1,11,12
Amendments			
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	
Support			
Sources	#5a	Indicate sources of financial or other support for the review	Page 12
Sponsor	#5b	Provide name for the review funder and / or sponsor	Page 12
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	Page 12
Introduction			
Rationale	#6	Describe the rationale for the review in the context of what	Page 2,3,4,5

		is already known	
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 5,6,7
Methods			
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 7,8
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 7,8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 8
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 8
Study records -	#11c	Describe planned method of extracting data from reports	Page 8,9

data collection process		(such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 8
Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 6,7
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Page 8
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	Page 9
Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	Page 9
Data synthesis	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Page 9,10
Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the	Page 9

		type of summary planned	
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Page 8,9,10
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Page 9