Review question / Objective: This study will evaluate the efficacy and safety of interleukin 6 receptor (IL-6R) inhibitors in neuromyelitis optica spectrum disorders (NMOSD) patients.

Condition being studied: Neuromyelitis optica spectrum disorder (NMOSD) is a group of inflammatory disorders of the central nervous system characterized by immune-mediated demyelination and axonal damage, mainly involving optic nerves and spinal cord. NMOSD is usually prone to recurrence and is characterized by repeated severe attacks that lead to accumulation of neurological dysfunction. Azathioprine, mycophenolate mofetil, prednisolone, and rituximab are commonly used therapies to prevent recurrence. In addition, eculizumab has been shown to reduce the relapse rate of AQP4-IgG-positive NMOSD patients by targeting the complement protein C5. Novel therapies for NMOSD are needed to improve the prevention of relapses. Over recent years, increasing evidences have shown the role of the IL-6 signalling pathway in the pathogenesis of NMOSD. The initial case reports and case series of tocilizumab indicate that this interleukin 6 receptor (IL-6R) inhibitor may reduce the recurrence rate of NMOSD patients. Recently, two randomized controlled trials analysed the novel IL-6R inhibitor satralizumab in patients with NMOSD. Therefore, this study will aim to assess the efficacy and safety of IL-6R inhibitors in treating for patients with NMOSD.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 August 2020 and was last updated on 13 August 2020 (registration number INPLASY202080055).
recurrence rate and high disability rate. For this reason, the main goal of NMOSD treatment is to prevent disease relapses. Various studies reported that IL-6R inhibitors can be used to treat patients with NMOSD. Therefore, this study will summarize the latest studies to further evaluate the efficacy and safety of IL-6R inhibitors for the treatment of NMOSD.

Condition being studied: Neuromyelitis optica spectrum disorder (NMOSD) is a group of inflammatory disorders of the central nervous system characterized by immune-mediated demyelination and axonal damage, mainly involving optic nerves and spinal cord. NMOSD is usually prone to recurrence and is characterized by repeated severe attacks that lead to accumulation of neurological dysfunction. Azathioprine, mycophenolate mofetil, prednisolone, and rituximab are commonly used therapies to prevent recurrence. In addition, eculizumab has been shown to reduce the relapse rate of AQP4-IgG-positive NMOSD patients by targeting the complement protein C5. Novel therapies for NMOSD are needed to improve the prevention of relapses. Over recent years, increasing evidences have shown the role of the IL-6 signalling pathway in the pathogenesis of NMOSD. The initial case reports and case series of tocilizumab indicate that this interleukin 6 receptor (IL-6R) inhibitor may reduce the recurrence rate of NMOSD patients. Recently, two randomized controlled trials analysed the novel IL-6R inhibitor satralizumab in patients with NMOSD. Therefore, this study will aim to assess the efficacy and safety of IL-6R inhibitors in treating for patients with NMOSD.

METHODS

Search strategy: We will search the following electronic databases with no language restriction up to September 30, 2020: PUBMED, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal database (VIP) and Wan fang Database. We will apply a combination of Medical Subject Heading (MeSH) and free-text terms incorporating database-specific controlled vocabularies and text words to implement search strategies. Besides, we will also search other resources, such as thesis, conference papers, dissertations, and reference lists of related reviews.

Participant or population: We will include studies on patients have been diagnosed as NMOSD based on any recognized diagnostic criteria, with no restriction of age, race, sex, and nationality.

Intervention: All patients underwent IL-6R inhibitors in the treatment of NMOSD will be included in this study.

Comparator: All patients received any other management for the treatment of NMOSD will be considered for inclusion.

Study designs to be included: This study includes all studies about the use of IL-6R inhibitors in NMOSD patients.

Eligibility criteria: All studies about the use of IL-6R inhibitors in NMOSD patients are included. We will exclude some studies, such as animal studies, review, case reports or studies < 2 patients.

Information sources: PUBMED, EMBASE, Web of Science, Cochrane Library, China National Knowledge Infrastructure Database (CNKI), Chinese Biomedical Literature Database (CBM), China Science and Technology Journal database (VIP) and Wan fang Database. Besides, we will also search other resources, such as thesis, conference papers, dissertations, and reference lists of related reviews.

Main outcome(s): Primary outcomes include differences in the annualized relapse rate (ARR) ratio, the mean expanded disability status scales (EDSS) score and relapse-free status before and after IL-6R inhibitors therapy.

Additional outcome(s): Secondary outcomes include the proportion of
adverse effects, serious adverse effects and death.

**Data management:** Two reviewers will independently extract data using a predefined data extraction form. Any divergences between the two reviewers will be solved by the third reviewer through discussion. For each study, the following data will be extracted: the first author, publication year, country, number of participants, mean age and gender of participants, interventions details in treatment and control groups, duration, main outcomes, additional outcomes and adverse events. Any insufficient or missing data will be required from original trial authors by email, fax, or telephone.

**Quality assessment / Risk of bias analysis:** Two reviewers will independently assess the risk of bias for each trial using Cochrane risk of bias tool. This tool covers seven domains and each aspect is further rated as high, unclear, or low risk of bias. Divergences between the two reviewers will be solved through discussion with the help of the third reviewer.

**Strategy of data synthesis:** We will use I² statistics to detect statistical heterogeneity across included trials. I² ≤ 50% indicates acceptable heterogeneity, and we will use a fixed-effects model. I² > 50% means obvious heterogeneity, and we will utilize a random-effects model. The possible reasons of heterogeneity will be analysed by sensitivity analysis or subgroup analysis.

**Subgroup analysis:** We will conduct a subgroup analysis to examine obvious heterogeneity according to the different types of study characteristics, details of treatments and comparators, and outcome indicators.

**Sensibility analysis:** We will undertake a sensitivity analysis to check the robustness of merged outcome results by removing trials with low quality. The main decision includes sample size, quality of studies, methodological and missing data.

**Language:** No language restriction.

**Country(ies) involved:** China.

**Keywords:** Neuromyelitis optica spectrum disorders; Interleukin 6; Tocilizumab; Satralizumab; Annualized relapse rate.

**Contributions of each author:**
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