INPLASY PROTOCOL

To cite: Wang et al. Adverse events of Rituximab in Neuromyelitis Optica Spectrum Disorder: A Protocol for Systematic Review and Meta-analysis. Inplasy protocol 202150034. doi: 10.37766/inplasy2021.5.0034

Received: 08 May 2021

Published: 09 May 2021

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Support: **No.**

Review Stage at time of this submission: **Formal screening of search results against eligibility criteria.**

Conflicts of interest:
None declared.

Adverse events of Rituximab in Neuromyelitis Optica Spectrum Disorder: A Protocol for Systematic Review and Meta-analysis

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Review question / Objective: **When treating Neuromyelitis Optica Spectrum Disorder (NMOSD), the adverse events (AEs) of rituximab (RTX), especially the rates of AEs, and the AE risks between RTX and other treatments were still unknown. To fill this knowledge gap, we plan to conduct this systematic review and meta-analysis to analyze the rates of AEs, and the AE risks between RTX and other treatments when treating NMOSD.**

Condition being studied: **Neuromyelitis Optica Spectrum Disorder (NMOSD) is a group of inflammatory disorders of the central nervous system. The characters of NMOSD mostly include immune-mediated demyelination and axonal damage, such as optic neuritis and myelitis. NMOSD is typically subject to recurrence and is characterized by repeated serious seizures that lead to neurological dysfunction. To prevent recurrence, azathioprine, mycophenolate mofetil, and prednisolone are commonly used. Recently, rituximab (RTX) is increasingly used in NMOSD, however, studies on adverse events (AEs) of RTX, especially the rates of AEs, and the AE risks between other therapies and RTX for NMOSD were still insufficient. In addition, an increasing number of evidence, such as two randomized controlled trials, were published over recent years. Therefore, it is necessary to conduct a comprehensive study on the safety (adverse events) of RTX for NMOSD. Here we are planning to conduct this systematic review and meta-analysis to analyze the rates of AEs, and the AE risks between RTX and other treatments when treating NMOSD.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 May 2021 and was last updated on 09 May 2021 (registration number INPLASY202150034).

INTRODUCTION

Review question / Objective: **When treating Neuromyelitis Optica Spectrum Disorder (NMOSD), the adverse events (AEs) of rituximab (RTX), especially the rates of AEs, and the AE risks between RTX and other treatments were still unknown. To fill this knowledge gap, we plan to conduct this systematic review and meta-analysis to**

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Rationale: Neuromyelitis Optica spectrum disorder (NMOSD) is a central nervous system disease. Recently, rituximab (RTX) is increasingly used in NMOSD. However, studies on adverse events (AEs) of RTX, especially the rates of AEs, and the AE risks between other therapies and RTX for NMOSD were still insufficient. In addition, a more comprehensive understanding of the safety of RTX in NMOSD can better guide the clinical practice. Thus, this study will analyze the rates of AEs, and the AE risks between RTX and other treatments when treating NMOSD.

Condition being studied: Neuromyelitis Optica Spectrum Disorder (NMOSD) is a group of inflammatory disorders of the central nervous system. The characters of NMOSD mostly include immune-mediated demyelination and axonal damage, such as optic neuritis and myelitis. NMOSD is typically subject to recurrence and is characterized by repeated serious seizures that lead to neurological dysfunction. To prevent recurrence, azathioprine, mycophenolate mofetil, and prednisolone are commonly used. Recently, rituximab (RTX) is increasingly used in NMOSD, however, studies on adverse events (AEs) of RTX, especially the rates of AEs, and the AE risks between other therapies and RTX for NMOSD were still insufficient. In addition, an increasing number of evidence, such as two randomized controlled trials, were published over recent years. Therefore, it is necessary to conduct a comprehensive study on the safety (adverse events) of RTX for NMOSD. Here we are planning to conduct this systematic review and meta-analysis to analyze the rates of AEs, and the AE risks between RTX and other treatments when treating NMOSD.

METHODS

Search strategy: The following electronic databases were searched with no language restriction: 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 Wanfang Data. Clinical Trials.gov.; the National Institute for Health and Care Excellence (NICE); National Guideline Clearinghouse (NGC); GIN (the guidelines international network); Cumulative Index to Nursing & Allied Health Literature (CINAHL); World Health Organization (WHO) and Medlive were also searched. A combination of Medical Subject Headings (MeSH) and free text terms incorporating database-specific controlled vocabularies and text words was used to implement search strategies. The search time was from the construction of the databases to November 21, 2020. In order to perform a complete search for adverse events, our search terms also included other related diseases, such as Myelin oligodendrocyte glycoprotein antibody disorders (MOGAD) and Chronic Relapsing Inflammatory Optic Neuropathy,., as studies of these diseases may involve adverse events of NMOSD. The PUBMED search strategy is: ((((((("Optic Neuritis"[Mesh]) OR ("Neuromyelitis Optica"[Mesh])) OR ("Myelin-Oligodendrocyte Glycoprotein"[Mesh])) OR (((((((((("Optic Neuriti*"[Title/Abstract]) OR ("Neuropapilliti*"[Title/Abstract])) OR ("Anterior Optic Neuriti*"[Title/Abstract])) OR ("Retrobulbar Neuriti*"[Title/Abstract])) OR ("Posterior Optic Neuriti*"[Title/Abstract])) OR ("acute optic neuritis"[Title/Abstract])) OR ("inflammatory optic neuropath*"[Title/Abstract])) OR ("neuritis optica"[Title/Abstract])) OR ("opticus neuritis"[Title/Abstract]))) OR ((((((((((((((((("Neuromyelitis Optica"[Title/Abstract]) OR ("myelooptic neuropathy"[Title/Abstract])) OR ("NMO Spectrum Disorder*"[Title/Abstract])) OR ("Neuromyelitis Optica (NMO) Spectrum Disorder*"[Title/Abstract])) OR ("Neuromyelitis Optica Spectrum Disorder*"[Title/Abstract])) OR ("Devic Neuromyelitis Optica*"[Title/Abstract])) OR ("Devic* Disease"[Title/Abstract])) OR ("Devic* Syndrome"[Title/Abstract])) OR ("Devic's Disease"[Title/Abstract])) OR ("Devic's Syndrome"[Title/Abstract])) OR

("Devic's Neuromyelitis Optica"[Title/Abstract])) OR ("Devic* Neuromyelitis Optica"[Title/Abstract])) OR ("myelo optico neuropathy"[Title/Abstract])) OR (Myeloopticoneuropathy[Title/Abstract])) OR (neuropticomyelitis[Title/Abstract])) OR (NMO[Title/Abstract])) OR ("optic neuromyelitis"[Title/Abstract])) OR ("neuromyelitis optica"[Title/Abstract]))) OR ((((((((((("Myelin-Oligodendrocyte Glycoprotein"[Title/Abstract]) OR ("Myelin oligodendrocyte glycoprotein antibod*"[Title/Abstract])) OR ("MOG autoantibod*"[Title/Abstract])) OR ("MOG antibod*"[Title/Abstract])) OR ("MOG-Ab"[Title/Abstract])) OR ("MOG-ab"[Title/Abstract])) OR ("MOG-IgG"[Title/Abstract])) OR (MOGAD[Title/Abstract])) OR ("Chronic Relapsing Inflammatory Optic Neuropathy"[Title/Abstract])) OR (CRION[Title/Abstract]))) AND (("Rituximab"[Mesh]) OR (((((Rituximab [Title/Abstract]) OR ("Rituximab CD20 Antibody"[Title/Abstract])) OR (Mabthera[Title/Abstract])) OR (Rituxan[Title/Abstract])) OR (RTX[Title/Abstract]))) Filters: Humans.

Participant or population: We will include patients who have been diagnosed as NMOSD based on any recognized diagnostic criteria such as 2015, 2006, or 1999 NMO/NMOSD diagnostic consensus criteria, with no restriction of age, race, sex, and nationality.

Intervention: All patients underwent any dose of RTX with or without glucocorticoid therapy and other standard-care treatment will be included in this study.

Comparator: All patients received any other management (including placebo) for the treatment of NMOSD in the control groups (if any) will be considered for inclusion.

Study designs to be included: This study will include randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), cohort studies, case-control studies, and case series about the use of RTX in NMOSD patients.

Eligibility criteria: All randomized controlled trials (RCTs), non-randomized controlled trials (NRCTs), cohort studies, case-control studies, and case series about the use of RTX in NMOSD patients are included. We will exclude some studies, such as animal studies, review, case reports or studies < 5 patients and studies on RTX biosimilars.

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 Wanfang Data. Clinical Trials.gov.; the National Institute for Health and Care Excellence (NICE); National Guideline Clearinghouse (NGC); GIN (the guidelines international network); Cumulative Index to Nursing & Allied Health Literature (CINAHL); World Health Organization (WHO) and Medlive were also searched. Besides, we also searched other resources, such as thesis, conference papers, dissertations, and reference lists of related reviews.

Main outcome(s): The primary outcomes are the rates of any AEs and the risks of any AEs between RTX and other different therapies (any AEs mean any undesirable occurrence that happened during the use of RTX for NMOSD). The secondary outcomes are the rates of serious adverse events (SAEs), and the risks of SAEs between RTX and other therapies. SAEs are defined as SAEs reported by the authors or AEs causing death, interruption or discontinuation of the therapy, hypotension (blood pressure <90/60 mmHg), prolongation of hospitalization (subject to the reports), requiring a blood transfusion.

Additional outcome(s): Other outcomes include infection, death associated with RTX, drug withdrawal or change due to AEs, infusion-related AEs, neoplasms, organ impairments (e.g., liver or kidney impairments), and hematologic complications (e.g., blood immune cells and immunoglobulins decline), etc.

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 or median age and gender of participants, interventions details in treatment and control groups (if any), duration, follow-up period (if any), main outcomes, additional outcomes. Any insufficient or missing data will be required from original authors by email, fax, or telephone.

Quality assessment / Risk of bias analysis: Two reviewers will independently assess the risk of bias for each study. Different tools will be used for different studies, including the Cochrane risk of bias assessment tool (Cochrane-ROB, version 6) for RCTs; Newcastle-Ottawa Scale (NOS) for cohort and case-control studies; Joanna Briggs Institute (JBI) for case series studies, and methodological index for non-randomized studies (MINORS) for NRCTs. After the discussion, the studies, which were considered as ones with low risks of bias when the high bias items of Cochrane-ROB were no more than 5 and the NOS, JBI, and MINORS scores were respectively greater than or equal to 6, 5, and 12, were included in the final analyses.

Strategy of data synthesis: The incidence of each AE will be pooled through data from the case series. The rates of AEs in each study will be calculated by dividing the patient number of each AE by the total sample size. We will transform the data via the transformation method of "odds data" and modify an offset of 0.5 for all 0 cells. The specific transformation method is: P=ln("odds")=ln(X/(n-X)), SE(P)=SE(ln("odds")) =√(1/X+1/(n-X)). In this calculation, "P" means the incidence of AEs, "SE" means the standard error, "X" means the number of AEs and "n" means the total number of observed populations. The "P" and "SE" values will be used to summarize the pooled "odds ratio" (OR) and its 95% confidence intervals (CIs). After the summary, the following transformation will be required to obtain to the final AE rate and its 95% CIs: Pf=OR/(1+OR), LL=LL_OR/(1+LLOR), UL=UL_OR/(1+ULOR). In this transformation, "Pf" means the transformed final rate of AEs, "LL" means the transformed final lower limit of the 95% CI, "LLOR" means the lower limit of the 95% CIs before transformation, "UL" means the transformed final upper limit of the 95% CIs, and "ULOR" means the upper limit of the 95% CIs before transformation. The risks of each AE in various therapies will be compared by using data from studies with control groups. In studies involving multiple arms, the differences between the RTX arm and other arms were compared, respectively. RR or OR will be used to present the risk. RR or OR suggests a higher risk of AEs in the RTX group than in the control group when the value exceeded 1. We will use I2 statistics and Chi2 -based-Q-statistics test to detect statistical heterogeneity across included trials. I2≤50% shows acceptable heterogeneity, and I2>50% means obvious heterogeneity. We will select the random effects model in advance because of expected heterogeneity in study designs. The reasons for heterogeneity will be analyzed 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.

Sensitivity analysis: We will undertake a sensitivity analysis through leave-one-out approach 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. Studies with a clear source of heterogeneity will be excluded.

Language: No language restriction.

Country(ies) involved: China.

Other relevant information: None.

Keywords: Safety, adverse events, Rituximab, Neuromyelitis Optica spectrum disorder, Systematic review and Meta-analysis.

Contributions of each author:

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