INPLASY PROTOCOL

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None declared.

The efficacy and safety of anti-CD20 antibody treatments in relapsing multiple sclerosis: a systematic review and network meta-analysis

Xin, W[1].

Review question / Objective: **The objectives of this systematic review were to evaluate the efficacy and safety of the three existing anti-CD20 antibodies for the treatment of relapsing multiple sclerosis and to aid clinicians in choosing medications.**
Eligibility criteria: **We set the inclusion criteria as follows: (1) study type: RCT; (2) language restriction: only available in English; (3) participants: patients ≥18 years of age diagnosed with relapsing MS, whether with a relapsing–remitting course or a secondary progressive course; (4) intervention: anti-CD20 antibody treatments including ocrelizumab, ofatumumab, rituximab, and corresponding control including placebo and active treatments; (5) outcomes: clinical outcomes including annualized rate of relapse (ARR), the number of patients free of relapse, and the number of patients with confirmed disease progression (CDP); magnetic resonance imaging(MRI) outcomes including gadolinium-enhancing lesion change in T1, change in the volume of lesions on T2, the number of patients with no new or newly enlarged lesions in T2 and the brain volume change (BVC); safety outcomes including adverse events (AEs) and serious adverse events (SAEs). Included RCTs were not requested to supply all the outcomes mentioned above. We set the exclusion criteria as follows: (1) study type: retrospective studies, cohort studies, case reviews and case reports; (2) patients diagnosed with primary progressive MS.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 June 2022 and was last updated on 17 June 2022 (registration number INPLASY202260075).

INTRODUCTION

Review question / Objective: **The objectives of this systematic review were to evaluate the efficacy and safety of the three existing anti-CD20 antibodies for the treatment of relapsing multiple sclerosis and to aid clinicians in choosing medications.**

Condition being studied: **Multiple sclerosis (MS) has been historically considered as the most common neuroinflammatory disease of the central nervous system (CNS). The pathogenesis of MS involves a failure of the myelin repair mechanism, the loss of oligodendrocytes, and the cumulative loss of axons and neurons**

under the interaction of the environmental factors and the polygenic susceptibility background. This results in inflammatory demyelination in gray and white matter of the CNS. Although the triggers of MS are still unclear, it is generally believed that autoreactive CD4+ T helper cells, which are activated in the periphery by viral persistence, bystander activation, or molecular mimicry are the key to the initiation of inflammatory demyelination in MS. Increasing evidence indicates that B lymphocytes also play a key role in the pathogenesis of MS. At present, it is believed that B lymphocytes primarily contribute to MS pathogenesis in three ways. First, they can secrete pro- and anti-inflammatory cytokines. Second, they can release various auto-antibodies. Third, B lymphocytes can capture myelin antigens in low concentration and activate myelin-reactive T cells by acting as antigen-presenting cells (APCs). For example, they are involved in the presentation of auto-antigens to CD4+T-cells and promote the Th1 and Th17 responses, which are known to be triggers of MS activity. There are a number of drugs available for the treatment of MS patients. The long-term application of these drugs is challenging due to safety concerns, compliance issues, and individual immunological changes. Only a small number of therapeutic agents exert beneficial effects for the progressive forms of MS. Hence, research should explore these new and effective treatment modalities for MS. Since the surface molecule CD20 is expressed by the B cell lineage, it has become a specific target for monoclonal antibodies. Currently, there are several major anti-CD20 monoclonal antibodies (mAbs), including rituximab, ocrelizumab, ofatumumab and ublituximab, that have been used for the treatment of MS or included in clinical trials. Their mechanism of action is to achieve the effect of B-cell depletion and CD20-positive T cell depletion possibly by binding to distinct or overlapping epitopes on B cells and CD20-positive T cells. The efficacy and safety of these anti-CD20 mAbs have been well verified in several large randomized controlled trials (RCTs). To our knowledge, there have been no systematic comparisons among these variables. In addition, more sufficient evidence is needed for clinicians to support their decision-making for patients with MS. In this study, we pooled data from previous RCTs and conducted a systematic review and network meta-analysis to investigate the difference between the efficacy and safety of these anti-CD20 mAbs for the treatment of MS.

METHODS

Search strategy: The following search strategy was employed: (anti-CD20[Title/Abstract]) AND (multiple sclerosis[Title/Abstract]) for MEDLINE; “anti-CD20”/exp AND “multiple sclerosis”/exp for EMBASE; "anti-CD20" in Title Abstract Keyword AND "multiple sclerosis" in Title Abstract Keyword for Cochrane Library; “anti-CD20 | multiple sclerosis” for ClinicalTrials.gov. Additionally, the reference lists of RCTs, relevant systematic reviews and meta-analyses were also screened independently and manually to ensure a more comprehensive search.

Participant or population: Patients ≥18 years of age diagnosed with relapsing MS, whether with a relapsing–remitting course or a secondary progressive course.

Intervention: Anti-CD20 antibody treatments including ocrelizumab, ofatumumab, rituximab.

Comparator: Corresponding control including placebo and active treatments

Study designs to be included: RCT.

Eligibility criteria: We set the inclusion criteria as follows: (1) study type: RCT; (2) language restriction: only available in English; (3) participants: patients ≥18 years of age diagnosed with relapsing MS, whether with a relapsing–remitting course or a secondary progressive course; (4) intervention: anti-CD20 antibody treatments including ocrelizumab, ofatumumab, rituximab, and corresponding control including placebo and active treatments; (5) outcomes: clinical

outcomes including annualized rate of relapse (ARR), the number of patients free of relapse, and the number of patients with confirmed disease progression (CDP); magnetic resonance imaging(MRI) outcomes including gadolinium-enhancing lesion change in T1, change in the volume of lesions on T2, the number of patients with no new or newly enlarged lesions in T2 and the brain volume change (BVC); safety outcomes including adverse events (AEs) and serious adverse events (SAEs). Included RCTs were not requested to supply all the outcomes mentioned above. We set the exclusion criteria as follows: (1) study type: retrospective studies, cohort studies, case reviews and case reports; (2) patients diagnosed with primary progressive MS.

Information sources: MEDLINE, EMBASE, the Cochrane Library and ClinicalTrials.gov.

Main outcome(s): outcomes: clinical outcomes including annualized rate of relapse (ARR), the number of patients free of relapse, and the number of patients with confirmed disease progression (CDP); magnetic resonance imaging(MRI) outcomes including gadolinium-enhancing lesion change in T1, change in the volume of lesions on T2, the number of patients with no new or newly enlarged lesions in T2 and the brain volume change (BVC); safety outcomes including adverse events (AEs) and serious adverse events (SAEs). Included RCTs were not requested to supply all the outcomes mentioned above.

Quality assessment / Risk of bias analysis: The risk of bias plot was evaluated with the Review Manager 5.3 software. The uniform criteria of the Cochrane Collaboration were used to assess the risk of bias for RCTs, which included: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. Each bias criterion was classified as "low", "high", or "unclear". The assessment was carried out independently by two authors. Disagreements were settled by consulting with a third author.

Strategy of data synthesis: We used Review Manager 5.3 software to perform pairwise meta-analysis of direct evidence. The relative risk (RR) and mean difference (MD) with 95% confidence interval (95% CI) were analyzed and calculated with a random effect model for the dichotomous and continuous outcomes, respectively. We then estimated heterogeneity through the I2 statistic as follows: I2 50% denotes "substantial heterogeneity". A sensitivity analysis was also carried out to explore the stability of the consolidated results. Network meta-analysis was performed for each outcome using R 3.5.2 software. The network relationships between the various interventions were drawed. The size of the circles represents the number of participants for each intervention, and the width of lines represents the number of trials compared between treatments. Treatment efficacy and safety were compared via direct and indirect evidence using the RR values, along with 95% CI. To rank the performance of three anti-CD20 antibody treatments and placebo in each outcome, the surface under curve ranking area (SUCRA) was created. For each outcome, a larger SUCRA value indicated a better rank for the intervention. The ranking probabilities were calculated as cumulative probabilities with each intervention being ranked. For all the analyses, two tailed tests were performed and a P value < 0.05 was considered to be statistically significant.

Subgroup analysis: Not applicable.

Sensitivity analysis: For data with heterogeneity greater than 50%, a sensitivity analysis was performed.

Country(ies) involved: China.

Keywords: Multiple sclerosis, rituximab, ocrelizumab, ofatumumab, anti-CD20 antibody.

Contributions of each author:

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