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# Risk of Secondary Immune Thrombocytopenia following Alemtuzumab Treatment for Multiple Sclerosis: A Systematic Review and Meta-analysis

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## ADMINISTRATIVE INFORMATION

**Support -** None.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202430007

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 01 March 2024 and was last updated on 01 March 2024.

## INTRODUCTION

**Review question / Objective** Object: The purpose of this study was to evaluate the risk of secondary immune thrombocytopenia in multiple sclerosis patients treated with alemtuzumab through a meta-analysis. Methods: We searched databases including PubMed, Web of Science, OVID, EMBASE, SINOMED, and the Cochrane Central Register of Controlled Trials for studies reporting changes in platelet levels in MS patients treated with alemtuzumab from their inception until May 2023 and performed a meta-analysis. Information and data were screened and extracted by 2 researchers. The obtained data were analyzed using the R software meta package. Quality assessment was conducted using Newcastle-Ottawa Scale(NOS). The causes of heterogeneity were analyzed using subgroup analysis and sensitivity analysis. Publication bias was evaluated using Begger funnel plots and Egger test. Results: A total of 15 studies were included, encompassing 1,729 multiple sclerosis patients. Meta-analysis of overall secondary ITP in the included studies yielded a pooled rate of 0.0243. The overall incidence of secondary autoimmune events was 0.2364. In addition, subgroup analysis was applied using study regions and study types. The results showed that the incidence rate of secondary ITP in Europe was about 0.0207, while the incidence of autoimmune events(AEs) was 0.2158. The incidence rate of secondary ITP and AEs in North America was significantly higher than in Europe, being 0.0352 and 0.2622. And the analysis showed that the incidence rates of secondary ITP and AEs in prospective studies were 0.0391 and 0.1771. Retrospective studies had an incidence rate of secondary ITP at 2.16, and an incidence rate of AEs at 0.2743. Conclusion: This study found that there was a certain incidence of Immune thrombocytopenia in multiple sclerosis patients after treatment with alemtuzumab, and alemtuzumab may have some interference with platelet levels, and the mechanism may be associated with Treg cells. Before initiating alemtuzumab, clinical physicians

should perform a comprehensive assessment of the patient's benefit-to-risk ratio.

**Condition being studied** The treatment of multiple sclerosis is a challenge for clinicians. In recent years, alemtuzumab has been widely concerned as an effective drug for the treatment of multiple sclerosis. However, the occurrence of adverse events has become a problem that bothering us, such as the occurrence of secondary immune thrombocytopenia, which seriously affects the use of drugs and the prognosis of patients. Observational studies have investigated the risk of secondary immune platelet events in patients with multiple sclerosis treated with alemtuzumab. However, to date, there has been no systematic review and meta-analysis of pooled data to provide a reliable risk of secondary immune thrombocytopenia in patients with multiple sclerosis treated with alemtuzumab to guide our clinical treatment and research.

## METHODS

**Participant or population** Multiple sclerosis patient.

**Intervention** Not applicable.

**Comparator** Not applicable.

**Study designs to be included** Clinical study of alemtuzumab as the sole treatment for patients with multiple sclerosis.

**Eligibility criteria** Inclusion criteria: (1) Patients diagnosed with MS according to McDonald's criteria; (2) Patients who received ALZ as a therapeutic drug for MS; (3) Patients who had their platelet levels evaluated after treatment with ALZ.Exclusion criteria: Studies that conducted a re-analysis of previously published data, including meta-analyses and studies with duplicated data, Literature reviews, case reports, commentaries, letters, and meeting abstracts were excluded.

**Information sources** We searched databases including PubMed, Web of Science, OVID, EMBASE, SINOMED, and the Cochrane Central Register of Controlled Trials for studies reporting changes in platelet levels in MS patients treated with alemtuzumab from their inception until May 2023 and performed a meta-analysis.

**Main outcome(s)** A total of 15 studies were included, encompassing 1,729 multiple sclerosis patients. Meta-analysis of overall secondary ITP in the included studies yielded a pooled rate of 0.0243. The overall incidence of secondary autoimmune events was 0.2364. In addition, subgroup analysis was applied using study regions and study types. The results showed that the incidence rate of secondary ITP in Europe was about 0.0207, while the incidence of autoimmune events(AEs) was 0.2158. The incidence rate of secondary ITP and AEs in North America was significantly higher than in Europe, being 0.0352 and 0.2622. And the analysis showed that the incidence rates of secondary ITP and AEs in prospective studies were 0.0391 and 0.1771.

**Quality assessment / Risk of bias analysis** Quality assessment was conducted using Newcastle-Ottawa Scale(NOS). The causes of heterogeneity were analyzed using subgroup analysis and sensitivity analysis. Publication bias was evaluated using Begger funnel plots and Egger test.

**Strategy of data synthesis** The meta-analysis was conducted using the "meta" package in R 4.2.2 software. Initially, the data was transformed using logarithmic transformation, logit transformation, arcsine transformation, and Freeman-Tukey double arcsine transformation based on the original rate. The Shapiro-Wilk normality test was performed to assess the normality of each data set. The appropriate data transformation method was selected for datasets that demonstrated normal distribution. Subsequently, the overall incidence rates of secondary thrombocytopenia and autoimmune diseases in multiple sclerosis patients treated with ALZ were calculated, along with their respective 95% confidence intervals (CIs).Information and data were screened and extracted by 2 researchers. The obtained data were analyzed using the R software meta package. Quality assessment was conducted using Newcastle-Ottawa Scale(NOS). The causes of heterogeneity were analyzed using subgroup analysis and sensitivity analysis. Publication bias was evaluated using Begger funnel plots and Egger test.

**Subgroup analysis** Two subgroup analyses were conducted in this study: one based on regional differences and the other based on different study types.

**Sensitivity analysis** The sensitivity analysis using the sequential omission method did not detect any studies that would significantly affect the results.

**Country(ies) involved** China.

**Keywords** Secondary immune thrombocytopenia, Secondary Autoimmune events,Alemtuzumab, Multiple Sclerosis, adverse events, meta-analysis.

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