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INPLASY

Risk of secondary autoimmune diseases with alemtuzumab treatment for multiple sclerosis: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION

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INTRODUCTION

Review question / Objective P: patients with multiple sclerosis I: alemtuzumab C: - O: secondary autoimmune diseases S: a systematic review and meta-analysis.

Condition being studied Multiple sclerosis (MS) is an immune-mediated central nervous system demyelinating disease of unknown etiology (1). The majority of MS patients experience reversible episodes of neurological dysfunction and have a remitting-relapsing course (remitting-relapsing MS, RRMS). Currently, two main treatment strategies of MS are commonly employed: escalation therapy or induction of immune reset therapy. Alemtuzumab (ALZ) is one of the cutting-edge therapeutic agents in the MS treatment arsenal. In the escalation therapy strategy, ALZ is commonly considered as a second- or third-line treatment option after inadequate response to conventional disease-modifying therapies (DMTs). Among the induction immune reset strategies, some scholars have advocated the use of ALZ as a first-line medication to induce long-term stability over the course of the disease (2). The mechanism of action of ALZ primarily involves the rapid depletion of white blood cells expressing CD52 through cell lysis, leading to long-term reduction and stabilization of T lymphocytes and inducing a prolonged quiescent state (3). The profound impact of ALZ's capacity to induce immune reconstitution on the immune system, coupled with the fact that autoimmune diseases tend to arise from lymphocyte depletion, has made secondary autoimmune diseases a relatively common adverse reaction during the use of ALZ (4, 5).

Current perspectives suggest that incomplete T-cell repertoire renewal, reduced thymopoiesis, homeostatic proliferation with disparate dynamics of clonal T- and B-cell expansions may be associated with the development of SAEs following the administration of ALZ (6, 7). Furthermore, imbalances among distinct subsets of helper T cells could potentially influence selfreactive T-cell populations, thereby contributing to autoimmune

tissue damage (8). The underlying mechanisms behind these conditions, though, currently lack a universally accepted explanation (9, 10).
In summary, ALZ as a significant treatment modality for MS has garnered considerable attention from researchers. However, the occurrence of secondary autoimmune diseases following ALZ infusion should not be overlooked. In light of this, we have conducted a meta-analysis on this topic, aiming to provide comprehensive insights into the incidence of secondary autoimmune diseases related to ALZ and further guide clinical practice.

METHODS

Search strategy The search strategy was developed following the PICOS principle, which involved identifying key indexing terms such as “secondary autoimmunity”, “Autoimmunity”, “Autoimmune Diseases”, “Alemtuzumab” and “Multiple Sclerosis”. The search was conducted using MeSH terms and Boolean operators. The detailed search strategy can be found in the Supplementary Materials. Renowned databases, including PubMed, Web of Science, OVID, EMBASE, and the Cochrane Library, were comprehensively searched to obtain relevant literature. The search results were then imported into EndNote X9.1 for efficient literature management. Two researchers conducted the initial screening of the retrieved articles based on reference relevance. In the event of any disagreement during the article selection process, a third author was consulted for resolution. The search was conducted up to May 2023.

Participant or population Patients diagnosed with multiple sclerosis (MS) according to the McDonald criteria.

Intervention Patients used alemtuzumab as the primary therapeutic intervention.

Comparator None reported.

Study designs to be included Clinical studies, including randomizedcontrolled trials, case-control studies, and cohort studies.

Eligibility criteria The inclusion criteria were as follows: (1) Studies involving individuals diagnosed with multiple sclerosis (MS) according to the McDonald criteria. (2) Studies investigating the therapeutic use of alemtuzumab as the primary intervention. (3) Studies assessing the occurrence of secondary autoimmune diseases in patients receiving ALZ treatment. (4) Clinical studies, including randomized controlled trials, case-control studies, and cohort studies.The inclusion criteria were as follows: (1) Studies involvingindividuals diagnosed with multiple sclerosis (MS) according to theMcDonald criteria. (2) Studies investigating the therapeutic use ofalemtuzumab as the primary intervention. (3) Studies assessing theoccurrence of secondary autoimmune diseases in patients receivingALZ treatment. (4) Clinical studies, including randomizedcontrolled trials, case-control studies, and cohort studies.

Information sources Renowned databases, including PubMed, Web of Science, OVID, EMBASE, and the Cochrane Library, were comprehensively searched to obtain relevant literature.

Main outcome(s) The search retrieved a total of 3530 papers from the databases. After screening, a total of 37 studies were included in the meta-analysis. The analysis results indicate that the pooled incidence rate of overall secondary autoimmune events (SAEs) in the included studies was 0.2824 [0.2348, 0.3300] (I^2=94%, p<0.01). The overall incidence of autoimmune thyroid events (ATE) was 0.2257 [0.1810, 0.2703] (I^2=94%, p<0.01).

Additional outcome(s) Among them, the rate of serious autoimmune thyroid events (SATE) was 0.0541 [0.0396, 0.0687] (I^2=0%, p=0.44). The incidence rates of different thyroid events were as follows: Graves’ disease (GD), 0.2266 [0.1632, 0.2900] (I^2=83%, p<0.01); Hashimoto thyroiditis (HT), 0.0844 [0.0000, 0.2262] (I^2=81%, p=0.02); Hashimoto thyroiditis with hypothyroidism (HTwH), 0.0499 [0.0058, 0.0940] (I^2=37%, p=0.21); fluctuating thyroid dysfunction (FTD), 0.0219 [0.0015, 0.0424] (I^2=0%, p=0.40); transient thyroiditis (TT), 0.0178 [0.0062, 0.0295] (I^2=0%, p=0.94). The overall incidence of hematological events was 0.0431 [0.0274, 0.0621] (I^2=70%, p<0.01). The incidence rates from high to low were as follows: lymphopenia, 0.0367 [0.0000, 0.0776] (I^2=81%, p=0.02); Idiopathic thrombocytopenic purpura (ITP), 0.0258 [0.0199, 0.0323] (I^2=25%, p=0.15); Hemolytic anemia (HA), 0.0177 [0.0081, 0.0391] (I^2=29%, p=0.23); pancytopenia, 0.0136 [0.0000, 0.0314] (I^2=0%, p=0.67); Neutropenia, 0.0081 [0.0000, 0.0183] (I^2=0%, p=0.42). After excluding thyroid and hematological diseases, the combined incidence of other related SAEs was 0.0061 [0.0014, 0.0109] (I^2=50%, p=0.02). The incidence of each disease ranked from highest to lowest as: skin psoriasis (SP), 0.0430 [0.0000, 0.0929] (I^2=0%, p=0.57); alopecia areata (AA), 0.0159 [0.0024, 0.0372] (I^2=19%, p=0.29); vitiligo,

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0.0134 [0.0044, 0.0223] (I^2=0%, p=0.81); inflammatory atrichia (IA), 0.0103 [0.0000, 0.0232] (I^2=0%, p=0.43); chronic urticaria (CU), 0.0107 [0.0000, 0.0233] (I^2=0%, p=0.60); and nephropathy, 0.0051 [0.0000, 0.0263] (I^2=62%, p=0.02).

Data management The search results were then imported into EndNote X9.1 for efficient literature management. Two researchers conducted the initial screening of the retrieved articles based on reference relevance. In the event of any disagreement during the article selection process, a third author was consulted for resolution. The search was conducted up to May 2023.

Quality assessment / Risk of bias analysis The quality assessment of the included studies was conducted using the Newcastle-Ottawa Scale (NOS), which can be accessed at http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Studies with NOS scores exceeding 5 points were deemed eligible for inclusion in the meta-analysis.

Strategy of data synthesis The meta-analysis was conducted using the "meta/metafor" package in R 4.2.2 software (11). Firstly, the original rates were transformed using logarithmic, logit, arcsine, and Freeman-Tukey double arcsine transformations. The Shapiro-Wilk normality test was employed to assess the normality of each dataset, and the appropriate transformation method was chosen based on the distribution. The overall incidence rate of secondary autoimmune diseases in MS patients treated with ALZ was then calculated, along with its 95% confidence interval (CI). The heterogeneity among the included studies was evaluated using the Cochrane Q test and I^2 statistic. If the Cochrane Q test yielded a p-value of ≤0.05 or I^2 was ≥50%, significant heterogeneity was deemed present.

Subgroup analysis Subgroup analysis was considered to observe whether heterogeneity was reduced among different subgroups. If the heterogeneity remained after these steps, a random-effects model was used to calculate the combined rate and its 95% CI, with a careful analysis of the source of heterogeneity. In the absence of significant heterogeneity, a fixed-effects model was used to combine the overall rates. Finally, a funnel plot and Egger's test were used to assess publication bias. In the presence of clear outliers, the possibility of excluding such studies may be considered after a meticulous analysis of potential sources of bias.

Sensitivity analysis In such cases, sensitivity analysis was conducted by omitting individual studies sequentially to assess the stability of the combined results. Studies that had an abnormal influence on the analysis results were excluded on a discretionary basis to observe if heterogeneity was eliminated.

Language restriction We included only English databases.

Country(ies) involved China.

Keywords secondary autoimmune diseases, alemtuzumab, multiple sclerosis, side effects, meta-analysis.

Contributions of each author

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