INPLASY PROTOCOL

To cite: Lin et al. Adverse events for monoclonal antibodies in patients with allergic rhinitis: A systematic review and meta-analysis of randomized clinical trials. Inplasy protocol 202310092. doi: 10.37766/inplasy2023.1.0092

Received: 31 January 2023

Published: 31 January 2023

Corresponding author:
Yuxi Lin

dllinyuxi@163.com

Author Affiliation:
Chinese Academy of Medical Sciences & Peking Union Medical Colleg.

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

Conflicts of interest:
None declared.

Adverse events for monoclonal antibodies in patients with allergic rhinitis: A systematic review and meta-analysis of randomized clinical trials

Lin, YX[1]; Wang, WQ[2]; Zhu, ZZ[3]; Aodeng SRT[4]; Wang, L[5]; Liu, YZ[6]; Li, JJ[7]; Zha, Y[8]; Wang, XW[9]; Lv, W[0].

Review question / Objective: **In this systematic review, we aimed to exhaustively search and summarize studies investigating monoclonal antibody treatments and their adverse events in patients with allergic rhinitis.**
Condition being studied: **Allergic rhinitis (AR) is one of the most common diseases in otolaryngology, affecting about 10-40% population worldwide, and its prevalence rate has increased progressively, especially in developed countries. Classic symptoms of AR include nasal itching, sneezing, rhinorrhoea, and nasal congestion. Additionally, ocular symptoms such as allergic rhinoconjunctivitis are common, causing itching and redness of the eyes and tearing, and other symptoms are itching of the palate, postnasal drip, and cough.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 January 2023 and was last updated on 31 January 2023 (registration number INPLASY202310092).

INTRODUCTION

Review question / Objective: **In this systematic review, we aimed to exhaustively search and summarize studies investigating monoclonal antibody treatments and their adverse events in patients with allergic rhinitis.**

Rationale: **There are various traditional treatments of allergic rhinitis (AR), including education, allergen avoidance, pharmacotherapy such as antihistamines and corticosteroids, and allergen-specific immunotherapy. Even so, current treatments are not efficacious for all patients, and thus, novel developments such as monoclonal antibodies (mAbs) are called for clinical needs. With the progress of research on the immunopathogenic mechanisms of AR, mAbs blocking**

essential disease-causing factors are proven to have promising therapeutic effects. However, the overall safety of mAbs is still in concern, with a poor understanding of the underlying mechanisms of many mAb-related adverse reactions. Safety assessment of novel biological therapies is a crucial aspect and one of the fundamental criteria, as much as efficacy, for the justification of their clinical applications. Therefore, a comprehensive safety profile of biologics in AR is in practical need.

Condition being studied: Allergic rhinitis (AR) is one of the most common diseases in otolaryngology, affecting about 10-40% population worldwide, and its prevalence rate has increased progressively, especially in developed countries. Classic symptoms of AR include nasal itching, sneezing, rhinorrhoea, and nasal congestion. Additionally, ocular symptoms such as allergic rhinoconjunctivitis are common, causing itching and redness of the eyes and tearing, and other symptoms are itching of the palate, postnasal drip, and cough.

METHODS

Search strategy: We searched PubMed, Web of Science, Medline and the Cochrane Central Register of Controlled Trials databases from inception to January 9, 2023 without language restrictions. Combinations of AR-related terms ("allergic rhinitis", "rhinitis", "rhino conjunctivitis", "nasal allergy", or "hay fever"), mAb-related terms ("monoclonal antibodies", "humanized", "anti-IgE", "omalizumab", "anti-IL4", "anti-IL13", "anti-IL4Ra", or "dupilumab") and therapy-related terms ("therapy", "treatment", or "management") were used when screening titles/abstracts/keywords of articles. We also manually searched reference lists and similar articles for additional relevant studies. Randomized controlled trials (RCTs) reporting the efficacy and safety of mAbs for the treatment of allergic rhinitis against placebo were retrieved for a full-text review and assessed for eligibility. For missing, unclear, or incomplete results, we contacted researchers for clarification before exclusion. Studies that met the inclusion criteria were included for further analysis.

Participant or population: Allergic rhinitis patients of any age groups, confirmed with a physician diagnosis and evidence of clinically relevant allergic sensitization.

Intervention: Monoclonal antibodies.

Comparator: Placebo.

Study designs to be included: Studies that met the following criteria were eligible for inclusion: (1) the study population comprised allergic rhinitis patients of any age groups, confirmed with a physician diagnosis and evidence of clinically relevant allergic sensitization; (2) RCTs comparing the use of monoclonal antibodies therapy with placebo; (3) safety assessment was accomplished by reporting adverse events.

Eligibility criteria: Studies that met the following criteria were eligible for inclusion: (1) the study population comprised allergic rhinitis patients of any age groups, confirmed with a physician diagnosis and evidence of clinically relevant allergic sensitization; (2) RCTs comparing the use of monoclonal antibodies therapy with placebo; (3) safety assessment was accomplished by reporting adverse events. Studies were excluded if: (1) allergic rhinitis was treated as a clinical manifestation or optional comorbid of other diseases; (2) the study design didn't follow RCTs; (3) patients were treated with any mAbs in the past 12 months before studies started; (4) the control group received treatment other than placebo; (5) the treatment group received mAbs along with any other treatments instead of mAbs alone.

Information sources: PubMed, Web of Science, Medline and the Cochrane Central Register of Controlled Trials databases.

Main outcome(s): We recorded basic information such as first author and year of publishment. We also collected information

on characteristics of the included RCTs, including countries where trials were conducted, sample size, monoclonal antibody given to the treatment group, intervention scheme, and follow-up time. Moreover, patients' baseline demographics in the included studies were collected, including age (range and mean), sex (male/female), race (White/Black/Asian/others), weight (range and mean), type of AR (seasonal allergic rhinitis (SAR)/perennial allergic rhinitis (PAR)), serum IgE (mean), and asthma history. Most importantly, for all included RCTs, we collected safety information about the frequency and detailed clinical manifestations of adverse events.

Quality assessment / Risk of bias analysis: Two investigators independently conducted the quality assessment for each included study using Cochrane risk-of-bias tool for randomized trials (RoB 2). We assessed 6 domains representing the selection, performance, detection, attrition, and reporting bias, and evaluated the risk as 3 levels: low, unclear, and high. The study was identified to be at low risk only if all 6 domains were at low risk. If at least 1 domain was at high risk, the overall risk level was high. If none of the domains was at high risk, but at least 1 domain had unclear risk, we considered the study as unclear risk. Furthermore, publication bias was assessed using funnel plots.

Strategy of data synthesis: Meta-analysis was conducted through RStudio using Mantel-Haenszel method. Heterogeneity was evaluated according to heterogeneity test and I^2 statistic. A p-value < 0.1 was considered as a significant heterogeneity. Meanwhile, I2 of 25%, 50%, and 75% represented a low, medium, and high heterogeneity, respectively. For I^2 < 50%, a fixed-effects model was used for meta-analysis. However, if I^2 > 50%, which means a high heterogeneity, a random-effects model should be used to maintain conservative. Lastly, we used RStudio to conduct subgroup analysis and present forest plots.

Subgroup analysis: Subgroup analysis was conducted to detect the source of heterogeneity using RStudio.

Sensitivity analysis: Different meta-analysis models and subgroups were analyzed to explore the effects as sensitivity analysis.

Language restriction: No language restrictions.

Country(ies) involved: China.

Keywords: allergic rhinitis; monoclonal antibodies; biologics; biological therapies; adverse events; safety; meta-analysis.

Contributions of each author:
Author 1 - Yuxi Lin.
Author 2 - Weiqing Wang.
Author 3 - Zhenzhen Zhu.
Author 4 - Surita Aodeng.
Author 5 - Lei Wang.
Author 6 - Yuzhuo Liu.
Author 7 - Jingjing Li.
Author 8 - Yang Zha.
Author 9 - Xiaowei Wang.
Author 10 - Wei Lv.

Support: National Natural Science Foundation of China (grant number 82071027 and 82101200); Nation-al High Level Hospital Clinical Research Funding (grant number 2022-PUMCH-B-096, 2022-PUMCH-A-030 and 2022-PUMCH-C-050).