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Infection related adverse events in adult patients with severe asthma treated with Tezepelumab, a systematic review and meta-analysis V.2

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We use this protocol and it's working

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Abstract

Asthma is a chronic respiratory disease with different phenotypes that are characterized by chronic airway inflammation. Severe asthma is a subset of difficult-to-treat asthma defined as uncontrolled asthma despite adherence to treatment with maximal optimized high-doses of ICS-LABA. Tezepelumab is a monoclonal antibody that blocks thymic stromal lymphopoietin (TSLP), a key cytokine involved in airway inflammation. It is approved for the treatment of severe asthma to reduce exacerbations and improve lung function. TSLP plays a role in response to several infections.
Prior meta-analyses have focused on determining safety and efficacy. In these studies infections were only analyzed as secondary outcomes. We aim to identify the risk of infection in patients with severe asthma undergoing therapy with Tezepelumab.

Search Strategy

1 ezspire("Severe asthma" OR "uncontrolled asthma") AND (tezepelumab OR "anti thymic stromal lymphopoietin" OR "anti-TSLP" OR tezspire) AND ("randomized controlled trial"[PT] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR ("randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

Cochrane search:
("Severe asthma" OR "uncontrolled asthma") AND (tezepelumab OR "anti thymic stromal lymphopoietin" OR "anti-TSLP" OR tezspire)

Eligibility Criteria

2 We will include studies evaluating patients with severe asthma despite optimal therapy, irrespective of age, sex, country, and ethnic group. Randomized controlled trial the study must compare Tezepelumab to placebo.

We will exclude studies involving patients with documented Asthma-COPD Overlap syndrome, other severe pulmonary diseases and children (under 18 years of age). If a study reports active smokers, we will exclude active smokers from analysis.

We excluded non-human studies and in vitro research, editorials, conference proceedings, commentaries, expert opinion, reviews, studies without original data, non-English publications, and duplicate publications.

Intervention(s), exposure(s)

3 Therapy with tezepelumab

Comparator/control

4 Placebo

Types of study to be included

5 Randomized control trial

Context

6 We will include only studies that report on any of the outcomes of interest, as reported below. We will also collect data on subgroups of sex, age, race, pulmonary function test, eosinophil counts, Quality of life scores, and frequency of exacerbations.

Main outcome(s)

7 We will extract data for a pooled analysis on the following outcomes: (1) Pneumonia (Lower respiratory tract infection); (2) Bronchitis; (3) Nasopharyngitis; (4) Upper Respiratory Tract Infections; (5) Other non-respiratory infectious adverse events

Measures of effect: Hazards ratio, and Odds ratio

Study Records

8 All protocol amendments, data extraction updates, and decisions regarding inclusion/exclusion will be logged in a version-controlled document to ensure auditability. The review will be conducted in accordance with the PRISMA and MOOSE guidelines for systematic reviews and meta-analyses.

Data Management

9 All data related to this systematic review and meta-analysis will be collected, managed, and stored in accordance with established methodological guidelines and principles of transparency and reproducibility. All extracted data will be stored securely in password-protected Excel spreadsheets.

Only authorized members of the review team will have access to the data files. Regular backups will be created to prevent data loss.

Selection Process

10 Titles and abstracts identified through the search strategy will be screened independently by two reviewers (FR and TT). Discrepancies between reviewers will be resolved through adjudication by a third, independent reviewer (ESN)

Data Collection process

11 **Data Extraction**
Data on each of the outcomes described will be collected.
Data will be extracted independently by two team members. If further information is required, authors from the original article will be contacted to obtain data not available in published reports.
A standardized data extraction form will be developed and pilot tested. The following data will be extracted from each included study:

- Study
  Characteristics: First author, publication year, country, study design, trial registration (if applicable), funding sources, and conflict of interest disclosures.

- Participant
  Characteristics: Sample size, mean age, gender distribution, baseline asthma severity, inclusion/exclusion criteria.

- Intervention
  Details: Dose, duration, and route of Tezepelumab administration; co-interventions; standard therapy components.

- Outcomes:
  Type and number of adverse events (including total AEs and specific types like infections), definitions used, follow-up duration, and method of adverse event reporting.

In addition, the following baseline characteristics will be collected: (1) race distribution; (2)

proportion of patients with severe persistent asthma with eosinophilia; (3) proportion of patients with severe persistent asthma without eosinophilia; (4) Quality of life scores; (5) comorbidities; and (6) follow-up in months. The data will be extracted and recorded on an Excel template by two authors: FR and TT.

Risk of Bias Assessment

12 We will use the Cochrane Collaboration's tool for assessing risk of bias in randomized trials for quality assessment of individual randomized studies.

Strategy for data synthesis

13 The systematic review and meta-analysis will be performed in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines.
A meta-analysis will be performed if ≥2 studies report the same outcome (e.g., adverse events or infections) in a comparable way.
We will extract the data from individual studies using hazard ratios (HR) to preserve time-to-event data from individual studies. Effects for binary endpoints ((e.g., incidence of adverse events, infections) will be compared using pooled HR or odds-ratios (OR) with 95% confidence intervals. Weighted mean differences will be used to pool continuous outcomes. Heterogeneity will be evaluated with Cochran Q test and I^2 statistics; p values inferior to 0.10 and I^2>25% will be considered significant for heterogeneity. The decision to use either a random-effect or fixed-effect model will be made after a critical appraisal of all included studies. Review Manager 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) will be used for statistical analysis

Analysis of subgroups or subsets

14 We will extract data and perform sub-analyses in the following subgroups: (1) male; (2) female; (3) age ≥65 years old; (4) age <65 years old; (5) by duration of follow up (less than 6 months and greater than 6 months); (7) By type of adverse event (e.g: infections vs general Adverse events)

Meta-bias Assessment

15 If ≥10 studies are included in a meta-analysis, publication bias will be assessed via:

- Visual inspection of funnel plots
- Egger's regression test for small-study effects

Keywords

16 Severe Asthma
Tezepelumab
Adverse drug reactions

Language

17 English

Conflicts of Interest

18 None

Funding

19 None

Protocol references

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