INPLASY PROTOCOL

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None declared.

Efficacy and Safety of Dupilumab in Bullous Pemphigoid: A Systematic Review and Meta-Analysis

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Review question / Objective: **We aimed to conduct a systematic review and meta-analysis about efficacy and safety of dupilumab in treating bullous pemphigoid.**
Condition being studied: **We aimed to conduct a systematic review and meta-analysis about efficacy and safety of dupilumab in treating bullous pemphigoid.**
Information sources: **Pubmed, Embase and SCI-Web of Science were searched up to 8 September 2022. References of included studies, relevant reviews and meta-analyses were examined for potential suitable studies. Authors of included studies were contacted to obtain the full text or further information when needed.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 13 November 2022 and was last updated on 13 November 2022 (registration number INPLASY2022110059).

INTRODUCTION

Review question / Objective: **We aimed to conduct a systematic review and meta-analysis about efficacy and safety of dupilumab in treating bullous pemphigoid.**

Rationale: **Bullous pemphigoid represents the most common autoimmune bullous disease, which occurs more frequently in elderly people, with an incidence of 150–330 new cases per million per year in those over 80. Current therapy relies on glucocorticoids, augmented by other**

immunosuppressive agents if needed. However, mortality from bullous pemphigoid is increasing due to adverse effects and iatrogenic immunosuppression. Hence, new treatments are being explored for higher efficacy and safety. Numerous studies related to bullous pemphigoid patients received dupilumab have been published over the last years. This systematic review aim to confirm the efficacy and safety of dupilumab for bullous pemphigoid and provide a basis for clinicians to choose treatment.

Condition being studied: Numerous studies related to bullous pemphigoid patients received dupilumab have been published over the last years. Nevertheless, the absence of evidence-based guidelines limited the approval of new indications, furthermore, hinder its use in the clinic. Cao et al. found an effective response rate of 66.7% (n = 24/36) limited by sample size and publication bias. In addition, several new clinical studies have been reported recently.

METHODS

Search strategy: Pubmed, Embase and SCI-Web of Science were searched up to 8 September 2022. Take Pubmed as an example, the searching strategy is:

#1: ("Pemphigoid, Bullous"[MeSH Terms] OR "Pemphigoid, Bullous"[Title/Abstract] OR "bullous pemphigoid"[Title/Abstract])

#2: ("dupilumab"[Title/Abstract] OR "dupixent"[Title/Abstract])

#3: ("biologic agent"[Title/Abstract] OR "biologic preparation"[Title/Abstract] OR "biologic product"[Title/Abstract] OR "biological agent"[Title/Abstract] OR "biologics"[Title/Abstract] OR "biopreparate"[Title/Abstract] OR "biopreparation"[Title/Abstract])

#4: (#1 AND #2) OR (#1 AND #3).

Participant or population: Patients with bullous pemphigoid confirmed by clinical and laboratory testsBullous Pemphigoid.

Intervention: Treatment with dupilumab.

Comparator: Not applicable.

Study designs to be included: RCT, non-random trial, observational study.

Eligibility criteria: The literature search strategy was based on the following inclusion criteria: (1) studies of dupilumab for bullous pemphigoid in adults (≥18 years old); (2) articles reporting diagnostic accuracy; (3) studies published in English. Summaries, systematic reviews, conference abstract and lacking primary data were excluded.

Information sources: Pubmed, Embase and SCI-Web of Science were searched up to 8 September 2022. References of included studies, relevant reviews and meta-analyses were examined for potential suitable studies. Authors of included studies were contacted to obtain the full text or further information when needed.

Main outcome(s): Primary outcomes included were objective response rate (defined as partial response or complete response) and rate of adverse events. A complete response was defined as the disappearance of skin blisters and pruritus. A partial reaction was defined as the disappearance of skin blisters but residual itching of the skin.

Data management: Two authors (LL and XH) independently screened the abstracts of the search results and assessed the remaining full-text articles for eligibility. Disagreement was resolved by consensus or discussion with a third researcher (NW).

Quality assessment / Risk of bias analysis: The quality of RCTs was assessed using Cochrane ROB tool. The quality of the cohort studies and case-control studies was assessed using the Newcastle-Ottawa Scale (NOS). The quality of non-random trials was assessed by the methodological index for non-randomized studies (MINORS), which contains 8 items for non-comparative studies and 4 extra items for comparative studies. The quality of all included studies was classified as low, moderate, and high quality

Strategy of data synthesis: The STATA software (version 17.0) was applied for synthesizing the results of outcomes. For rate of primary outcomes, I2 and p-value with 95% confidence intervals (CI) was calculated by command of "metaprop". Heterogeneity was assessed using I2, and tested using the χ2-based Q-test. The I2 cutoffs of 25%, 50%, and 75% were used to distinguish low, low-moderate, moderate-high, and high heterogeneity. We conducted sensitivity analysis to identify outlier studies when there was significant heterogeneity (I2 > 50%), and performed meta-analyses with and without outliers. A more conservative random-effect model was used when significant heterogeneity was present (I2 > 50%). Conversely, we chose to report the results of a fixed-effect model. Publication bias was assessed by funnel plots of Egger's test and Begg's test. If the P value of the tests was less than 0.1, there was publication bias. We chose the result of Egger's test if they were inconsistent. All statistical tests were two-tailed unless otherwise specified, and P ≤ 0.05 was considered significant.

Subgroup analysis: Subgroup analysis was carried out according to different adverse events.

Sensitivity analysis: Trim and fill method or fail-safe numbers method was considered to have sensibility analysis.

Language restriction: English.

Country(ies) involved: China.

Other relevant information: The GRADE system was employed to assess the evidence quality for prespecified outcomes. And the "Summary of findings" table was provided by GRADEpro Guideline Development T ool (GDT) online software (https://gradepro.org) to summarize the results.

Keywords: dupilumab; bullous pemphigoid; biologics; systematic review; meta-analysis.

Dissemination plans: Not yet.

Contributions of each author:

Author 1 - Lu Liu - Author 1 screened data and drafted the manuscript.
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Author 3 - Xin Huang - Author 3 searched studies and screened data.
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