INPLASY PROTOCOL

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None declared.

Anti-Vascular Endothelial Growth Factor (anti-VEGF) for Diabetic Macular Edema (DME): A Systematic Review and Network Meta-analysis

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Review question / Objective: **To assess the efficacy and safety of anti-VEGF for DME, to explore how big the differences are between the relevant options.**
Condition being studied: **Diabetic Macular Edema (DME).**
Information sources: **Databases of Medline, EMBASE, Cochrane Library, Web of Science, CBM, Wanfang, CNKI, and VIP.**
Main outcome(s): **Best-corrected Visual Acuity (BCVA) mean change from baseline; Proportion of participants with at least 15 ETDRS letters (3 ETDRS lines or 0.3 logMAR).**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 05 June 2021 and was last updated on 05 June 2021 (registration number INPLASY202160009).

INTRODUCTION

Review question / Objective: **To assess the efficacy and safety of anti-VEGF for DME, to explore how big the differences are between the relevant options.**

Condition being studied: **Diabetic Macular Edema (DME).**

METHODS

Search strategy: **A systematic search in the databases of Medline, EMBASE, Cochrane Library, Web of Science, CBM, Wanfang,**

CNKI, and VIP were conducted in literatures published from inception to November 2020 without limitations on date/time, language, or document type.

Participant or population: A systematic search in the databases of Medline, EMBASE, Cochrane Library, Web of Science, CBM, Wanfang, CNKI, and VIP were conducted in literatures published from inception to November 2020 without limitations on date/time, language, or document type.

Intervention: All anti-VEGF drugs (DME indication approved), including aflibercept, ranibizumab, and conbercept; To supplement the analysis and increase the available indirect information in the network we also considered the following interventions: bevacizumab, laser, dexamethasone implant, and placebo (sham injection or sham laser) as eligible. Mono therapy; no limitation on dosage, frequency, time, method of administration, treatment duration.

Comparator: All anti-VEGF drugs (DME indication approved), including aflibercept, ranibizumab, and conbercept; To supplement the analysis and increase the available indirect information in the network we also considered the following interventions: bevacizumab, laser, dexamethasone implant, and placebo (sham injection or sham laser) as eligible. Mono therapy; no limitation on dosage, frequency, time, method of administration, treatment duration.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: Exclusion criteria: Literatures not reported in English or Chinese; Literatures only available with abstract without full reports; Literatures without peer review (e.g. thesis); If multiple publications were reported for the same trial or included the same or overlapping patient groups, only publications with available data of targeted outcomes or with largest sample size will be included.

Information sources: Databases of Medline, EMBASE, Cochrane Library, Web of Science, CBM, Wanfang, CNKI, and VIP.

Main outcome(s): Best-corrected Visual Acuity (BCVA) mean change from baseline; Proportion of participants with at least 15 ETDRS letters (3 ETDRS lines or 0.3 logMAR).

Additional outcome(s): Proportion of participants with at least 10 ETDRS letters (2 ETDRS lines or 0.2 logMAR); Mean change in central retinal thickness (CRT) from baseline; Proportion of patients with complete disappearance of retinal edema after treatment; Quality of life; Adverse events (serious; ocular; systemic); Number of injections.

Data management: For each study, the following information will be extracted into Excel by two authors independently: the first author's name, the published year, country, center, diagnosis, diagnostic criteria, clinical stage, inclusion criteria, exclusion criteria, sample sizes, sex and age of patients, baseline VA, baseline CRT, duration of diabetes, history of hypertension, history of smoking, other biochemical indexes (HbA1c, blood pressure, blood lipid), time of follow-up, intervention, dosage of intervention, pre-defined outcomes and results data. Disagreements will be resolved by discussion, with assistance from a third party if necessary.

Quality assessment / Risk of bias analysis: Two authors will independently assess the risk of bias in the included RCTs. Seven domains of the Cochrane 'Risk of Bias' tool will be evaluated, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. Disagreements will be resolved by discussion, with assistance from a third party if necessary.

Strategy of data synthesis: A Bayesian network meta-analysis will be performed

by R software. The pooled estimation and the probability of which drug is the best was obtained by the Markov Chains Monte Carlo method. The model convergence will be assessed by trace plots and Brooks-Gelman-Rubin plots. The results of dichotomous outcomes will be reported as odds ratio (OR) and its 95% credible intervals (CrIs); the results of continuous outcomes will be reported as mean difference (MD) and its 95% CrIs. Evidence inconsistency and clinical similarity in patient characteristics and settings across trials will be carefully assessed. Network geometry used nodes to represent different interventions and edges to represent the head-to-head comparisons between interventions. The size of nodes and thickness of edges will be associated with sample sizes of intervention and numbers of included trials, respectively.

Subgroup analysis: Low vision versus non-low vision (low vision defined as less than 20/40, [or less than 0.5 (decimal); more than 0.3 (LogMAR); less than 70 or 73 letters]). Treatment naïve versus previously treated.

Sensitivity analysis: None.

Language: No language limitation on the search. Records with language other than in English or Chinese were excluded when screening.

Country(ies) involved: China.

Keywords: Diabetic macular edema; anti-vascular endothelial growth factor; network meta-analysis.

Contributions of each author:
Author 1 - Kun Liu - drafted and revised the protocol.
Author 2 - Jing Wu - drafted and revised the protocol.
Author 3 - Xiaoning He - drafted the protocol.
Author 4 - Jia Liu - drafted the protocol.
Author 5 - Fang Qi - drafted the protocol.