INPLASY PROTOCOL

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Conflicts of interest:
All authors report no conflicts of interest in this study.

Effect of Febuxostat on Blood Pressure in Hyperuricemic Patients: A protocol for a systematic review and Meta-analysis

Yao, J[1]; Shi, X[2]; Fan, S[3]; Gao, Y[4]; Hu, H[5]; Wang, PP[6]; Chen, Q[7].

Review question / Objective: **Whether febuxostat could reduce systolic blood pressure in hyperuricemic patients? Whether febuxostat could reduce diastolic blood pressure in hyperuricemic patients? Whether febuxostat could reduce the serum creatinine level in hyperuricemic patients? Whether febuxostat could reduce the eGFR in hyperuricemic patients?**
Condition being studied: **In recent years, a series of RCTs have been conducted to clarify whether febuxostat could also lower blood pressure or influence the natural history of hypertension. However, results of these RCTs remain controversial with some studies reported positive results, others found it had no significant effect. A systematic review and meta-analysis would be appropriate to resolve the current controversy and reach a conclusive result. Thus, the aim of this systematic review and meta-analysis was to evaluate the effect of febuxostat on BP in hyperuricemic patients. And such a study may find a new therapeutic option, that of control of a biochemical cause of hypertension.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 May 2020 and was last updated on 09 May 2020 (registration number INPLASY202050031).

INTRODUCTION

Review question / Objective: **Whether febuxostat could reduce systolic blood pressure in hyperuricemic patients? Whether febuxostat could reduce diastolic blood pressure in hyperuricemic patients? Whether febuxostat could reduce the serum creatinine level in hyperuricemic patients? Whether febuxostat could reduce the eGFR in hyperuricemic patients?**

Rationale: **Increasing evidence connects serum uric acid (sUA) with hypertension. Previous studies on the efficacy of febuxostat on blood pressure (BP) in hyperuricemic patients have provided conflicting results. Thus, we aimed to**

perform a systematic review and meta-analysis to investigate the efficacy of febuxostat on BP.

Condition being studied: In recent years, a series of RCTs have been conducted to clarify whether febuxostat could also lower blood pressure or influence the natural history of hypertension. However, results of these RCTs remain controversial with some studies reported positive results, others found it had no significant effect. A systematic review and meta-analysis would be appropriate to resolve the current controversy and reach a conclusive result. Thus, the aim of this systematic review and meta-analysis was to evaluate the effect of febuxostat on BP in hyperuricemic patients. And such a study may find a new therapeutic option, that of control of a biochemical cause of hypertension.

METHODS

Search strategy: Databases including Medline, the Cochrane Library, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) will be searched.

Participant or population: Participants have a diagnosis of hyperuricemia or the diagnosis of gout based on the preliminary or updated ACR criteria, with or without hypertension.

Intervention: A febuxostat group. Any dose, dosing regimen was allowed.

Comparator: A control group.

Study designs to be included: RCTs.

Eligibility criteria: i) RCTs with any follow-up duration and sample size; ii) Participants studied had a diagnosis of hyperuricemia or gout based on the preliminary or updated American College of Rheumatology (ACR) criteria; iii) Febuxostat should be applied in participants as an intervention at any dose. iv) Reported quantitative outcomes: the primary outcome was BP, secondary outcomes were serum UA, serum creatinine (Cr) and estimated glomerular filtration rate (eGFR).

Information sources: Databases including Medline, the Cochrane Library, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) will be searched. The ClinicalTrials.gov registry was also searched for unpublished trials and authors were contacted for additional information if necessary. Relevant references from included studies were sought to retrieve additional eligible studies. No limits were set on language, publication date and type.

Main outcome(s): Blood pressure.

Additional outcome(s): Serum UA, serum creatinine (Cr) and estimated glomerular filtration rate (eGFR).

Data management: Relevant data extraction will be performed by two researchers (JY and XYS) independently, and the third researcher (SMF) will be involved in a discussion for any disagreements. The following information of eligible articles will be extracted to a prepared data extraction form: author, year of publication, country of origin of the population studied, study design, sample size, duration, health status, mean age, number of males, doses of febuxostat, comorbid conditions, intervention, and outcomes. If raw data will not be directly provided in the text or tables, figures in the study would be referred to. Once relevant details will be insufficiently reported in studies, authors will be contacted by e-mails and the ClinicalTrials.gov register will be searched for further information.

Quality assessment / Risk of bias analysis: According to the Cochrane collaboration's update tool for assessing the risk of bias (Version 5.1.0),[21] two reviewers (JY and XYS) will assess the quality of the studies independently, and the third researcher (SMF) will be consulted for any disagreements. The risk of bias will be classified as low, unclear, or high risk by evaluating the 7 components as random sequence generation, allocation

concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other bias. If necessary, we will try to e-mail the authors for extra information.

Strategy of data synthesis: Stata 12.0 software will be used for statistical analysis. Dichotomous data will be expressed as the odds ratio (OR) with a 95% confidence interval (CI), and continuous data will be presented as the mean difference (MD) with 95% CI. P<0.05 will be considered to indicate a statistically significant result.

Subgroup analysis: Subgroup analysis will be performed to explore the differences in the methodologic quality, race/ethnicity, sample size, and duration.

Sensibility analysis: Sensitivity analysis will be used to observe changes in the pooled effect size and heterogeneity between included studies, to assess the reliability and stability of the pooled results.

Language: No language limits will be imposed on the search.

Country(ies) involved: China.

Keywords: Febuxostat, blood pressure, hypertension, chronic kidney disease, meta-analysis.

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