INPLASY PROTOCOL

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None declared.

The Efficacy and Safety of Roxadustatfor Anemia in Patients With ChronicQ2 Kidney Disease: A Meta-Analysis

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Review question / Objective: **Chronic kidney disease (CKD) is a global public health problem, and anemia is a common complication in CKD patients. Roxadustat (FG-4592) is an oral hypoxiainducible factor (HIF) stabilizer. Roxadustat has been shown in studies to keep up with and increase hemoglobin better than placebo or erythropoietin. The purpose of this metaanalysis was to assess the efficacy and safety of roxadustat.**

Information sources: **Using a standardized form, two reviewers (Lijun Wang and Heng Yin) independently retrieved data from original trial reports. Data extracted included study characteristics (first author, publication year, single or multicenter, sample size, intervention and control, treatment period and duration of follow-up), patient characteristics (inclusion criteria, background treatments, mean age, proportion of men, baseline weight, and baseline Hb levels), reported outcomes (Hb, transferrin, hepcidin, ferritin, TSAT, AEs and SAEs), and methodology information.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 April 2022 and was last updated on 12 April 2022 (registration number INPLASY202240068).

INTRODUCTION

Review question / Objective: **Chronic kidney disease (CKD) is a global public health problem, and anemia is a common complication in CKD patients. Roxadustat (FG-4592) is an oral hypoxiainducible factor (HIF) stabilizer. Roxadustat has been shown in studies to keep up with and increase hemoglobin better than placebo or erythropoietin. The purpose of this metaanalysis was to assess the efficacy and safety of roxadustat.**

Condition being studied: **Renal anemia is a common complication in patients with**

CKD. Renal anemia has long been thought to be an independent risk factor that affects CKD patients' prognoses and increases their risk of cardiovascular complications and death. The incidence of anemia in the young and middle-aged nondialysis population with chronic kidney disease stages 3 to 5 is 28%, while the incidence of anemia in the young and middle-aged dialysis population with chronic kidney disease stage 5 is 53.9 %. The incidence of anemia in the elderly nondialysis population with chronic kidney disease stage 5 is as high as 72.8 %; among those getting dialysis, the incidence is significantly greater. In China, the prevalence of renal anemia is significant, but awareness, treatment, and compliance rates are poor. Failure to achieve standard Hb levels in both dialysis and nondialysis CKD patients will accelerate the progression of CKD.Current phase I, II, and III clinical trial findings for the new oral medication, hypoxia-inducible factor prolyl hydroxylase inhibitor (HIFPHI) roxadustat, suggest that themedicine can cure renal anemia.Despite the fact that various clinical trials and meta-analyses on the clinical effectiveness of roxadustat have been conducted in China and elsewhere, the results of the meta-analyses were inconsistent. We conducted a systematic analysis of published randomized controlled trials to assess the safety and efficacy of roxadustat for the treatment of renal anemia in patients with chronic kidney disease, as well as to offer evidence-based medical evidence for clinical management.

METHODS

Search strategy: We searched PubMed, Embase, Cochrane Library, Web of Science, SinoMed, China National Knowledge Infrastructure, WanFang, and VIP Information databases for clinical studies examining roxadustat for anemia in CKD patients. The search phrases were "roxadustat," "FG-4592," "anemia," "chronic kidney disease," "CKD," and "kidney disease." We also searched ClinicalTrials.gov and the references in selected papers and reviews for additional relevant material.

Participant or population: The individuals with chronic kidney disease anemia who were included in the study met the following criteria: ≥18 years old; CKD 3-5, in accordance with World Health Organization (WHO) anemic diagnostic criteria. Accept or refuse dialysis; Receiving maintenance hemodialysis three times a week for 12 weeks or longer; Before joining the trial, the HIF-PHIs preparation roxadustat was not used; gender, race, and area are not restricted.

Intervention: ≥18 years old; CKD 3-5, in accordance with World Health Organization (WHO) anemic diagnostic criteria. Accept or refuse dialysis; Receiving maintenance hemodialysis three times a week for 12 weeks or longer; Before joining the trial, the HIF-PHIs preparation roxadustat was not used; gender, race, and area are not restricted.Medications received include: Roxadustat.

Comparator: ≥18 years old; CKD 3-5, in accordance with World Health Organization (WHO) anemic diagnostic criteria. Accept or refuse dialysis;Receiving maintenance hemodialysis three times a week for 12 weeks or longer; Before joining the trial, the HIF-PHIs preparation roxadustat was not used; gender, race, and area are not restricted.Medications received include:1. Placebo; 2. Erythropoietin(EPO)or Epoetin alfa; 3.Darbepoetin alfa(DA).

Study designs to be included: RCT.

Eligibility criteria: (1)The individuals with chronic kidney disease anemia who were included in the study met the following criteria: ≥18 years old; CKD 3-5, in accordance with World Health Organization (WHO) anemic diagnostic criteria. Accept or refuse dialysis; Receiving maintenance hemodialysis three times a week for 12 weeks or longer; Before joining the trial, the HIF-PHIs preparation roxadustat was not used; gender, race, and area are not restricted. Randomized controlled studies, both published and unpublished.(2)

Intervention measures: ①Experimental group: Roxadustat; ②Control group: 1. Placebo; 2. Erythropoietin(EPO)or Epoetin alfa;3.Darbepoetin alfa(DA).(3) Outcome indicators: main indicators: the change of the average (Hb, Iron, transferrin, hepcidin, ferritin, TSAT)levels from baseline to the end, serious adverse events, adverse events.

Information sources: Using a standardized form, two reviewers (Lijun Wang and Heng Yin) independently retrieved data from original trial reports. Data extracted included study characteristics (first author, publication year, single or multicenter, sample size, intervention and control, treatment period and duration of follow-up), patient characteristics (inclusion criteria, background treatments, mean age, proportion of men, baseline weight, and baseline Hb levels), reported outcomes (Hb, transferrin, hepcidin, ferritin, TSAT, AEs and SAEs), and methodology information.

Main outcome(s): The change of the average (Hb, Iron, transferrin, hepcidin, ferritin, TSAT)levels from baseline to the end, serious adverse events, adverse events.

Quality assessment / Risk of bias analysis: Two reviewers independently reviewed the literature using the inclusion and exclusion criteria, and the included papers were appraised using the RCT quality evaluation criteria. When a disagreement arises throughout the screening and assessment process, it will be discussed, mediated, and resolved with the help of a third party.The Cochrane Collaboration's tool was used to assess the risk of bias in RCTs. The assessments were conducted separately by two investigators; disagreements were reviewed with a third party and resolved by consensus. Furthermore, the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework was used to assess the quality of evidence contributing to each estimate, which characterizes the quality of a body of evidence for the primary outcomes based on study limitations, imprecision, inconsistency, indirectness, and publication bias.

Strategy of data synthesis: Use RevMan5.3 program to do Meta analysis on all RCT data that satisfy the requirement, choose relative risk (Risk Ratio, RR) and its 95 % confidence interval (Confidence Interval, CI) to represent binary variables, and choose standard mean. Continuous variables are described using the Standardized Mean Difference (SMD) and its 95 % confidence interval (CI). Sensitivity analysis assesses heterogeneity changes using an alternative analysis of the random effects model and the fixed effects model, and it summarizes the results' stability.The χ^2 test was employed to examine the study heterogeneity. Use I^2 and P to undertake a quantitative study of the collected literature's statistical heterogeneity. If $I^2<50\%$, it means that there is statistical homogeneity among the studies, and the fixed-effects model is used in the result analysis; if $I^2\geq50\%$, it means that there is statistical heterogeneity among the studies, and the source of the heterogeneity will be further investigated, and subgroup analysis will be performed based on the factors that may cause the heterogeneity. The random effects model is employed for analysis in studies that still cannot remove statistical heterogeneity and have no clear clinical heterogeneity, and the difference is statistically significant with $P<0.05$.

Subgroup analysis: We conducted separate subgroup analyses for outcome indicators with significant heterogeneity by area and control group, although heterogeneity remains due to the small number of included studies.

Sensitivity analysis: None.

Country(ies) involved: China.

Keywords: Anemia, chronic kidney disease, meta-analysis, roxadustat, CKD, FG-4592.

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