INPLASY PROTOCOL

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None declared.

Effect of tumor necrosis factor inhibitors on the risk of adverse cardiovascular events in patients with psoriasis

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Review question / Objective: **Previous studies have indicated a cardioprotective effect of tumor necrosis factor inhibitor (TNFi) therapy in adult patients with psoriasis (Pso). However, most were retrospective studies, and the association between cardiometabolic comorbidities and major adverse cardiovascular events (MACE) has not been validated in randomized controlled trials (RCTs).**
Condition being studied: **Because the available evidence has recently increased, we performed the present updated meta-analysis and meta-regression of cohort studies and RCTs to evaluate whether TNFi therapy can decrease the risk of MACE among patients with Pso and to assess the associations between cardiometabolic comorbidities and MACE.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 August 2022 and was last updated on 23 August 2022 (registration number INPLASY202280090).

INTRODUCTION

Review question / Objective: **Previous studies have indicated a cardioprotective effect of tumor necrosis factor inhibitor (TNFi) therapy in adult patients with psoriasis (Pso). However, most were retrospective studies, and the association between cardiometabolic comorbidities and major adverse cardiovascular events (MACE) has not been validated in randomized controlled trials (RCTs).**

Rationale: **Psoriasis (Pso) is a chronic inflammatory skin disorder with a prevalence of 0.5% to 11.4%, and it affects nearly 60 million adults and children worldwide. Pso is mainly characterized by dry, round, erythematous, and scaly patches on the skin. It often affects patients' daily activities and sleep, significantly reducing their quality of life. Pso has been identified as a multiple-system inflammatory disease with several comorbidities. Pso shares several risk**

factors with cardiovascular disease (CVD), such as hypertension, metabolic syndrome (MS), smoking, and diabetes. Several studies have shown that patients with Pso have an increased risk of CVD. The effect of tumor necrosis factor inhibitor (TNFi) therapy on major adverse cardiovascular events (MACE) is controversial.

Condition being studied: Because the available evidence has recently increased, we performed the present updated meta-analysis and meta-regression of cohort studies and RCTs to evaluate whether TNFi therapy can decrease the risk of MACE among patients with Pso and to assess the associations between cardiometabolic comorbidities and MACE.

METHODS

Search strategy: We searched MEDLINE (source, PubMed from January 2005 to July 31, 2022), EMBASE (January 2005 to July 2022), the Cochrane Central Register of Controlled Trials (to July 31, 2022), Google Scholar (to July 31, 2022), SinoMed (to July 31, 2022), and the ClinicalTrials.gov website (to July 31, 2022) using the terms "psoriasis," "psoriatic arthritis," "TNF inhibitor," "infliximab," "etanercept," "adalimumab," "certolizumab," "golimumab," "placebo," "cardiovascular event," "myocardial infarction," "stroke," "mortality," "cohort study," and "randomized controlled trial." No language restrictions were applied.

Participant or population: (1) included patients aged ≥18 years; (2) included patients diagnosed with Pso or psoriatic arthritis.

Intervention: Interventions in the TNFi group consisted of TNFi agents, including infliximab, etanercept, adalimumab, certolizumab, or golimumab.

Comparator: (4) interventions in the control group consisted of non-biologics.

Study designs to be included: The study had a observational design and included at least 1,000 patients, or a RCT design with at least one case of MACE.randomized clinical study or cohort study

Eligibility criteria: Exclusion criteria were as follows: (1) patients hospitalized for CVD (MI, stroke, acute coronary syndrome, or heart failure) within 12 months before admission; (2) patients with HIV/AIDS, a malignancy other than nonmelanoma skin cancer, end-stage renal disease, or treatment by dialysis or renal transplantation; (3) single-arm studies; (4) no primary outcome; (5) animal studies, case reports, or reviews; and (6) duplication of data.

Information sources: We searched MEDLINE (source, PubMed from January 2005 to July 31, 2022), EMBASE (January 2005 to July 2022), the Cochrane Central Register of Controlled Trials (to July 31, 2022), Google Scholar (to July 31, 2022), SinoMed (to July 31, 2022), and the ClinicalTrials.gov website (to July 31, 2022).

Main outcome(s): The primary outcome was the occurrence of MACE (composite rate of MI, stroke, and cardiovascular mortality).

Additional outcome(s): The secondary outcomes were the rates of MI, stroke, and cardiovascular mortality, respectively.

Data management: The data analysis was completed by three reviewers (L.P., L.L., and Q.S.B.). The pooled RR for dichotomous outcomes was calculated with its 95% CI. Heterogeneity was assessed by the I2 statistic and the chi-squared test. I2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high levels of heterogeneity, respectively [18]. For outcomes with significant heterogeneity, a random-effects model was used [18]; for all others, a fixed-effects model was used [18]. Publication bias was tested using a funnel plot with Begg's test and Egger's test (P for significant asymmetry < 0.1) [19]. Furthermore, a sensitivity analysis was performed by eliminating one study at a time to evaluate the influence of each trial

on the primary outcome (MACE) and the robustness of the result.

Quality assessment / Risk of bias analysis: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [15] to perform the quality evaluation. Two reviewers (L.L. and Q.S.B.) assessed the quality of the selected RCTs. The components used for quality assessment were the methods used for random sequence generation, allocation concealment, blinding of the outcome assessment, and selective outcome reporting [16]. Additionally, two reviewers evaluated the methodological quality using the Newcastle–Ottawa scale (NOS) [17]. The NOS scale score ranges from 0 to 9 and uses eight criteria that cover three components: patient selection, study group comparability, and outcome assessment. Studies with an NOS score of ≥6 were considered "high quality," while those with a score of <6 were considered "low quality."

Strategy of data synthesis: The data analysis was completed by three reviewers (L.P., L.L., and Q.S.B.). The pooled RR for dichotomous outcomes was calculated with its 95% CI. Heterogeneity was assessed by the I2 statistic and the chi-squared test. I2 values of 25%, 50%, and 75% were considered to indicate low, moderate, and high levels of heterogeneity, respectively [18]. For outcomes with significant heterogeneity, a random-effects model was used [18]; for all others, a fixed-effects model was used.

Subgroup analysis: The studies were divided into two subgroups according to the study design: RCTs and cohort studies. The studies were further classified into subgroups based on their baseline clinical factors: sample size (<22,225 or ≥22,225 patients), age (<49.1 or ≥49.1 years), proportion of men (<55.0% or ≥55.0%), proportion of current smokers (<31.5% or ≥31.5%), proportion of patients with hypertension (<35.7% or ≥35.7%), proportion of patients with diabetes (<13.1% or ≥13.1%), proportion of patients with hyperlipidemia (<23.6% or ≥23.6%), and follow-up period (<28.7 or ≥28.7 months). Finally, the studies were divided into subgroups based on the treatment in the control group: topical/phototherapy, methotrexate, or placebo.

Sensitivity analysis: Furthermore, a sensitivity analysis was performed by eliminating one study at a time to evaluate the influence of each trial on the primary outcome (MACE) and the robustness of the result.

Language restriction: No.

Country(ies) involved: China.

Keywords: Psoriasis; Tumor necrosis factor inhibitor; Major adverse cardiovascular events; Meta-analysis.

Contributions of each author:

Author 1 - Peng Li analyzed the data and wrote the manuscript.
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