INPLASY PROTOCOL

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Corresponding author:
Tong Zhang

tom611@126.com

Author Affiliation:
School of Rehabilitation Medicine, Capital Medical University.

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TNF alpha antagonists improve oxidative stress and atherosclerosis induced by rheumatoid arthritis

Wang, J[1]; Wang, CC[2]; Fu, HJ[3]; Liu, ZZ[4]; Zhang, YM[5]; Zhang, T[6].

Review question / Objective: **Carotid artery intima- medial thickness is well-established marker for atherosclerosis, which accounts for 30–40% of excess mortality in rheumatoid arthritis patients. Our objective was to determine whether anti-TNF-α agents has a beneficial effect on oxidative stress and atherosclerosis in rheumatoid arthritis.**
Eligibility criteria: **Studies were considered eligible if they were randomized clinical trials, observational studies, compared cIMT in the "anti-TNF-α drug and disease-modifying anti-rheumatic drugs(DMARD)" group versus the "DMARD" group, and provided information on cIMT. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently, and inconsistencies were resolved by consensus.There were no significant differences in baseline data between the intervention and control groups in any of the studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 12 January 2023 and was last updated on 12 January 2023 (registration number INPLASY202310033).

INTRODUCTION

Review question / Objective: **Carotid artery intima- medial thickness is well-established marker for atherosclerosis, which accounts for 30–40% of excess mortality in rheumatoid arthritis patients. Our objective was to determine whether anti-TNF-α agents has a beneficial effect on oxidative stress and atherosclerosis in rheumatoid arthritis.**

Rationale: **We searched the PubMed, Embase, EBSCO, Web of Science, and Cochrane Controlled Register of Trials databases from inception to September 2022 for studies. The intervention groups received Anti-TNF-α agents and disease-modifying anti-rheumatic drugs; the control**

groups only received disease-modifying anti-rheumatic drugs. After the literature had been selected and extracted, RevMan 5.3 software was used for the meta-analysis. Data were screened and extracted independently by 2 authors.

Condition being studied: Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease predisposing to atherosclerosis. And it plays a major role in the pathogenesis of atherosclerosis which is characterized by increased mortality. RA is characterized by an inflammatory syndrome leading to a significant risk of atherosclerosis, as assessed by carotid artery intima-media thickness (cIMT). Rheumatoid arthritis causes an increased risk of cardiovascular disease and death. Classic cardiovascular risk factors, including smoking, high blood pressure, dyslipidemia, insulin resistance and diabetes, obesity, and physical inactivity, do not seem to explain the excessive cardiovascular risk of RA. A very important link between RA and cardiovascular disease is inflammation, as inflammation plays a key role in all stages of atherosclerosis: from endothelial dysfunction to plaque rupture and thrombosis. It can also affect and exacerbate some traditional cardiovascular risk factors, such as dyslipidemia, obesity and insulin resistance. To date, the exact pathophysiological mechanisms of this relationship between cardiovascular disease and rheumatoid arthritis are not fully understood. Therefore this study was required to dissect the relationship between anti-TNF-α therapy, cIMT and cardiovascular events, in order to provide certain help to doctors in clinical drug selection.

METHODS

Search strategy: A literature search was performed in September 2022 without restriction of language, region, or publication type. The databases of MEDLINE, EMBASE, PubMed, CINAHL, Bandolier, and the Cochrane Controlled Register of Trials were searched from their inception to September 2022 by two of the authors(Congcong Wang and Hongjuan Fu) using the string ("carotid artery intima-media thickness" OR "intima-media thickness" OR "IMT") AND ("rheumatoid arthritis") AND ("infliximab" OR "adalimumab" OR "etanercept" OR "certolizumab" OR "golimumab" OR "anti TNF"). When multiple similar reports were published, the most recent report was used. And inconsistencies were resolved by consensus.

Participant or population: Patients with rheumatoid arthritis, and provided information on cIMT.

Intervention: "anti-TNF-α drug and disease-modifying anti-rheumatic drugs(DMARD)" group versus the "DMARD"group.

Comparator: anti-TNF-α drug

Study designs to be included: We searched the PubMed, Embase, EBSCO, Web of Science, and Cochrane Controlled Register of Trials databases from inception to September 2022 for studies. The intervention groups received Anti-TNF-α agents and disease-modifying anti-rheumatic drugs; the control groups only received disease-modifying anti-rheumatic drugs. After the literature had been selected and extracted, RevMan 5.3 software was used for the meta-analysis. Data were screened and extracted independently by 2 authors.

Eligibility criteria: Studies were considered eligible if they were randomized clinical trials, observational studies, compared cIMT in the "anti-TNF-α drug and disease-modifying anti-rheumatic drugs(DMARD)" group versus the "DMARD" group, and provided information on cIMT. Full texts were sourced for relevant articles. Inclusion criteria were assessed independently, and inconsistencies were resolved by consensus.There were no significant differences in baseline data between the intervention and control groups in any of the studies.

Information sources: A literature search was performed in September 2022 without

restriction of language, region, or publication type. The databases of MEDLINE, EMBASE, PubMed, CINAHL, Bandolier, and the Cochrane Controlled Register of Trials were searched from their inception to September 2022 by two of the authors(Congcong Wang and Hongjuan Fu) using the string ("carotid artery intima-media thickness" OR "intima-media thickness" OR "IMT") AND ("rheumatoid arthritis") AND ("infliximab" OR "adalimumab" OR "etanercept" OR "certolizumab" OR "golimumab" OR "anti TNF"). When multiple similar reports were published, the most recent report was used. And inconsistencies were resolved by consensus.

Main outcome(s): Six observational studies that had enrolled a total of 249 patients were included in the meta-analysis. After medical treatment, the carotid artery intima-media thickness was different between the intervention groups and control groups(P < 0.05, WMD = –0.08, 95% CI = –0.11 to –0.05, I2 = 32%). In subgroup analyses, the carotid artery intima-media thickness was significantly different(P < 0.05, WMD = –0.09, 95% CI = –0.12 to –0.06, I2 = 0) in patients followed for more than 1 year; it was not different(P = 0.99, WMD = 0, 95% CI = –0.09 to 0.09, I2 = 17%) in patients followed for less than 1 year.

Quality assessment / Risk of bias analysis: Risk of Bias Assessment - We used the Cochrane risk of bias tool to assess methodological quality of eligible trials[26]. Studies were assessed on random sequence generation, allocation concealment, blinding of participants, blinded outcome assessment, completeness of outcome data and other biases. Risk of bias assessments were performed independently by 2 reviewers, and disagreements were resolved by a third reviewer.
Quality assessment and statistical analysis - The quality of the studies were quantified using the Newcastle–Ottawa quality assessment scale(NOS), which consists of three parts: patient selection, comparability of the study groups, and assessment of outcomes.

Strategy of data synthesis: Review Manager 5.3 was used for the meta-analysis. The weighted mean difference (WMD) and 95% confidence interval (CI) were used to estimate the overall pooled effect for continuous data in each study. The relative risk and 95% CI were used to evaluate the dichotomous data. If heterogeneity was significant (P ≤ 0.05), a random-effects model was used. If heterogeneity was not significant (P > 0.05), a fixed-effects model was used.

Subgroup analysis: In the subgroup analysis of the effect of anti-TNF-α on cIMT, the cIMT showed a significant difference between the intervention and control groups in studies with more than 1 year of follow-up (P < 0.05, WMD = –0.09, 95% CI = –0.12 to –0.06, I2 = 0, fixed-effects model), and not in studies with less than 1 year of follow-up (P =0.27, WMD = 0, 95% CI = –0.09 to –0.09, I2 = 17%, fixed-effects model).

Sensitivity analysis: Considering that the existence of publication bias would affect the results of meta-analysis, we used funnel plot to test this bias in the analysis. Meta-analysis funnel plot of the included studies showed left-right symmetry , indicating no publication bias.

Language restriction: None.

Country(ies) involved: China (School of Rehabilitation Medicine, Capital Medical University).

Keywords: Keywords: rheumatoid arthritis, intima-media thickness, atherosclerosis, TNF-α, meta-analysis.

Contributions of each author:
Author 1 - Jun Wang - Conceptualization.
Email: abcd2878@126.com
Author 2 - Congcong Wang - Data curation; Funding acquisition; Writing–review & editing.
Email: 1413138161@qq.com
Author 3 - Hongjuan Fu - Funding acquisition; Methodology.
Email: 748661050@qq.com

Author 4 - Zezhong Liu - Project administration; Supervision.
Email: liuzezhong02@qq.com
Author 5 - Yimin Zhang - Supervision.
Email: rmyyzhangyimin@wfmc.edu.cn
Author 6 - Tong Zhang - Writing–review & editing.
Email: tom611@126.com

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