INPLASY PROTOCOL

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None declared.

Effect of tumor necrosis factor inhibiting treatment on arterial stiffness and arterial wall thickness in rheumatoid arthritis patients: protocol for a systematic review and planned meta-analysis

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Review question / Objective: **The aim of this systematic review is to evaluate the effect of TNF inhibiting treatment on arterial stiffness (as measured with pulse wave velocity and augmentation index) and arterial wall thickness (as measured with carotid intima media thickness) in rheumatoid arthritis patients.**
Condition being studied: **Rheumatoid arthritis is a chronic autoimmune disorder, which affects approximately 1% of the population worldwide.**
Information sources: **The following electronic databases will be searched for potentially eligible studies: EMBASE, MEDLINE, ClinicalTrials.gov and WHO International Clinical Trials Registry Platform. For the studies identified as eligible for inclusion, similarity tracking will be used to identify more potentially relevant articles with the 'related article' feature in PubMed. In addition, a citation search will be performed for included studies to identify articles that have cited them. Reference lists of the included studies and previous reviews on the subject will be searched for potentially relevant studies. ResearchGate profiles of top authors on the subject will be investigated to identify potentially relevant data points. For ongoing or finished studies that are potentially eligible, but without a publication, study authors will be contacted for information. When additional information is needed, study authors will be contacted as well.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 January 2022 and was last updated on 28 January 2022 (registration number INPLASY202210131).

INTRODUCTION

Review question / Objective: **The aim of this systematic review is to evaluate the effect of TNF inhibiting treatment on arterial stiffness (as measured with pulse wave velocity and augmentation index) and arterial wall thickness (as measured with**

carotid intima media thickness) in rheumatoid arthritis patients.

Condition being studied: Rheumatoid arthritis is a chronic autoimmune disorder, which affects approximately 1% of the population worldwide.

METHODS

Participant or population: We will include studies of participants diagnosed with rheumatoid arthritis. At least 80% of the study population need to be rheumatoid arthritis patients.

Intervention: Any intervention or combination of interventions that includes TNF inhibiting treatment. Any dosage and duration of the TNF inhibiting treatment is allowed. Patients need to be starting with the intervention directly after the baseline visit, or in case of follow-up of at least 12 months, no later than 3 months after the baseline visit. Studies with and without comparative treatment are included. At least 80% of the patients need to receive TNF inhibiting treatment.

Comparator: Not applicable.

Study designs to be included: Clinical trials (whether or not randomized or controlled) and observational studies are eligible. Case-control studies, case series and case reports are excluded, as these have high potential for bias. Cross-sectional studies comparing outcomes at only one timepoint are excluded. There will be no restriction on language. There will be no restriction on publication type, effort will be made to also search for unpublished materials and abstracts. Abstract will only be included if sufficient data are available to evaluate study eligibility.

Eligibility criteria: Participants: We will include studies of participants diagnosed with rheumatoid arthritis. At least 80% of the study population need to be rheumatoid arthritis patients. Intervention and comparators: Any intervention or combination of interventions that includes TNF inhibiting treatment. Any dosage and duration of the TNF inhibiting treatment is allowed. Patients need to be starting with the intervention directly after the baseline visit, or in case of follow-up ≥ 12 months no later than 3 months after the baseline visit. Studies with and without comparative treatment are included. At least 80% of the patients need to receive TNF inhibiting treatment. Outcomes: Studies assessing data on pulse wave velocity, augmentation index and/or carotid intima media thickness. Studies not providing longitudinal data (pre-post treatment values or change over time) of the outcome are excluded. For PWV and AIx, all measurements sites are allowed (e.g. carotid-femoral PWV, carotid-radial or brachial PWV, brachial-ankle PWV, invasive aortic PWV, radial AIx, carotid AIx) and all measurement methods are allowed (e.g. applanation tonometry, MRI). For IMT only carotid ultrasound measurements will be allowed.

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Main outcome(s): Pulse wave velocity, augmentation index and carotid intima media thickness, measured longitudinally (pre-post treatment values or change over time). For PWV and AIx, all measurements

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Quality assessment / Risk of bias analysis: Risk of bias of all included studies will be assessed using the Downs & Black checklist by two authors independently. In case of discrepancies, differences will be discussed until consensus is reached, or whenever necessary, a third author will be consulted. Consensus meetings will be performed in which the criteria will be discussed and applied to several articles.

Strategy of data synthesis: The findings of the included studies will be textually described and tabulated, grouped on outcome measure. Relationships within and between studies will be explored, special attention will be paid to the duration of the intervention, different types of TNF inhibitors and comedication. For narrative synthesis, both results of (primary aim) studies investigating the differences in arterial stiffness and arterial wall thickness over time in the same group of patients, and (secondary aim) studies investigating differences over time between TNF inhibitors and other treatment strategies (control groups) will be used. When appropriate, meta-analysis will be performed on the studies investigating the differences over time in the same group of patients (primary aim). Summary statistics will be combined, resulting in a weighted mean difference before and after treatment. Studies are weighted in inverse proportion to their variance, so that essentially more weight is given to studies with larger sample sizes and less weight to smaller studies. A random-effects model will be used to allow for both within studies variance and between-study variance, by weighting studies using a combination of their own variance (like described above) and the between-study variance. We think this is necessary because we do not expect a single effect across the studies because of differences in TNF inhibitor used, treatment duration and comedication. Results of meta-analysis will be reported using forest plots.

Subgroup analysis: Meta-analysis will be performed separately for the three different outcome measures and separate for short and long-term effects if samples size allows this. Only when the number of studies allow further subgroup analysis, we will investigate differences in TNF inhibitor used and comedication.

Sensitivity analysis: A fixed-effects model will also be run to investigate differences of the two models and test robustness of the choice of statistical model.

Language: No restrictions on language.

Country(ies) involved: Netherlands.

Keywords: rheumatoid arthritis; intima media thickness; pulse wave velocity; augmentation index; arterial stiffness; TNF inhibitors.

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