INPLASY PROTOCOL

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Review Stage at time of this submission: **Piloting of the study selection process.**

Conflicts of interest:
None declared.

Therapeutic drug monitoring in the inflammatory arthritis; Which drug level should we aim for? A systematic literature review

Layegh, Z[1]; Krieckaert , CLM[2]; de Jong, PHP[3]; Wolbink, GJ[4].

Review question / Objective: **What is the minimum target serum concentration of registered TNF inhibitors needed to achieve biological and clinical effect in the inflammatoryarthritis?**
Condition being studied: **The treatment of inflammatory arthritis has evolved dramatically the past decades; more therapeutic agents have been come available and more insight in treatment strategy is gained. An increasing number of biological anti-rheumatic drugs have been introduced the past decade. Therapeutic drug monitoring (TDM) has been suggested as a clinical tool to optimize treatment with biologics in rheumatology. TDM refers to the principle of using drug serum concentrations and/or anti-drug antibodies (ADAb) to optimise treatment for an individual patient. The hypothesis is that there is a relation between dose and drug serum concentration and between concentration and therapeutic effects. However, it is unclear what the minimum drug concentration is to sustain a biological and clinical effect.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 November 2022 and was last updated on 21 November 2022 (registration number INPLASY2022110108).

INTRODUCTION

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METHODS

Participant or population: Patients diagnosed with inflammatory arthritis (rheumatoid arthritis; psoriatic arthritis and spondyloarthritis).

Intervention: Measuring serum drug levels (adalimumab, infliximab, etanercept, golimumab en certolizumab pegol) in patients with inflammatory arthritis.

Comparator: Notapplicable.

Study designs to be included: all observational studies and intervention studies.

Eligibility criteria: Inclusion criteria 1. Study designs: all observational studies and interventionstudies. 2. Studies that report serum concentration of the following TNF inhibitors adalimumab, infliximab, etanercept, golimumab en certolizumabpegol. 3. Adult patients with inflammatory arthritis; rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, and healthy volunteers. Exclusioncriteria 1. Non-humanstudies 2. Case-reports, conference abstracts, editorials 3. Papers not inEnglish 4. Not full papersavailable.

Information sources: Studies of interest will be systematically searched in different bibliographic databases; Embase, Medline ALL, Web of Science Core Collection, Cochrane Central Register of Controlled Trials and Google Scholar. To ensure a proper and high quality search for potentially relevant studies, a systematic search strategy will be conducted by one investigator together with an experienced librarian and biomedical information specialist. The search strategy will be first developed for PubMed and subsequently used in all other databases.
The main review question is disembody in to the key words to retrieve a effective search strategy as following;
- inflammatory arthritis
- TNF inhibitors; adalimumab, infliximab, etanercept, golimumab and certolizumab pegol
- minimum concentration in serum
Furthermore, to achieve a complete overview of existing literature different matching synonyms were used and search elements were combined with the Boolean operators and/OR (detailed searched strategy).
Hand-searching
Extra articles will be added to the reference list when eligible and matching the inclusion criteria. This could be the articles from the reference list of the other articles found in our search. Furthermore a list of pharmaceutical studies which are not found in our search will be added to the list, specially phase II and dose finding pharmaceutical studies from the FDA and the EMA. We will also collect information from experts opinion.

Main outcome(s): The minimum concentration of TNF inhibitors adalimumab, infliximab, etanercept, golimumab or certolizumab pegol to achieve a biologic and/or clinical effect.

Quality assessment / Risk of bias analysis: The risk of bias will be performed using different tools depending on the type of study including (PRISMA) reporting guidelines.
-RCTs : Cochrane Risk of bias 2 (Rob2) tool
- Systematic review : A MeaSurement tool
- observational (cohort and case-control) studies: the Quality In Prognosis Studies tool and Newcastle-Ottowa Scale.

Strategy of data synthesis: After search done by one of the investigators and an experienced librarian and biomedical information specialist, two reviewers independently will screen title and abstract

using endnote. Subsequently, full text reading will be done by the two reviewers. Afterwards, the list of the articles found from other references, the FDA/EMA article and the expert opinion will be added to the list. Eventually, characteristics of interest will be extracted from the full text. For the important characteristics of interest see the evidence table attached.

Subgroup analysis: We will perform subgroups analysis; The TNFi adalimumab and rheumatoid arthritis will be analyzed in subgroup. In addition, we also intent to analyze each TNFi separately.

Sensitivity analysis: Sensitivity analysis will not be performed

Language restriction: Only English.

Country(ies) involved: Netherlands.

Keywords: TDM, minimum effective drug concentrations, TNFi and inflammatory arthritis.

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