

Principal Investigator

First Name: Giovanni

Last Name: Cagnotto

Degree: MD

Primary Affiliation: Clinical Sciences Malmö, Lund University, Malmö

E-mail: cagnog@gmail.com

State or Province: Malmö

Country: Sweden

General Information

Key Personnel (other than PI):

First Name: Carl

Last name: Turesson

Degree: Medicine, MD, PhD, Professor

Primary Affiliation: Lund University, Sweden

SCOPUS ID: 6701468867

Requires Data Access? Unknown

First Name: Giovanni

Last name: Cagnotto

Degree: Medicine, MD

Primary Affiliation: Lund University, Sweden

SCOPUS ID: 55428700100

Requires Data Access? Unknown

First Name: Lennart

Last name: Jacobsson

Degree: Medicine, MD, PhD, Professor

Primary Affiliation: Sahlgrenska Akademin, Gothenburg, Sweden

SCOPUS ID: 35602323600

Requires Data Access? Unknown

First Name: Cinzia

Last name: Del Giovane

Degree: Statistics, PhD

Primary Affiliation: University of Modena and Reggio Emilia, Italy

SCOPUS ID: 35572846200

Requires Data Access? Unknown

First Name: Compagno

Last name: Michele

Degree: Medicine, MD, PhD

Primary Affiliation: Lund University

SCOPUS ID: 6603359417

Requires Data Access? Unknown

First Name: Ankita

Last name: Sharma

Degree: Microbiology, Master in Public Health

Primary Affiliation: Lund University

SCOPUS ID:

Requires Data Access? Unknown

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

https://yoda.yale.edu/wp-content/uploads/2019/12/coi_form_as.pdf
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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00269867 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment](#)
2. [NCT00207714 - A Randomized, Double-blind, Dose-ranging Trial of CNTO 148 Subcutaneous Injection Compared With Placebo in Subjects With Active Rheumatoid Arthritis Despite Treatment With Methotrexate](#)
3. [NCT00264550 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$ Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Efficacy and safety of tumor necrosis factor inhibitors (TNFi) in seronegative rheumatoid arthritis patients who are inadequate responders to csDMARDs

Narrative Summary:

Rheumatoid arthritis (RA) is chronic arthritis that is characterised by circulating autoantibodies, rheumatoid factor and anti-citrullinated protein antibodies. However, 20% of patients with RA do not have antibodies in their blood (seronegative RA). TNF inhibitors (TNFi) are an established treatment for RA, but reliable data on their efficacy in seronegative RA are scarce. Therefore, we want to perform a research and judgment of all the available evidence on effect and safety of TNFi on seronegative RA in the published and unpublished literature (systematic literature review with meta-analysis). Our results may inform treatment strategy for patients with seronegative RA.

Scientific Abstract:

BACKGROUND: Rheumatoid arthritis (RA) is a chronic autoimmune disease which is characterised by circulating autoantibodies, rheumatoid factor (RF) and anti-citrullinated peptides antibodies (ACPA). Beside their diagnostic value, RF and ACPA are well recognised as markers of a more aggressive phenotype of RA.

However, up to 48% of patients with RA test negative for these antibodies in clinical practice. This group of patients is considered to be affected by seronegative RA. Tumor necrosis factor inhibitors (TNFi) are well established drugs for RA. However, the majority of patients included in randomised clinical trials (RCTs) on RA are seropositive for RF and/or ACPA. As such we have no available high-quality data on the efficacy of TNFi in patients with seronegative RA. The aim of this systematic review is to fill this knowledge gap.

Objective: To assess the benefits and harms of TNF inhibitors in patients affected by seronegative RA with inadequate response to conventional synthetic DMARDs (csDMARDs).

Study design: systematic literature review with meta-analysis. We will include RCTs and quasi RCT investigating effect of TNFi compared to placebo in patients with seronegative RA and inadequate response to csDMARDs. We will request trialists/sponsors of RCTs on RA to provide us with disaggregated data for seronegative patients. Search strategy includes: Cochrane Central Register of Controlled Trials (Central), Pubmed and Embase.

Participants: adults aged 18 years or older, with a diagnosis of seronegative RA with an inadequate response or intolerance to previous treatment with one or more csDMARDs. The diagnosis of seronegative RA will be defined by fulfillment of ACR 1987 or ACR/EULAR 2010 classification criteria for RA and by the absence of RF and ACPA.

Primary outcome: disease remission, clinical response, disability, radiographic progression, safety.

Secondary outcomes: low disease activity, minor clinical response, health related quality of life.

Statistical analysis: We will pool outcome estimates from each included RCT by using a random effect meta-analysis and we will analyse them as described below:

we will analyse dichotomous data as risk ratios or Peto odds ratios when the outcome is a rare event (approximately less than 10%) and use 95% confidence intervals (CIs). Continuous data will be analysed as mean difference or standardised mean difference in case of different scales across studies and 95% CIs.

We will undertake meta-analyses only where this is meaningful. We will pool all TNF inhibitors and comparing to a common comparator: placebo

We will use a random-effects effect model. Clinical and methodological diversity will be assessed in terms of participants, interventions, outcomes and study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will be conducted by observing these data from the data extraction tables. Statistical heterogeneity will be assessed by visual inspection of the forest plot to assess for obvious differences in results between the studies and using the I and χ^2 statistical tests. Risk ratios will be reported for dichotomous outcomes and mean differences for continuous outcomes. The absolute percent difference, the relative percent change from baseline, the number needed to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) will be provided.

Brief Project Background and Statement of Project Significance:

Rheumatoid arthritis (RA) is a chronic autoimmune disease which if not treated can lead to joint destruction, impaired joint function and increased mortality.

Rheumatoid factor (RF) and anti-citrullinated peptides antibodies (ACPA) are the hallmark of the disease. Beside their diagnostic value, RF and ACPA are well recognized as markers of a more aggressive phenotype of RA. However, between 10% and 48% of patients with RA test negative for these antibodies in clinical practice. This group of patients is considered to be affected by seronegative RA. Albeit seronegative RA is supposed to be a milder form of RA, it can cause pain, impaired joint function and radiographic joint changes. Moreover, the lack of diagnostic markers implicates that diagnosing seronegative RA with confidence is quite challenging. Our group recently demonstrated that females with seronegative RA may be a difficult to treat patient population. However, the preponderant majority of patients included in randomised clinical trials (RCTs) on RA are seropositive for RF and/or ACPA. The majority of cohorts studies involve mainly seropositive patients. Therefore, we have no available high-quality data on the efficacy and safety of biologic

DMARDs (bDMARDs) in patients with seronegative RA. Our project aims to fill this knowledge gap, by retrieving all the available pieces of evidence on efficacy of TNFi in patients with seronegative RA. Our results may inform an evidence based treatment strategy for patients with seronegative RA.

Specific Aims of the Project:

Aim of our work is to evaluate effects and harms of TNFi compared to placebo in patients with seronegative RA with inadequate response to treatment with csDMARDs.

Our hypothesis is that TNFi are more effective than placebo in patients with seronegative RA.

Study Design:

Meta-analysis (analysis of multiple trials together)

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

We will include RCTs and quasi RCTs investigating treatment with TNFi compared to placebo in adults (18 year or older) patients with seronegative RA and with inadequate response to csDMARDs. We will include RCTs and quasi RCTs on RA if disaggregated data for seronegative patients will be available.

Seronegative RA is defined by fulfillment of ACR 1987 or ACR/EULAR 2010 classification criteria for rheumatoid arthritis and by the absence of RF and ACPA.

We will not include studies including RA patients in clinical remission or in low disease activity.

Individual patient data from included RCTs will be retrieved from the platforms YODA and VIVLI.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary outcomes:

- Disease remission as measured by proportion of patients in remission according to SDAI or ACR/EULAR Boolean criteria or CDAI or DAS28/DAS.
- Clinical response as measured by proportion of patients achieving ACR 50 response or SDAI moderate response or CDAI moderate response.
- Functional response as measured by the mean reduction in Health Assessment Questionnaire (HAQ) score or in modified HAQ score.
- Radiographic progression as measured according to Sharp-Van der Heijde scoring method, or other validated methods.
- Number of serious adverse events
- Number of withdrawals due to adverse events.

Secondary outcomes:

- Low disease activity as measured by SDAI low disease activity or CDAI low disease activity or DAS28/DAS low disease activity.
- Clinical response as measured by ACR 20 response or SDAI minor response or CDAI minor response.
- Health related quality of life as measured by the Medical Outcome Study Short Form (SF)-36 health survey questionnaire, or by other validated questionnaire.
- Pain as measured by VAS or NRS pain scale.
- Fatigue as measured by Functional Assessment of Chronic Illness Therapy - fatigue scale (FACIT-F) or by Fatigue VAS.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

We will look at comparison between TNFi and placebo in patients with seronegative RA and inadequate response to methotrexate

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

We will perform subgroup analysis stratifying the results for sex and disease duration.

Statistical Analysis Plan:

We will pool outcome estimates from each included RCT by using a random effect meta-analysis and we will analyse them as described below:

We will analyse dichotomous data as risk ratios or Peto odds ratios when the outcome is a rare event (approximately less than 10%) and use 95% confidence intervals (CIs). Continuous data will be analysed as mean difference or standardised mean difference in case of different scales across studies and 95% CIs.

Strategy for data synthesis

We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will pool all TNF inhibitors and comparing to a common comparator: placebo

We will use a random-effects effect model and perform a sensitivity analysis with a fixed-effect model.

Clinical and methodological diversity will be assessed in terms of participants, interventions, outcomes and

study characteristics for the included studies to determine whether a meta-analysis is appropriate. This will

be conducted by observing these data from the data extraction tables. Statistical heterogeneity will be

assessed by visual inspection of the forest plot to assess for obvious differences in results between the

studies and using the I and chi statistical tests. The interpretation of an I value of 0% to 40% might not be

important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial

heterogeneity; and 75% to 100% represents considerable heterogeneity. We will keep in mind that the

importance of I depends on: (i) magnitude and direction of effects and (ii) strength of evidence for heterogeneity.

The chi test will be interpreted where a P value ≤ 0.10 will indicate evidence of statistical heterogeneity.

If we identify substantial heterogeneity we will report it and investigate possible causes.

Risk ratios will be reported for dichotomous outcomes and mean differences for continuous outcomes.

The absolute percent difference, the relative percent change from baseline, the number needed to treat for

an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome

(NNTH) will be provided.

Analysis of subgroups or subsets

We plan to carry out the following subgroup analyses:

- Efficacy and harms of TNFi in patient with early and with established seronegative RA
- Efficacy and harms of TNFi in male patients and in female patients with seronegative RA

Early RA will be defined as RA with a disease duration of less than 36 months.

We will use the following outcomes in subgroup analysis:

1. Disease remission
2. Clinical response
3. Withdrawal due to adverse events

We will use the formal test for subgroup interactions in Review Manager (RevMan) and will use caution in the

interpretation of subgroup analyses.

Project Timeline:

Target Analysis Start Date

October 22

Estimated Analysis Completion Date

April 23

Dissemination Plan:

We declare that we will try to publish our work in peer-reviewed medical journals, such as Rheumatology.

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