

## Principal Investigator

**First Name:** Sophie  
**Last Name:** Derolez  
**Degree:** Resident  
**Primary Affiliation:** Tours (France)  
**E-mail:** [sophie.derolez@etu.univ-tours.fr](mailto:sophie.derolez@etu.univ-tours.fr)  
**Phone number:** +33668778974  
**Address:** 2 boulevard Tonnelle

**City:** Tours  
**State or Province:** Centre  
**Zip or Postal Code:** 37000  
**Country:** France

## General Information

### Key Personnel (in addition to PI):

**First Name:** Sophie  
**Last name:** Derolez  
**Degree:** Resident (10th year of Medical School)  
**Primary Affiliation:** University Hospital of Tours (France)  
**SCOPUS ID:**

**First Name:** Theodora  
**Last name:** Bejan-Angoulvant  
**Degree:** PhD MD  
**Primary Affiliation:** University Hospital of Tours (France)  
**SCOPUS ID:**

**First Name:** Denis  
**Last name:** Mulleman  
**Degree:** PhD MD  
**Primary Affiliation:** University Hospital of Tours (France)  
**SCOPUS ID:**

**First Name:** Marc Antoine  
**Last name:** Sparfel  
**Degree:** Intern of Rheumatology  
**Primary Affiliation:** University Hospital of Tours (France)  
**SCOPUS ID:**

**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/system/files/coi\\_dm.pdf](https://yoda.yale.edu/system/files/coi_dm.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. [NCT00264537 - C0524T05 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$  Monoclonal Antibody, Administered Subcutaneously, in Methotrexate-naïve Subjects with Active Rheumatoid Arthritis](#)
2. [NCT00264550 - C0524T06 - 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](#)
3. [NCT00299546 - C0524T11 - 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 and Previously Treated with Biologic Anti TNF \$\alpha\$  Agent\(s\)](#)
4. [NCT00361335 - C0524T12 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNF \$\alpha\$  Monoclonal Antibody, Administered Intravenously, in Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)
5. [NCT01248780 - C0524T28 - A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects with Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)
6. [NCT00269867 - C0168T22 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in Patients With Active Rheumatoid Arthritis Despite Methotrexate Treatment](#)
7. [NCT00236028 - C0168T29 - A Randomized, Double-blind, Trial of Anti-TNF \$\alpha\$  Chimeric Monoclonal Antibody \(Infliximab\) in Combination With Methotrexate Compared With Methotrexate Alone for the Treatment of Patients With Early Rheumatoid Arthritis](#)
8. [NCT00973479 - CNTO148ART3001 - A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNF \$\alpha\$  Monoclonal Antibody, Administered Intravenously, in Patients With Active Rheumatoid Arthritis Despite Methotrexate Therapy](#)
9. [NCT00207714 - C0524T02 - 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](#)
10. [NCT00202852 - P04280 - A Placebo-Controlled, Double-Blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody \(cA2\) in Korean Patients With Active Rheumatoid Arthritis Despite Methotrexate](#)
11. [C0168T14 - Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis](#)

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

## Research Proposal

### Project Title

Influence of demographic and environmental factors on anti-TNF efficacy in rheumatoid arthritis: a systematic review and meta-analysis of RCT

### Narrative Summary:

The treat-to-target strategy in RA has been proposed to increase the therapeutic efficacy while minimizing the risk of adverse events. Therefore, it is important to assess if demographics and environmental factors (age, gender, disease duration, disease activity, CRP/ESR levels, RF and ACPA status, smoking status, BMI, physical activity) could influence anti-TNF treatment effect and the direction of this influence. These factors could therefore be considered when initiating anti-TNF in RA in order to increase response rate and anticipate and avoid failure.

Prospero registration number: CRD42018071079

### **Scientific Abstract:**

**Background :** Rheumatoid arthritis is a relatively frequent immune mediated disease with a prevalence of 3 to 8/1,000 patients. RA alters quality of life and increases cardiovascular, infectious and other morbidity risks. Anti-TNF drugs are efficient, yet primary or secondary failure is still a problem for one patient out of 3, even if exposition to anti-TNF drugs is correct. Therefore, searching for determinants of treatment response is essential.

**Objective :** To study the influence of demographics and disease-related factors on anti-TNF drugs' efficacy in randomized controlled trials (RCT) in rheumatoid arthritis.

**Study design :** Systematic review and meta-analysis of published RCT following the PRISMA recommendations.

**Participants :** Adults (?18 years of age) with RA according to ACR 1987 or ACR/EULAR 2010 criteria.

**Outcomes:** primary: ACR20, secondary: ACR50, ACR70, DAS28-CRP, DAS28-ESR, CDAI, SDAI.

**Statistical analysis:** A meta-analysis of aggregate data will be performed. A fixed effect model will be performed first, with addition of a random effect model in case of significant heterogeneity.

Prospero registration number: CRD42018071079.

### **Brief Project Background and Statement of Project Significance:**

Rheumatoid arthritis (RA) is a relatively frequent immune mediated disease with a prevalence of 3 to 8/1,000 patients. RA alters quality of life and increases cardiovascular, infectious and other morbidity risks. Anti-TNF drugs are efficient, yet primary or secondary failure is still a problem for one patient out of 3, even if exposition to anti-TNF drugs is correct. Therefore, searching for determinants of treatment response is essential. Description of the treatment effect modifiers considered in this review and how these factors could influence the response to anti-TNF drugs

We considered the following demographic and environmental factors that could modify the response to anti-TNF drugs:

- Age and gender. Elderly patients with RA have an increased risk of serious infection. Female gender was shown to be independently associated with a lower rate of remission and a lower response rate to anti-TNF drugs.
- Disease duration. A long disease duration was associated with a poor response rate to anti-TNF.
- Disease activity and/or severity markers such as disease activity score on 28 joints status (DAS28), CRP level, rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA). In a prospective register, ACPA positivity was negatively related to clinical response and ACPA and RF-positivity was predictive of poor response. High disease activity at baseline was directly associated with favorable response as measured by ACR50 and ACR70 but GISEA study confirmed that high disease activity at baseline was associated with lower response.
- Smoking status. Current cigarette smoking was shown to be associated with a lower response rate to infliximab, and cigarette smoking is a well-recognized risk factor for the development of RA and has also been associated with a more severe disease, disability and extra-articular manifestations, particularly nodules
- Weight or body mass index (BMI). Baseline BMI was shown to be positively correlated with DAS28, indicating a more-active disease in overweight patients. Further, a higher BMI was shown to be associated with a decreased clinical response to infliximab.
- Physical activity. Findings indicate that RA patients who participate in appropriate exercises programs may lessen fatigue levels and experience other positive effects without worsening their condition but we did not found studies that showed that physical activity could influence the response to anti-TNF drugs.

Why it is important to do this review

The treat-to-target strategy in RA has been proposed to increase the therapeutic efficacy while minimizing the risk of adverse events. Therefore, it is important to assess if demographics and environmental factors listed above could influence anti-TNF treatment effect and the direction of this influence. These factors could therefore be considered when initiating anti-TNF in RA in order to increase response rate and anticipate and avoid failure. That is why we are studying the treatment effect in subgroups of interest (eg treatment effect measured by age or gender).

### **Specific Aims of the Project:**

To study the influence of demographics and disease-related factors on anti-TNF drugs' efficacy in randomized controlled trials (RCT) in rheumatoid arthritis.

**What is the purpose of the analysis being proposed? Please select all that apply.**

Confirm or validate previously conducted research on treatment effectiveness

Summary-level data meta-analysis

Summary-level data meta-analysis pooling data from YODA Project with other additional data sources

Participant-level data meta-analysis pooling data from YODA Project with other additional data sources

## Research Methods

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

In a first step, we searched CENTRAL, PubMed and EMBASE and selected eligible studies.

- Inclusion criteria: randomized controlled trials comparing an anti-TNF drug (infliximab, adalimumab, golimumab, certolizumab pegol or etanercept) versus placebo or conventional DMARDs, in rheumatoid arthritis (RA) patients and reported efficacy data by subgroups of demographic and disease related factors of interest.

The following factors of interest will be considered: age, sex, BMI, smoking status, disease duration, DAS28, CRP, ACPA, RF, and physical activity.

- Exclusion criteria: non-randomized controlled trials, observational studies, randomized trials comparing 2 anti-TNF drugs without a control group.

**Main Outcome Measure and how it will be categorized/defined for your study:**

Primary outcome : ACR20

The ACR20 is reported as ?20% improvement, comparing disease activity at baseline and post-baseline comparison.

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

- Age : <50 or ? 50 years
- gender : woman or man
- Disease duration : < 2 or ? 2 years
- DAS28 : ?3,2, between 3,2 and 5,1, ? 5,1
- CRP : < 10 mg/l or ? 10 mg/l
- rheumatoid factor (RF) positivity or negativity
- anti-citrullinated protein antibody (ACPA) positivity or negativity
- Smoking status : current, non-current smoker
- Body Mass Index (BMI) : ? 25 or > 25
- physical activity < 30 min/week or ? 30 min/week

We created an excel extraction sheet if you need for collecting the data.

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

none

**Statistical Analysis Plan:**

A meta-analysis of aggregate data will be performed, following appropriate methods (relative risks or standardized mean difference) depending of the nature of the outcome considered. A fixed effect model will be performed first, with addition of a random effect model in case of significant heterogeneity. Heterogeneity will be considered significant if the m-value of the heterogeneity test is <0.10 or I<sup>2</sup> is higher than 50%.

**Project Timeline:**

Estimation dates :

project start date : november 2017

analysis completion date : july 2018

date manuscript drafted : october 2018

first submitted : october-november 2018

date results reported back to the YODA Project : october-november 2018

### Dissemination Plan:

EULAR congress 2019

JBS, Rheumatology, Arthritis & care, BMJ, Journal of Rheumatology, ARD.

### Bibliography:

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**Supplementary Material:**

[https://yoda.yale.edu/sites/default/files/protocol\\_.docx](https://yoda.yale.edu/sites/default/files/protocol_.docx)