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NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

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

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

01/09/2016

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

30/06/2018

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

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Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	No	No
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Sophie Derolez

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic email address of the named contact.

sophie.derolez@gmail.com

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

CHRU Trousseau-Rhumatologie, avenue de la République, 37170 Chambray les Tours

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

None

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Dr Sophie DEROLEZ. Centre hospitalier rhumatologique d'Uriage

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Professor Theodora Bejan-Angoulvant. CHRU TOURS
Professor Denis Mulleman. CHRU TOURS
Dr Marc-Antoine SPARFEL. CHRU TOURS
Dr Johan LAW-WAN. CHRU TOURS

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

CHRU TOURS

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

We aim to study the influence of demographic and environmental factors on anti-TNF efficacy in rheumatoid arthritis from randomized clinical trials that evaluated efficacy of TNF inhibitors compared to placebo in subgroups of interest.

Patients: Adults (≥18 years old) with RA according to ACR 1987 or ACR/EULAR 2010 criteria.

Interventions: all anti-TNF drugs (infliximab, adalimumab, etanercept, golimumab, certolizumab), either alone or in combination with conventional DMARD.

Comparator: placebo or conventional DMARD, including corticosteroids, methotrexate, salazopyrine or leflunomide.

Outcomes:

- primary: Between-treatment groups difference in DAS28(CRP) change (?DAS28(CRP)) from baseline until 6 months

- secondary: between-treatment groups difference in final DAS28(CRP) measured until 6 months and EULAR response criteria until 6 months

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or

attachment below.)

Search strategy:

For the first step, we searched CENTRAL and selected eligible studies. After review of full-text articles, we observed that data of interest were very rarely reported. We therefore decided to ask the data from the authors. We will complete the search in two other electronic databases: PubMed and EMBASE, and perform hand searches of references list of included studies or relevant reviews and meta-analyses. We will also search clinical trial registries in search of unpublished clinical trials.

Selection of articles

We will select potential articles on title and abstract, then assess the full eligibility criteria on the full-text articles.

Data collection and analysis

Study selection

- First step: eligible studies selected by title and abstract: randomized controlled trial evaluating the efficacy of an anti-TNF compared to placebo or DMARD in RA.

- Second step: review of the full text of eligible studies and inclusion of studies that reported data of efficacy by subgroups of interest. At this step, reasons for exclusion will be registered.

We will extract the following data: age, sex, BMI, physical activity, smoking status, disease duration, DAS28, CRP, ACPA status, RF status, author, year of publication, study acronym, journal, PMID, NCT or clinical trial registry number, anti-TNF evaluated and type of control, number of patients included, main outcome, time for main outcome, duration, extension, sponsor.

Assessment of risk of bias following the Cochrane Risk of Bias Tool for randomized controlled trials will be evaluated in duplicate.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly

accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search **results**.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Clinical trials being the less prone to bias, we decided to consider the randomized controlled trials which reported the effect of factors that modify treatment effects (interaction factors).

- 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: smoking status, physical activity, sex, age, BMI, ACPA, RF, disease duration and initial DAS28CRP.

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

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

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

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Interventions: all anti-TNF drugs (infliximab, adalimumab, etanercept, golimumab, certolizumab), either alone or in combination with conventional DMARD.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared

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(e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Comparator: placebo or conventional DMARD, including corticosteroids, methotrexate, salazopyrine or leflunomide.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Randomized controlled trials.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

- 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: smoking status, physical activity, sex, age, BMI, ACPA, RF, disease duration and initial DAS28CRP .

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

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The predefined primary end-point was ACR20 score after 6 months of follow up. Due to the impossibility to obtain ACR response from the raw dataset for 8 trials, we decided in November 2019 to modify the primary endpoint to between-treatment groups difference in DAS28(CRP) change (?DAS28(CRP)) from baseline to 6 months (or as close as 6 months depending on each trial available data).

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Secondary end-points were ACR50, ACR70, DAS28(CRP) and DAS28(ESR) but have been changed in

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November 2019 by : between-treatment groups difference in final DAS28(CRP) measured at 6 months (or as close as 6 months) and EULAR response criteria at 6 months (or as close as 6 months).

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

- First step : eligible studies selected by title and abstract: randomized controlled trial evaluating the efficacy of anti-TNF compared to placebo in DMARD-IR RA and inclusion of studies that reported data of efficacy
- Second step : review of the full text of included studies

by subgroups of interest. These subgroups will be : smoking status (never / ever smokers), current physical activity (yes / no), sexe (men / women), age (? 50 / 50 years), BMI (30 / ? 30 kg/m2), RF status (positive / negative), ACPA status (positive / negative), RA disease duration (2 / 2 to 10 / ? 10 years), baseline DAS28(CRP) (?5.1 / 5.1)

Given the unavailability of published subgroup of interest analyses, we will contact the corresponding authors and/or sponsors of these trials in order to obtain aggregated data and/or individual patient data (IPD) and perform a pooled analysis. Since most of the data were stored securely on data sharing platforms, we will request each of these platforms an access to the raw dataset.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Assessment of risk of bias following the Cochrane Risk of Bias Tool for randomized controlled trials will be evaluated in duplicate.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Statistical analyses will be performed using R Studio software. Descriptive results will be presented as median (min-max) or mean (interquartile range) unless stated otherwise. Pooled odds ratios (OR) or mean difference (MD) with 95% Confidence intervals (95% CI) for EULAR response and for DAS28(CRP) differences, respectively, between TNF inhibitors and placebo will be calculated using two step meta-analyses.

- First step : aggregate data regarding treatment response in each subgroup of interest will be estimated from IPD.
- Second, a random-effect Mantel-Haenszel model will be applied to calculate pooled effect.

We will consider a significant difference between subgroups if p0.05. Between-study heterogeneity will be quantified using Cochrane Q and I² statistics.

IPD from two platforms (YODA and Vivli) will be used to perform 2 separate linear meta-regressions with final DAS28(CRP) as independent variable adjusted on baseline DAS28(CRP), trial, and treatment by subgroup variable interaction (bivariate analyses). Multivariate metaregressions of final DAS28(CRP) adjusted on baseline DAS28(CRP), trial, age and subgroup variables with a p value for interaction 0.20 in bivariate analyses will also be performed.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

Subgroups analyses of efficacy by smoking status, physical activity, sex, age, BMI, ACPA, RF, disease duration, baseline DAS28(CRP)

Intervention: all TNFi drugs (infliximab, adalimumab, etanercept, golimumab, certolizumab), either alone or in combination with conventional DMARD.

Randomized controlled trials.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
Yes

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
Yes

Methodology
No

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

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Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders

No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
Yes

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

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Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

France

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

The raw data were not extracted but analyzed remotely from the YODA (https://yoda.yale.edu/) and Vivli platforms (https://vivli.org).

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

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No

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.