Demyelinating Risk with TNF Inhibitors versus Other Targeted DMARDs in Rheumatoid Arthritis: A French Nationwide Claims Study (DEMY-TNF)

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Study Ongoing

Administrative details

EU PAS number

EUPAS1000001021

Study ID

1000001021

DARWIN EU® study

No

Study countries

France

Study description

This is an active-comparator, new-user cohort study using data from the French National Health Data System (SNDS). The objective of the study is to compare the risk of nervous system demyelinating events in patients with rheumatoid arthritis (RA) initiating TNF inhibitors versus CTLA4-Ig or IL-6 inhibitors as first-line biologic therapy after at least one conventional synthetic DMARD (csDMARD) (target trial emulation (TTE) 1: TNFi vs [CTLA4-Ig or IL-6i]).
Secondary objectives are to assess the risk of demyelinating events considering those affecting the central nervous system (CNS) and the peripheral nervous system (PNS) separately, in RA patients initiating treatment with TNF inhibitors versus CTLA4-Ig or IL-6 inhibitors, as first-line biologic therapy after csDMARD (TTE 1: TNFi vs [CTLA4-Ig + IL-6i]).
To compare the risk of nervous system demyelinating events in patients with RA initiating TNF inhibitors versus:
- CTLA4-Ig or IL-6 inhibitors or Janus kinase inhibitors (JAK inhibitors) (TTE 2: TNFi vs [CTLA4-Ig or IL-6i or JAKi])
- CTLA4-Ig (TTE 3: TNFi vs CTLA4-Ig)
- IL-6 inhibitors (TTE 4: TNFi vs IL-6i)
- JAK inhibitors (TTE 5: TNFi vs JAKi)

Study status

Ongoing

Research institutions and networks

Institutions

Centre de pharmaco-épidémiologie (Paris Pharmacoepidemiology Centre), Assistance Publique, Hôpitaux de Paris

France

First published: 14/11/2011

Last updated: 22/07/2015

Institution | Outdated | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Contact details

Study institution contact

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Primary lead investigator

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 01/11/2025

Actual: 17/04/2026

Study start date
Planned: 01/05/2026

Actual: 01/05/2026

Data analysis start date
Planned: 30/06/2026

Date of interim report, if expected
Planned: 31/12/2026

Date of final study report
Planned: 30/06/2027

Sources of funding

- Other public funding (e.g. hospital or university)

Study protocol

study_protocol_DEMY-TNF_20260603.pdf (947.05 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

observational longitudinal study using SNDS data between January 1, 2014 and December 31, 2025.
analytical framework: a head-to-head, new-user, active-comparator design under the as-treated estimand.
To emulate randomization at treatment initiation, inverse probability of treatment weighting (IPTW).

Main study objective:

To compare the risk of nervous system demyelinating events in patients with rheumatoid arthritis (RA) initiating TNF inhibitors versus CTLA4-Ig or IL-6 inhibitors as first-line biologic therapy after at least one conventional synthetic DMARD (csDMARD) (target trial emulation (TTE) 1: TNFi vs [CTLA4-Ig or IL-6i]).

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

REMICADE

HUMIRA

CIMZIA

SIMPONI

Medicinal product name, other

TNF inhibitor

Study drug International non-proprietary name (INN) or common name

INFLIXIMAB

ETANERCEPT

ADALIMUMAB

GOLIMUMAB

CERTOLIZUMAB PEGOL

Anatomical Therapeutic Chemical (ATC) code

(L04AB01) etanercept

etanercept

(L04AB02) infliximab

infliximab

(L04AB04) adalimumab

adalimumab

(L04AB05) certolizumab pegol

certolizumab pegol

(L04AB06) golimumab

golimumab

Medical condition to be studied

Rheumatoid arthritis

Population studied

Short description of the study population

The study population will be extracted from the source population (extraction period: January 1, 2006 to December 31, 2024). The following individuals will be included:

- Adult beneficiaries (aged ≥18 years): this choice is justified by the fact that the vast majority of rheumatoid arthritis (RA) cases occur in adulthood. Therefore, excluding the pediatric population—who are also difficult to identify in the SNDS—should not bias the results.

- Diagnosis of RA: identified using ICD-10 codes recorded before the index date, either in the long-term disease (ALD) registry or in the hospital discharge database (PMSI MCO; primary, related, or associated diagnoses). Previous studies have shown that RA can be reliably identified in the SNDS.

- History of treatment with at least one csDMARD: defined by at least one dispensing in the 6 month before the index date. This reflects current treatment guidelines, where targeted therapies are initiated after inadequate response to csDMARDs.

The index date is defined as the date of initiation of the first TNFi, CTLA4-Ig, or

IL-6i.

The inclusion period will extend from January 1, 2014 to December 31, 2024. The observation period will extend from January 1, 2014 to December 31, 2025, to allow for at least one year of follow-up; and the data extraction period from January 1, 2006 to December 31, 2025, to allow for measurement of baseline covariates and a look-back period to exclude prevalent users of tDMARDs.
For TTE 2 and 5, since JAKi are prescribed as second line biotherapies in RA since 2017, the inclusion period will start on January 1, 2017.
Non-inclusion criteria:

- History of demyelinating events before baseline, identified using ICD-10 codes (ALD registry or PMSI MCO hospitalization).

- Prior exposure to any tDMARD (including JAKi and anti-CD20) before the index date.

- History of any tDMARD use during the look-back period (January 1, 2006 to January 1, 2014), to ensure inclusion of new users.

- History of cancer in the 5 years before the index date: identified using ICD-10 codes recorded before the index date, either in the long-term disease (ALD) registry or in the hospital discharge database (PMSI MCO; primary, related, or associated diagnoses). Previous studies have shown that cancer can be reliably identified in the SNDS.

Age groups

- **Adult and elderly population (≥18 years)**
    - Adults (18 to < 65 years)

        - Adults (18 to < 46 years)
        - Adults (46 to < 65 years)
    - Elderly (≥ 65 years)
        - Adults (65 to < 75 years)
        - Adults (75 to < 85 years)
        - Adults (85 years and over)

Estimated number of subjects

65.000

Study design details

Setting

Extraction of all the patients following the inclusion criteria defined in the study population.

Comparators

IL-6 inhibitors, CTLA4-Ig, and JAKi.

Outcomes

Occurrence of a first ICD-10 code for a demyelinating event affecting the central nervous system (CNS) or the peripheral nervous system (PNS) after the index date.
Incident demyelinating events will be identified using ICD-10 codes from MCO hospitalizations (primary or related diagnosis: DP/DR) and long-term disease (ALD) records.

Data analysis plan

Propensity score:

The variables included in the propensity score are: sex, age at baseline, year at baseline, Charlson’s Comorbidity Index (version adapted to the SNDS), proxies for heavy tobacco or alcohol consumption, obesity, care consumption in the year before baseline (number of hospitalizations for RA), cumulative corticosteroids dose in the year before baseline, exposure to NSAIDs in the year before baseline, and full health expense coverage for low income.

The propensity score will be estimated using a logistic regression model to calculate the probability of receiving TNFi vs comparator according to baseline covariates.
Patients will then be weighted using the IPTW (Inverse Probability of Treatment Weighting) method, applying stabilized weights.

Quality of the weighting:

To assess the quality of the matching, standardized mean differences between the two treatment groups will be calculated, and histograms of the propensity score will be plotted. Differences less than 10% will indicate balance between treatments.

Statistical estimator of the treatment effect:

Hazard ratios (HRs) and 95% Cis will be estimated using Cox proportional hazards regression models incorporating inverse probability of treatment weights for the primary end point. Absolute risks and risk differences at 10 years will be derived from weighted Kaplan-Meier estimates.

Data management

Data sources

Data source(s)

Système National des Données de Santé (French national health system main database)

Data sources (types)

Administrative healthcare records (e.g., claims)

Other

Data sources (types), other

medical and administrative database

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

No