The comparative safety of first-line conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) used for the treatment of rheumatoid arthritis: protocol for a multi-database real-world cohort study

First published: 30/01/2020

Last updated: 30/01/2020

Study Ongoing

Administrative details

EU PAS number

EUPAS33214

Study ID

33215

DARWIN EU® study

No

Study countries

Belgium
Estonia
France
Germany
Japan
Netherlands
Spain
United Kingdom
United States

Study description

We studied the comparative safety of first-line conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) as prescribed for the treatment of rheumatoid arthritis (RA). Drugs of interest were informed by a parallel drug utilisation study, and included methotrexate, hycroxychloroquine, sulfasalazine, and leflunomide. Study outcomes included cardiovascular disease (myocardial infarction, stroke), infection/s (any, serious, opportunistic), cancer (any, lung, colo-rectal, leukemia, lymphoma) and leukopenia/pancytopenia. Routine (real world) electronic medical records and/or claims data from Germany, Spain, Belgium, France, Netherlands, United Kingdom, Estonia, Japan, and the United States of America were analysed. All subjects aged 18+, with 1+ year run-in, a diagnosis of RA, and a first-line csDMARD were included at therapy initiation. Propensity score stratification was used to minimise confounding by indication, and negative control outcomes analyses to identify residual (unobserved) confounding.

Study status

Ongoing

Research institutions and networks

Institutions

Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences (NDORMS), University of Oxford

United Kingdom

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility

Centre for Statistics in Medicine

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 09/07/2026

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Erasmus Medical Centre Rotterdam

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Erasmus Medical Centre Rotterdam, the Netherlands

Networks

European Health Data Evidence Network (EHDEN)

Netherlands

First published: 01/02/2024

Last updated: 04/08/2025

Network

Observational Health Data Sciences and Informatics (OHDSI) Network

First published: 01/02/2024

Last updated: 01/02/2024

Network

Contact details

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Study contact

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Primary lead investigator

Daniel Prieto-Alhambra

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 01/11/2018

Actual: 01/11/2018

Study start date

Planned: 01/01/2005

Actual: 01/01/2005

Data analysis start date

Planned: 13/01/2020

Actual: 13/01/2020

Date of final study report

Planned: 31/01/2020

Sources of funding

- EU institutional research programme

More details on funding

IMI2 European Health Data and Evidence Network (EHDEN)

Study protocol

raple_eupas_protocol.pdf (306.42 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 type list

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Main study objective:

1. To assess the cardiovascular safety of MTX compared to LEF, HCQ, and SSZ2. To estimate the risk of infections associated with the use of MTX compared to LEF, HCQ, and SSZ3. To study the risk of cancer associated with the use of MTX compared to LEF, HCQ, and SSZ4. To study the risk of leukopenia/pancytopaenia associated with the use of MTX compared to LEF, HCQ, and SSZ

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(P01BA02) hydroxychloroquine

hydroxychloroquine

(L04AX03) methotrexate

methotrexate

(L04AA13) leflunomide

leflunomide

(A07EC01) sulfasalazine

sulfasalazine

Medical condition to be studied

Rheumatoid arthritis

Population studied

Age groups

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

Estimated number of subjects

300.000

Study design details

Outcomes

Myocardial infarction, stroke, serious infection, opportunistic infection, any infection, lymphoma, leukemia, lung cancer, colo-rectal cancer, any cancer, leukopenia/pancytopenia

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Data analysis plan

Propensity scores will be estimated using LASSO and used for stratification (primary) and matching (secondary analysis). Balance will be assessed using standardised mean difference. Cox models will be used to estimate hazard ratios according to exposure. Negative control outcomes will be used to assess residual confounding, and for calibration where applicable. Study diagnostics (power, propensity score distribution, covariate balance) were evaluated by clinicians and epidemiologists to determine which database-target-comparator-outcome-analyses warrant further consideration. Database-target-comparator that identified <10 outcomes in the time-at-risk or contained analyses with baseline covariate with standardized mean difference>0.1 and covariate prevalence difference>0.05 were excluded. All the analyses will be conducted

for each database separately, with estimates combined in fixed effects meta-analysis methods where I2 is <=40%.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Signed checklist for study protocols

raple_eupas_checklist.pdf (217.19 KB)

Data sources

Data source(s)

THIN® (The Health Improvement Network®)

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

THIN, SIDIAP

Data sources (types)

Administrative healthcare records (e.g., claims)

Drug dispensing/prescription data

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No