The impacts of the coronavirus pandemic on rheumatoid arthritis care and non-COVID outcomes using the OpenSAFELY platform

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Version: 1.0

Date: 08/02/2023

Version history	Date	Comment
0.1	03/05/2022	Initial draft created by Ruth Costello
1.0	08/02/2023	Final draft after updates from team

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Background

Rheumatoid arthritis (RA) is a chronic inflammatory condition that requires ongoing specialist care. Rheumatologists employ a treat to target strategy, with the goal of keeping disease activity low, with frequent monitoring and adaptation of treatments to reach this goal (1). To achieve this monthly monitoring is recommended, and only moves to annual reviews once disease is stable, though patients should have access to specialist care in the case of disease flares between annual reviews (2). The annual reviews are to monitor disease activity as well as the development of comorbidities. In addition to this, the drugs used to treat RA can have harmful effects primarily to the liver, kidneys and blood, therefore regular blood tests are required to monitor for these toxicities, these blood tests usually take place in primary care. Rheumatology services were affected by the pandemic with rheumatologists frequently seconded to help with treating COVID-19 patients, rheumatology and primary care appointments were moved to telephone or video consultations and drug monitoring was reduced (3). It's not clear how this impacted people with RA. Diversion of healthcare resources to pandemic management has negatively affected non-COVID-related healthcare provision more broadly, including prevention activities, potentially creating or worsening physical and mental health (4). In RA specifically, there have been reports of medication interruptions during the pandemic, resulting in disease flares, however many of these studies are based on self-reported data (5,6). This study aims to investigate the impact of changes to rheumatology healthcare on patients with RA using the electronic health record data using the OpenSAFELY platform.

Aims and Objectives

Aim

In patients with RA, to determine the impact of population-wide restrictions and the diversion of healthcare resources on rheumatology hospital care, and hospital admissions, drug monitoring in primary care, and mortality for non-COVID outcomes in England, Wales and Scotland.

Objectives

1. To estimate rheumatology outpatient healthcare utilisation between the period prior to the pandemic (March 2018-March 2020) and since the start of the pandemic (March 2020 onwards).
2. To estimate how proxies for disease severity: inpatient admissions for RA, or complications associated with RA, glucocorticoid and opioid prescriptions,have changed between the period prior to the pandemic (March 2018-March 2020) and since the start of the pandemic (March 2020 onwards).
3. To estimate how DMARD blood monitoring changed between the period prior to the pandemic (March 2018-March 2020) and since the start of the pandemic (March 2020 onwards), and

whether changes were associated with poorer outcomes (transaminitis, cytopenia and kidney disease).

4. To estimate how mortality has changed between the period prior to the pandemic (March 2018-March 2020) and since the start of the pandemic (March 2020 onwards).

Methods

Database Description: England

For the England based analysis, we will use data from general practice (GP) records, obtained from the GP software provider TPP, linked to the Emergency Care Data Set, Admitted Patient Care and ONS mortality records. The data will be accessed, linked and analysed through openSAFELY.org - a data analytics platform created on behalf of NHS England to address urgent questions relating to the epidemiology and treatment of COVID-19. OpenSAFELY provides a secure software interface allowing the analysis of pseudonymised primary care patient records from England in near real-time within the EHR vendor's highly secure data centre, avoiding the need for potentially disclosive pseudonymised patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimises any risk of re-identification. Similarly pseudonymised datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data. Descriptions of OpenSAFELY have been previously published (REF), and more information can be found on https://opensafely.org/.

Primary care records retrieved from the TPP SystmOne electronic health record system include diagnoses (SNOMED or Read 3 CTV3), prescriptions (dictionary of medicines and devices), basic sociodemographics and vital signs for 22 million individuals – approximately 40% of the English population. Data extracted by SystmOne have previously been used in medical research, as part of the ResearchOne dataset (REFS).

All data are held in a secure research environment hosted by TPP, which is a Tier 3 data centre, accredited to NHS Digital standards for centrally hosted clinical systems (ISO 27001 standard and IG Toolkit version 2). We received ethics approval to conduct the data linkage and analyses by the London - City & East Research Ethics Committee on the 2nd of April 2020 (REC reference: 20/LO/0651) and LSHTM Ethics Board (ref 21863). No further ethical or research governance approval was required by the University of Oxford but copies of the approval documents were reviewed and held on record.

Latest Database Description available here:

https://docs.google.com/document/d/1d6fw9sc80_N_UQO7qib_R8yBZGObLEzPS_xcri222rA/edit]

Information Governance

NHS England is the data controller; TPP is the data processor; and the key researchers on OpenSAFELY are acting on behalf of NHS England. Patient data have been pseudonymized for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymized datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is through a virtual private network (VPN) connection; the researchers hold contracts with NHS England and only access the platform to

initiate database queries and statistical models; all database activity is logged; and only aggregate statistical outputs leave the platform environment following best practice for anonymization of results such as statistical disclosure control for low cell counts. **The OpenSAFELY research platform adheres to the data protection principles of the UK Data Protection Act 2018 and the EU General Data Protection Regulation (GDPR) 2016.** In March 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 (COPI) to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak and incidents of exposure. Together, these provide the legal basis to link patient datasets on the OpenSAFELY platform. GP practices, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform.

Database Description: Wales

SAIL team to complete

Database Description: Scotland

To be added.

Study Design and Population

This will be a retrospective cohort study of patients with prevalent or incident RA between 1st March 2018 and 1st May 2022. The following broad inclusion and exclusion criteria will be applied:

Inclusion Criteria

- Age ≥18 at the start of follow-up
- Registered with a primary care practice, with at least three months of continuous GP registration.
- Diagnosis of RA, defined as either 1) having at least one SNOMED/Read code for RA and at least two prescriptions for a disease-modifying anti-rheumatic drug (DMARD) with no alternative indication in 5 years prior (alternative indications: IBD, psoriasis, psoriatic arthritis, SLE, haematological cancer) or 2) ≥2 codes RA codes on different dates + no alternative diagnosis after RA code (psoriatic arthritis, ankylosing spondylitis and other spondyloarthropathies) (7).

Exclusion criteria

- People with missing age, sex, Sustainability and Transformation Partnership (STP) region or individual level index of multiple deprivation, since these are likely to indicate poor data quality.

The cohort will be followed until 30th April 2022. People will be followed from either the start of the study period, GP registration or RA diagnosis, whichever is latest. Patients will be followed until the earliest of:

- Death;
- De-registration from GP practice from TPP;
- Latest TPP data are available;
- End of study (30/04/2022).

The study design, including additional inclusion and exclusion criteria, for each objective are described below.

Objectives 1 & 4

No additional inclusion or exclusion criteria.

Objective 2

The study period for this part of the study will be from 1st April 2019 - 1st April 2022, as outpatient data is only available from 1st April 2019.

Objective 3:

For the first part of this objective describing blood monitoring, people will be required to be 1) currently prescribed DMARDs methotrexate, leflunomide or azathioprine for at least one year prior to entering the cohort, defined as having at least 4 prescriptions and 2) have at least one year of blood monitoring prior to entering each cohort, defined as having at least 3 blood tests for red blood cells (representing full blood count), ALT (representing liver toxicity) and eGFR (representing renal toxicity).

Study design

This objective will include patients prescribed DMARDs (specific DMARDs to be included defined below) who have RA, or psoriasis or psoriatic arthritis. Two cohorts will be identified from the broad cohort for this objective covering the following periods:

1. 1st March 2018 - 22nd March 2020
2. 23rd March 2020 - 1st May 2022

Additional inclusion Criteria

- Prescribed DMARDs methotrexate, leflunomide or azathioprine for at least one year prior to entering each cohort, defined as having at least 4 prescriptions.
- At least one year of blood monitoring prior to entering each cohort, defined as having at least 3 blood tests for red blood cells (representing full blood count), ALT (representing liver toxicity) and eGFR (representing renal toxicity).

- A diagnosis of RA, psoriasis or psoriatic arthritis prior to DMARD prescriptions.

Study Measures

Objectives 1 & 2

Each month it will be evaluated if cohort members were 1) seen in rheumatology outpatients and the mode of the appointment, 2) admitted to hospital with the primary reason of RA, 2) admitted to hospital with primary reason of complications associated with RA (vasculitis, lung disease, CVD, serious infections), 3) prescribed glucocorticoids, 4) prescribed opioids. Each of these outcomes will only be counted once per month, but people can be counted in multiple months.

In addition the number of hospital outpatient appointments with rheumatology per year (April to April) and the mode of appointment will also be identified where available.

For hospital admissions for RA, admissions will be stratified by whether or not they were a day case admission (as this likely indicates admission for treatment such as a biologic).

Objective 3

Each month it will be evaluated if cohort members are: 1) currently prescribed DMARDs, defined as a prescription in the last 3 months, 2) whether there is a blood test (red blood cells, ALT or eGFR) that month. For each blood test identified it will be determined if the blood test is more than 3 months from the previous test, if so this would be flagged as a prolonged interval.

For the second part of this objective (England only) it will be determined the blood test was out of range (at all or severely). Alongside this, diagnoses of transaminitis, cytopenia and kidney disease will be identified using SNOMED codes. To flag potential discontinuations, it will be determined for each test if there is a prescription within 90 days of the test.

Exposures

- For the first part of this objective describing changes in monitoring, the exposure will be the pandemic.
- For the second part of this objective, to understand whether changes in monitoring were associated with worse outcomes, there will be two exposures: 1) the pandemic, 2) time since the previous blood test, classified as ≤90 days or >90 days.

Outcomes

- For the first part of this objective the outcome will be time since the previous blood test, classified as ≤90 days or >90 days.

- For the second part of this objective the outcome will be measured in two ways:
    a. Whether consecutive blood tests were out of range - where the exposure would be measured on the first out of range blood test.
    b. a single blood test was severely out of range defined as: LFT = 3x upper limit of normal, FBC = 20% below lower limit of normal, eGFR = <60
    c. A diagnosis of transaminitis, cytopenia or chronic kidney disease and ceasing current DMARD medication defined above.

Stratification

- Different levels of risk based on age and comorbidity is likely to affect both blood monitoring and outcomes, therefore the cohort will be stratified by high vs low risk at cohort entry. People will be considered high risk if they are age > 60 or have any of the following comorbidities: chronic kidney disease (stage 3-5), liver disease, diabetes or CVD (8).

Potential confounders

- Age (using restricted cubic splines),
- Sex,
- Region (Sustainability Transformation Partnership level (STP, English NHS administrative region)),
- Urban/rural location,
- SES (IMD, in quintiles)
- Ethnicity
- Time since DMARD first prescribed in years at baseline.
- Time since first RA, psoriasis or psoriatic arthritis code at baseline.
- BMI at baseline
- Biologic prescribed prior to 2020
- Practice/CCG

Note: I don't expect region, urban/rural location or SES to be true confounders but think it will be useful to explore these to understand who was missing blood tests.

Objective 4

Each month it will be evaluated if cohort members died within that month and the cause of death.

Table 1 Codelists for inclusion criteria

Inclusion / Exclusion Criteria	OpenCodelists Definition
Rheumatoid arthritis (needs reviewing)	https://www.opencodelists.org/codelist/user/ruthcostello/rheumatoid-arthritis/7b1fe01e/
Methotrexate	https://www.opencodelists.org/codelist/opensafely/methotrexate-oral/041a8320/
Leflunomide	https://www.opencodelists.org/codelist/opensafely/leflunomide-dmd/1765d120/
Sulfasalazine	https://www.opencodelists.org/codelist/opensafely/sulfasalazine-oral-dmd/1a189116/
Hydroxychloroquine	https://www.opencodelists.org/codelist/opensafely/hydroxychloroquine/2020-06-15/
Azathioprine	https://www.opencodelists.org/codelist/opensafely/azathioprine-dmd/78f0ddfe/
Psoriasis (needs reviewing)	https://www.opencodelists.org/codelist/user/ruthcostello/psoriasis/2d3ec689/
Psoriatic arthritis	https://www.opencodelists.org/codelist/opensafely/psoriatic-arthritis/2020-10-21/
Inflammatory bowel disease	https://www.opencodelists.org/codelist/opensafely/inflammatory-bowel-disease/2020-04-07/
SLE (needs reviewing)	https://www.opencodelists.org/codelist/user/ruthcostello/systemic-lupus-erythematosus/142f5354/
Haematological cancer	https://www.opencodelists.org/codelist/opensafely/haematological-cancer/2020-04-15/
Spondyloarthropathy (needs reviewing)	https://www.opencodelists.org/codelist/user/ruthcostello/spondyloarthropathy/3809c661/

Statistical Analysis

The characteristics of the cohort overall will be described.

For all outcomes the rate of each outcome per month will be determined and plotted in line graphs. Interrupted time-series analysis will be used to measure the impact of the pandemic, specifically a Newey-West model with heteroskedasticity-consistent standard errors, which account for clustering and other violations. The interruption will be the onset of the 2020 covid-19 pandemic in England (23rd March 2020).

Outpatient appointments:

- The number of rheumatology appointments per year from March to March, from 2018 to 2022 will be categorised as none, 1-2, 3-6, 7-12, >12 per year and tabulated.
- The median year-on-year difference in the number of appointments will be calculated.
- People will be grouped by whether the number of outpatient appointments decreased, remained the same or increased and characteristics will be described, including age, sex, urban-rural classification ethnicity and IMD.
- Describe the mode of appointment per year.

Patient characteristics characteristics will be described stratified by each outcome: categories of outpatient appointments during the pandemic, having at least one prolonged interval in blood monitoring, being admitted for RA or a complication of RA.

The characteristics to be described will be:

- Age categories,
- Sex,
- Region (Sustainability Transformation Partnership level (STP, English NHS administrative region)),
- Urban/rural location,
- SES (IMD, in quintiles)
- Ethnicity
- Time since first RA code at baseline.
- BMI at baseline
- Smoking status at baseline
- Biologics prescribed prior to 2020

Objective 3

- To measure the association between prolonged intervals and outcomes, firstly, unadjusted and fully adjusted logistic regression models will be used to estimate association between the exposure (prolonged intervals) and the outcomes (out of range blood tests / diagnosis) in those at low risk only. These will be run individually within each cohort and then combined with an interaction term to test the impact of the pandemic. Confounders will be reviewed to understand if there are particular groups at higher risk.
    - Subanalysis will further stratify the second cohort by pandemic waves:
        - 23rd March 2020 to 30th June 2020 (wave 1, lockdown), monitoring
        - 1st July 2020 to 31st October 2020 (easing restrictions), outcome
        - 1st November 2020 to 31st March 2021 (wave 2),
        - 1st April 2021 to 31st November 2021 (easing restrictions)
        - 1st December 2021 to 1st May 2022 (Omicron wave).
- The same analysis will then be conducted in those at high risk.
- A sensitivity analysis will exclude people with a cancer diagnosis in the 5 years prior to baseline to see if this impacts results.
- Alternative analysis: matched analysis where people with prolonged intervals are matched in terms of age, gender, STP, risk status to people without prolonged intervals and outcomes are compared.

Software and Reproducibility

Data management will be performed using Python 3.8 and SQL with analysis carried out using Stata 17. Code for data management and analysis as well as codelists will be archived online.

Table shells

Power

Limitations

References

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