Study Protocol:

Tocilizumab versus sarilumab in preventing mortality in hospitalised COVID-19 patients in England: a comparative effectiveness study in the OpenSAFELY platform under the target trial emulation framework

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Background

Tocilizumab and sarilumab are two monoclonal antibodies against the interleukin (IL)-6 receptor, both typically used for the treatment of rheumatoid arthritis. Since the beginning of the COVID-19 pandemic, the IL-6 inhibitors targeting hyperinflammation have been proposed and tested for treating patients with severe or critical COVID-19 [1]. Such repurposed use has been mainly supported by two large-scale platform randomised controlled trials, the REMAP-CAP trial [2] and the RECOVERY trial [3], conducted during the wild-type and Alpha-variant waves.

Both tocilizumab and sarilumab were added to the NHS national guidance for COVID-19 treatment in January 2021 [4], and later based on a growing body of supportive evidence on the efficacy of tocilizumab, tocilizumab was formally licenced for COVID-19 by the European Medicines Agency (EMA) in December 2021. Consequently, sarilumab was only recommended when tocilizumab is unavailable or contraindicated by the updated NHS national guidance [5] and the NICE Rapid Guideline on managing COVID-19 [6]. However, the WHO living guideline, even the latest version in November 2023, did not distinguish between tocilizumab and sarilumab in their recommendation of COVID-19 treatment options [7].

Based on the electronic health record data in the OpenSAFELY platform [8], this study aims to examine and compare the effectiveness of tocilizumab and sarilumab in adult patients hospitalised due to COVID-19 in England between July 2021 and February 2022, when both drugs were frequently prescribed for COVID-19 treatment [9], following the target trial emulation framework.

Objectives

Primary Objectives

To compare the risk of all-cause mortality in hospitalised COVID-19 adult patients receiving tocilizumab vs. sarilumab during the follow-up period of 28 days from treatment initiation.

Secondary Objectives

To compare the risk of longer-term all-cause mortality in hospitalised COVID-19 adult patients receiving tocilizumab vs. sarilumab.

To compare the time to discharge from hospital since treatment initiation between adult patients receiving tocilizumab vs. sarilumab.

Methods

Data Sources

Primary care records managed by the GP software provider, TPP were linked to the Office for National Statistics (ONS) death data through OpenSAFELY, a data analytics platform created by our team on behalf of NHS England to address urgent COVID-19 research questions (https://opensafely.org). 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 large volumes of 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. Further details on our information governance can be found on information governance and ethics.

The dataset analysed within OpenSAFELY is based on 24 million people currently registered with GP surgeries using TPP SystmOne software. It includes pseudonymised data such as coded diagnoses, medications and physiological parameters. The primary care records are securely linked to other similarly pseudonymised datasets, including the Office for National Statistics (ONS) mortality database, inpatient hospital records from the Secondary Uses Service (SUS), national coronavirus testing records from the Second Generation Surveillance System (SGSS), and the COVID-19 therapeutics dataset, a patient level dataset derived from Blueteq software that was used to notify NHS England of the prescribed COVID-19 treatments in both hospital and community settings. Patient level vaccination status was available in the GP records directly from the National Immunisation Management System.

Study Design and Population

We will use the target trial emulation framework to structure our analysis (table 1). We will conduct a population-based cohort study with all adults (≥ 18 years old) within OpenSAFELY who had treatment records of either tocilizumab and sarilumab for in-patient treatment of COVID-19 between July 2021 and February 2022. Patients with no recorded region or sex information were excluded, as well as patients with a tocilizumab prescription and sarilumab prescription on the same date.

Patients were required to be hospitalised for COVID-19 (as recorded in COVID-19 therapeutics dataset) before treatment initiation. According to the NHS national guidance for COVID-19 treatment [4,5], patients who were eligible to receive these treatments should have had COVID-19 infection confirmed by microbiological testing or clinical diagnosis; were receiving dexamethasone or an equivalent corticosteroid unless contraindicated; and either had hypoxaemia with evidence of inflammation but not yet critically ill requiring respiratory support or in the early stages of critical illness requiring respiratory support, regardless of inflammation level.

Study Measures

Exposure

The exposure of interest is treatment with tocilizumab and sarilumab. In OpenSAFELY, exposure status of each patient will be ascertained from the COVID-19 therapeutics dataset based on the national Blueteq system.

Outcome

The primary outcome is all-cause mortality within 28 days after tocilizumab or sarilumab treatment initiation, extracted from the Office for National Statistics (ONS) mortality database in OpenSAFELY.

Secondary outcomes include longer-term all-cause mortality, and time to hospital discharge since treatment initiation.

Covariates

OpenSAFELY: The following potential confounding factors or moderators available in OpenSAFELY will be extracted at baseline, including age, sex, NHS region, ethnicity (grouped into five broad categories: White, Black or Black British, Asian or Asian British, Mixed, Other), Index of Multiple Deprivation (IMD, as quintiles derived from the patient's postcode at lower super output area level), calendar time of treatment initiation (to account for secular trend of prescription and COVID-19 outcomes), COVID-19 vaccination status (unvaccinated, one vaccination, two vaccinations, or three or more), SARS-CoV-2 re-infection status (positive test or clinical diagnosis code or exposure to COVID-19 drug at least three months before), body mass index (BMI, most recent record), comorbidities (diabetes, hypertension, chronic heart diseases, chronic respiratory diseases, moderate/severe renal disease, severe liver disease, solid cancer, hematological disease, immunosuppressive disease or treatment, solid organ transplant), and previous COVID-19 treatments (remdesivir, casirivimab/imdevimab and sotrovimab). Individuals with missing ethnicity, IMD, or BMI were included as "Unknown" category.

Statistical Analysis

Baseline demographic and clinical characteristics will firstly be compared between patients treated with tocilizumab vs. sarilumab. Follow-up time of individual patients will be calculated from the date of the treatment initiation record, until the date of the outcome event, 28 days since treatment initiation, or death, whichever occurred first.

The risk of all-cause mortality will be compared between the two groups using the Cox proportional hazards model, with follow-up period as the time scale. In the main analysis, the Cox model will be stratified by region to account for geographic heterogeneity in baseline hazards, and adjustment for the following: age, sex, calendar time, ethnicity, IMD (five categories), COVID-19 vaccination status, SARS-CoV-2 re-infection status, previous COVID-19 treatment, BMI, and history of a) solid cancer, b) hematological disease, c) moderate/severe CKD, d) liver disease, e) immunosuppressive treatment, f) immunosuppressive disease, g) solid organ transplant, h) diabetes, i) hypertension, j) chronic cardiac disease, k) chronic respiratory disease.

As an alternative approach to account for confounding bias, we will also use the propensity score weighting method to balance the distributions of relevant covariates between the two drug

groups. In this analysis, the propensity score for each patient was defined as the conditional probability of being treated with tocilizumab, estimated with a binary logistic regression of the actual treatment the patient received on all baseline covariates (see Model 1). The average treatment effect weighting scheme was then applied to the Cox model (without covariates) based on the estimated propensity scores. Balance check of baseline covariates after weighting was conducted with standardised mean differences between groups (with a threshold of <0.10 as the indicator of well balanced). Robust variance estimators were used in the weighted Cox model.

Regarding the secondary outcomes, Cox model with covariate adjustment will be used for the comparison of long-term mortality risk between groups. For the comparison of time to hospital discharge between the two drug groups, Cox regression with covariate adjustment will be used, with hospital discharge as the event of interest and the follow-up time since treatment initiation as the time scale. Deaths before discharge will be censored and assumed worst case (i.e., no discharge until follow-up endpoint).

To account for the difference in circulating variants (Delta vs. Omicron), a subgroup analysis will be conducted by the calendar time of treatment initiation, with before December 6 2021 (when the Omicron BA.1 variant became dominant) as Delta wave and after that as Omicron wave. Further exploratory analyses will be conducted by other subgroups (given sufficient sample size), including COVID-19 vaccination status, BMI categories, presence of comorbidities, age group, sex and ethnicity.

Several sensitivity analyses will be conducted to assess the robustness of main findings, including (1) using Multiple Imputation by Chained Equations instead of treating missing values as a separate category; (2) additionally adjusting for time between last COVID-19 vaccination and treatment initiation, days between hospital admission and treatment initiation, and rural/urban area; (3) adjusting for a reduced set of baseline covariates (age, sex, calendar time, ethnicity, IMD, COVID-19 vaccination status and SARS-CoV-2 re-infection status) and a minimal set (age, sex and calendar time); (4) conducting a Bayesian Cox regression to inform the strength of evidence in favour or against the null hypothesis; and (5) using COVID-19 specific mortality as an alternative outcome event.

Software and Reproducibility

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

References

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