OpenSAFELY Protocol: Effectiveness and safety of Paxlovid and sotrovimab for prevention of severe COVID-19 outcomes

Authors

Version: v1.0

Date: June 2022

Table of Contents

Background

On December 16, 2021, COVID-19 Medicine Delivery Units (CMDUs) were launched across England to provide antiviral medicines and neutralising monoclonal antibodies (nMAbs) to treat symptomatic COVID-19 patients in community settings who are at high risk of severe outcomes. The clinical guideline from NHS England [1,2] has been revised over time based on emerging evidence from randomised controlled trials (RCTs) and the approval of new medications by the UK Medicines and Healthcare products Regulatory Agency (MHRA). Since February 10, 2022, nirmatrelvir plus ritonavir (Paxlovid, an oral antiviral) and sotrovimab (an intravenous nMAB) have both been recommended as first-line treatments for non-hospitalised high-risk COVID-19 patients to prevent disease progression [2].

The approval and early routine clinical use of these two medications have been mainly supported by evidence from two RCTs in an unvaccinated population [3,4]. The EPIC-HR trial [3] was a phase 2/3 double-blind RCT for Paxlovid in symptomatic, non-hospitalised adults at high risk for progression to severe COVID-19. An interim analysis with 774 patients treated ≤3 days after symptom onset showed a reduced risk of COVID-19 related hospitalisation or all-cause death within 28 days in the Paxlovid group compared with the placebo group (0.77% vs. 7.01%; $P < 0.001$). Efficacy was maintained in the final analysis of 1379 patients (0.72% vs. 6.53%, absolute difference = -5.81%, 95% CI: -7.78% - -3.84%; $P < 0.001$; relative risk = 0.11). Similar results were reported for a secondary analysis involving 2085 patients treated ≤5 days after symptom onset (0.78% vs. 6.40%, absolute difference = -5.62%, 95% CI: -7.21% - -4.03%; $P < 0.001$; relative risk = 0.12). The COMET-ICE trial [4] was a phase 3 double-blind RCT that evaluated the use of intravenous sotrovimab in non-hospitalised high-risk adult patients with symptomatic COVID-19. An interim analysis with 583 patients treated ≤5 days after the onset of symptoms showed a reduced risk of all-cause hospitalisation or death within 29 days in the sotrovimab group compared with the placebo group (1% vs. 7%, $P = 0.002$) [4]. Similar results were reported for the final sample of 1057 patients, with the risk estimate of 1% with molnupiravir vs. 6% with placebo (absolute difference = -4.53%, 95% CI: -6.70% - -2.37%; adjusted relative risk = 0.21, 95% CI: 0.09 - 0.50; $P < 0.001$) [5].

However, it remains unclear whether their effectiveness persists in vaccinated populations, patients infected by the Omicron variant sublineages, and other subgroups underrepresented in clinical trials (e.g., immunosuppressive individuals or those with neurological conditions). Although both trials showed comparable risk of adverse events between treatment group and placebo group [3-5], some observed side effects of Paxlovid (e.g., dysgeusia and diarrhoea) and sotrovimab (e.g., diarrhoea, urticaria and anaphylaxis) still warrant further clinical monitoring. Validating the effectiveness of these drugs in preventing adverse outcomes in real-world settings with diverse populations and immediate post-marketing surveillance are thus crucial to support their large-scale clinical use among COVID-19 patients.

In addition, besides the consideration of several contraindications and potential drug interactions for the use of Paxlovid [2], to our knowledge there is no evidence or guidance for clinicians on how to choose between sotrovimab and Paxlovid and no comparative effectiveness study has ever been conducted. Given that sotrovimab is administered by

intravenous infusion, Paxlovid as an oral drug has the advantages of convenient and non-invasive administration. Moreover, FDA has recently suspended the emergency use authorisation of sotrovimab for treatment of mild-to-moderate COVID-19 [6] due to its possibly reduced efficacy against Omicron BA.2 variant [7], whilst Paxlovid was shown to remain active against this sub-variant [8]. Validation research directly comparing the effectiveness and safety profiles of these two first-line medications is urgently needed to further develop an up-to-date clinical management pathway.

Therefore, following the national CMDU rollout of these two first-line medications since February 10, 2022, this real-world observational study aims to examine and compare the effectiveness of Paxlovid and sotrovimab on preventing severe outcomes in non-hospitalised high-risk adult patients with COVID-19 across England, utilising the near real-time EHR data in the OpenSAFELY-TPP platform [9]. We will also explore their effectiveness in different patient groups by demographic and clinical factors, in comparison with molnupiravir [10], and evaluate their safety profiles.

Objectives

Primary Objectives

To compare the risk of COVID-19 related hospitalisation or death in non-hospitalised high-risk COVID-19 patients receiving Paxlovid vs. sotrovimab within 28 days from treatment, as well as risks of other outcomes (e.g., all-cause hospitalisation or death, 2-month and 3-month COVID-19 related hospitalisation or death).

Secondary/Exploratory Objectives

To explore the effectiveness of Paxlovid and sotrovimab in different high-risk cohorts defined by NHS England, and subgroups according to COVID-19 vaccination status, body mass index (BMI), presence of other comorbidities, age group, sex, ethnicity, time period or variants.

To compare the effectiveness of Paxlovid or sotrovimab with molnupiravir in order to (1) assess whether sotrovimab has limited effectiveness during the period when the BA.2 was the dominant variant (in comparison with our previous analysis in the BA.1 era [11]), though confounding by indication should be assessed before conducting this updated analysis; and (2) validate the current priority hierarchy of oral antivirals (Paxlovid as first-line and molnupiravir as third-line).

To explore the safety outcomes of Paxlovid and sotrovimab treatment, including allergic reactions (e.g., anaphylaxis and urticaria) and infusion-related reactions for sotrovimab, and dysgeusia and diarrhoea for Paxlovid.

Methods

Data Source

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. Patient-level vaccination status is available in the GP records directly via the National Immunisation Management System (NIMS). No free text data are included. The following linked data were also used for this study: accident and emergency (A&E) attendance and in-patient hospital spell records via NHS Digital's Hospital Episode Statistics (HES); national coronavirus testing records via the Second Generation Surveillance System (SGSS); and the "COVID-19 therapeutics dataset", a patient-level dataset on antiviral and nMAbs treatments, newly sourced from NHS England, derived from Blueteq software that CMDUs use to notify NHS England of COVID-19 treatments [9].

Data Sharing

All data were linked, stored and analysed securely within the OpenSAFELY platform https://opensafely.org/. All code is shared openly for review and re-use under MIT open license. Detailed pseudonymised patient data is potentially re-identifiable and therefore not shared. We rapidly delivered the OpenSAFELY data analysis platform without prior funding to deliver timely analyses on urgent research questions in the context of the global Covid-19 health emergency: now that the platform is established we are developing a formal process for external users to request access in collaboration with NHS England; details of this process will be published shortly on OpenSAFELY.org.

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. This implementation of OpenSAFELY is hosted within the TPP environment, which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant; patient data have been pseudonymised for analysis

and linkage using industry standard cryptographic hashing techniques; all pseudonymised 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 anonymisation 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 bases 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.

Study Design and Population

We will conduct a population-based cohort study with all adults (≥18 years old) within OpenSAFELY-TPP who had treatment records of either sotrovimab or Paxlovid from CMDUs since February 10, 2022 [9]. In addition, eligible patients in this study were required to be non-hospitalised for COVID-19 (as recorded in COVID-19 therapeutics dataset [9]), initiate treatment within 5 days after positive SARS-CoV-2 test, and be registered in GP surgeries before treatment initiation. Patients were excluded if they had treatment records of any other antivirals or nMAbs for COVID-19 before receiving sotrovimab or Paxlovid. Patients with treatment records of other antivirals or nMAbs after receiving sotrovimab or Paxlovid were censored at the start date of the second treatment.

According to the eligibility criteria from NHS England [2], to have received COVID-19 nMAb or antiviral treatment in the community during this period, patients needed to have SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) testing or lateral flow test, onset of COVID-19 symptoms within the last five days, and be a member of at least one of the following ten high-risk cohorts: patients with Down syndrome, a solid cancer, a haematological disease or stem cell transplant, renal disease, liver disease, immune-mediated inflammatory disorders, primary immune deficiencies, HIV/AIDS, solid organ transplant, or rare neurological conditions.

To be noted, patients can only be considered for treatment with Paxlovid if they do not have a history of advanced decompensated liver cirrhosis, stage 3-5 chronic kidney disease (CKD), solid organ transplant, and are not taking any of the medications with potential drug-drug interactions listed by NHS England [2]. Therefore, in all analyses involving Paxlovid, we will detect and exclude all patients with these contraindications based on diagnosis codes, clinical tests and medication records in OpenSAFELY-TPP to ensure comparability.

Study Measures

Exposure

The exposure of interest is treatment with sotrovimab or Paxlovid administered by CMDUs. Exposure status and date of treatment of each patient will be ascertained from the COVID-19 therapeutics dataset.

Outcome

The primary outcome is COVID-19 related hospital admission or death within 28 days of follow-up.

Secondary outcomes include 28-day all-cause hospital admission or death, 2-month and 3-month COVID-19 related hospital admission or death.

Safety outcomes include allergic reactions (e.g., anaphylaxis and urticaria), infusion-related reactions and diarrhoea for sotrovimab, and dysgeusia and diarrhoea for Paxlovid. We will also explore other rare adverse outcomes.

Covariates

The following potential confounding factors or effect modifiers available in OpenSAFELY-TPP will be extracted at baseline, including age, sex, NHS region of their registered GP practice (STP), 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 (to account for secular trend of prescription and COVID-19 outcomes), COVID-19 vaccination status (unvaccinated, one vaccination, two vaccinations, or three or more), BMI (most recent record), high-risk cohort categories as mentioned above (allowing multiple categories per patient), and other comorbidities (e.g., diabetes, hypertension, chronic heart diseases, chronic respiratory diseases).

Individuals with missing ethnicity, IMD or BMI were included as "Unknown" category.

Statistical Analysis

For the comparative effectiveness analysis, distributions of baseline characteristics will firstly be compared between patients treated with sotrovimab vs. Paxlovid. Follow-up time of individual patients will be calculated from the date of the treatment initiation record, until the date of outcome event, 28 days since treatment initiation, death, patient de-registration date, or the study end date (to be determined), whichever occurred first.

Risks of COVID-19 related hospital admission/death will be compared between the two groups using the Cox proportional hazards model, with time since treatment as the time scale. The Cox

models will be stratified by STP areas to account for geographic heterogeneity in baseline hazards, with sequential adjustment for other baseline covariates. As an alternative approach to account for confounding bias, we will use the propensity score weighting (PSW) method to balance the distributions of relevant covariates between groups. The propensity score for each patient is defined as the conditional probability of being treated with Paxlovid, estimated with a binary logistic regression of the actual treatment on relevant baseline covariates. The average treatment effect (ATE) weighting scheme will then be applied to the Cox model based on the estimated propensity scores. Balance check of baseline covariates after weighting will be conducted using standardised mean differences between groups. Robust variance estimators will be used in the weighted Cox model. Similar approach will be used for comparing risks of secondary outcomes and for the exploratory analyses with molnupiravir users as a reference group.

Further exploratory analyses will be conducted by different subgroups, including each high-risk cohort, COVID-19 vaccination status, BA.1 vs BA.2 variants (need to infer from calendar date as only a small proportion of patients had SGTF or detected variant information), BMI categories, presence of other comorbidities, time since test positive (<3 vs 3-5 days), age group, sex and ethnicity.

Several sensitivity analyses will be conducted to assess the robustness of main findings, including (1) using stratified Cox models by calendar weeks to account for temporal heterogeneity in baseline hazards; (2) using complete-case analysis or Multiple Imputation by Chained Equations instead of treating missing values as a separate category; (3) excluding patients with treatment records of both sotrovimab and Paxlovid, or any other treatments (i.e., casirivimab, molnupiravir, or remdesivir); (4) including patients with missing SARS-CoV-2 test information or initiating treatment after 5 days since positive SARS-CoV-2 test.

For safety outcomes, we will describe the incidence rates following treatment and then apply similar analytical approaches as the comparative effectiveness analyses (Cox regressions with PSW). An alternative approach we will consider is self-controlled case series (SCCS) method, firstly for each of the two medicines separately and then comparing the risks of adverse events between them. Only those who received the treatment and experienced the adverse outcome under investigation will be included, of whom the follow-up time period will be divided into an exposure risk period followed by a baseline period. Conditional Poisson regression will be conducted to estimate the IRR comparing the safety risks in exposure vs. baseline periods.

Software and Reproducibility

Data management will be performed using Python, with analysis carried out using Stata 16.1. Code for data management and analysis as well as codelists archived online.

References

[1] NHS. Neutralising monoclonal antibodies (nMABs) or antivirals for non-hospitalised patients with COVID-19. 2021. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103186

[2] NHS. Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies for non-hospitalised patients with COVID-19. 2022. https://www.england.nhs.uk/coronavirus/documents/c1603-interim-clinical-commissioning-policy-antivirals-or-neutralising-monoclonal-antibodies-for-non-hospitalised-patients-with-covid-19-version-5/

[3] Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022;386(15):1397-1408. doi:10.1056/NEJMoa2118542

[4] Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. N Engl J Med. 2021;385(21):1941-1950. doi:10.1056/NEJMoa2107934

[5] Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2022;327(13):1236-1246. doi:10.1001/jama.2022.2832

[6] FDA. FDA updates Sotrovimab emergency use authorization. 2022. https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization

[7] Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Nature 2022;604:553-6.

[8] Li P, Wang Y, Lavrijsen M, et al. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. Cell Res. 2022;32(3):322-324. doi:10.1038/s41422-022-00618-w

[9] The OpenSAFELY Collaborative. Trends, regional variation and clinical characteristics of recipients of antivirals and neutralising monoclonal antibodies for non-hospitalised COVID-19: a descriptive cohort study of 23.4 million people in OpenSAFELY. medRxiv. 2022; doi: https://doi.org/10.1101/2022.03.07.22272026

[10] Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386(6):509-520. doi:10.1056/NEJMoa2116044

[11] Zheng B, Green ACA, Tazare J, et al. Comparative effectiveness of sotrovimab and molnupiravir for prevention of severe COVID-19 outcomes in non-hospitalised patients: an observational cohort study using the OpenSAFELY platform. medRxiv. 2022; doi: https://doi.org/10.1101/2022.05.22.22275417