Association between ursodeoxycholic acid and COVID-19 severity

Study protocol

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0.1	09/02/2022	Initial draft created by Ruth Costello
1.0	21/06/2023	Finalised protocol version 1

Introduction

There is growing evidence that ursodeoxycholic acid (UDCA) may protect against severe COVID-19 infection (1–3). The mechanism for this is that UDCA suppresses the signalling of the Farnesoid X receptor (FXR). FXR controls expression of angiotensin-converting enzyme 2 (ACE2), which is a protein on the membrane of cells and is the main receptor of SARS-COV-2. By suppressing the signalling of FXR, ACE2 expression is reduced, thereby reducing the places where SARS-COV-2 can enter the body. Brevini et al reports how UDCA prevented COVID-19 transmission hamsters, ex-vivo human lungs and liver cells, the study also showed how UDCA treatment reduced ACE2 expression in human nasal epithelial cells. Further, small studies using observational data from registries and cohorts of people with chronic liver disease showed that UDCA exposure was associated with better COVID-19 outcomes, with reduced infection, hospitalisation with COVID-19 and death due to COVID-19 (1). However these studies were small, the largest was a cohort of 1607 people with cirrhosis who were exposed to UDCA and propensity score matched to people without UDCA exposure. Over follow-up, 235 people developed COVID-19, with 85 in the UDCA group. There was a 48% reduction in severe or critical COVID-19 in the UDCA group (aOR 0.48, 95% confidence interval (CI): 0.25, 0.94) (4).

UDCA is first-line therapy in the treatment of primary biliary cholangitis (PBC) (previously referred to as primary biliary cirrhosis). PBC is a rare, chronic liver disease that leads in many cases to cirrhosis and end-stage liver disease.. It typically affects females more than males (ratio 10:1) and usually presents at 50-60 years of age (5,6). UDCA has been shown to delay the progression of PBC, and is usually prescribed for life. UDCA is generally well-tolerated. An audit in the UK found that only 9.7% patients with PBC discontinued UDCA; nausea, diarrhoea and vomiting were the most frequent intolerances (7). It is, however, only moderately efficacious; an estimated 30-40% patients with PBC will have inadequate biochemical response to the drug (5). Second line therapy for people with inadequate UDCA response or UDCA intolerance is with obeticholic acid (OCA), a FXR agonist which is significantly more expensive than UDCA. UDCA is also widely prescribed in primary sclerosing cholangitis (PSC). PSC is a rare liver disease that similarly progresses over time to cirrhosis and end stage liver disease. PSC more frequently presents in males aged 30-40 years old, often with comorbid inflammatory bowel disease (8,9). Although UDCA is not recommended as a routine treatment (10), UDCA has been shown to improve liver biochemistry and is frequently used (9).

Given that a proportion of the population that are at high risk from severe COVID-19 (11), identifying prophylactic medications is important in preventing serious COVID-19 infections in these groups. As UDCA is widely used and known to be safe, it has the potential to be a useful preventative medication.

Objectives

To estimate the hazard of 1) hospitalisation for COVID-19 and 2) COVID-19 death comparing use of UDCA treatment versus no UDCA treatment in a population with PBC or PSC, adjusting for confounding variables.

Methods

Data Source

Primary care records managed by the GP software provider, TPP were linked to 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 pseudonymized 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 pseudonymized patient data to be transferred off-site. This, in addition to other technical and organisational controls, minimizes any risk of re-identification. Similarly pseudonymized datasets from other data providers are securely provided to the EHR vendor and linked to the primary care data. The dataset analysed within OpenSAFELY is based on 24 million people currently registered with GP surgeries using TPP SystmOne software. **It includes pseudonymized data such as coded diagnoses, medications and physiological parameters. No free text data are included**. Further details on our information governance can be found on here.

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 52,53; 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 counts54. **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 organizations 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 exposure55. 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 use a cohort study design to address our research questions. For this study we will assess the inclusion criteria on 1st March 2020, which is hypothesised to be the beginning of the pandemic in the UK.

The study population will be people with a diagnosis of PBC or PSC prior to study start.

We will select individuals using the following inclusion and exclusion criteria:

Inclusion Criteria

1. Diagnosed with PBC or PSC at least 6 months prior to study start.
2. ≥18 and ≤110 years of age at study start.

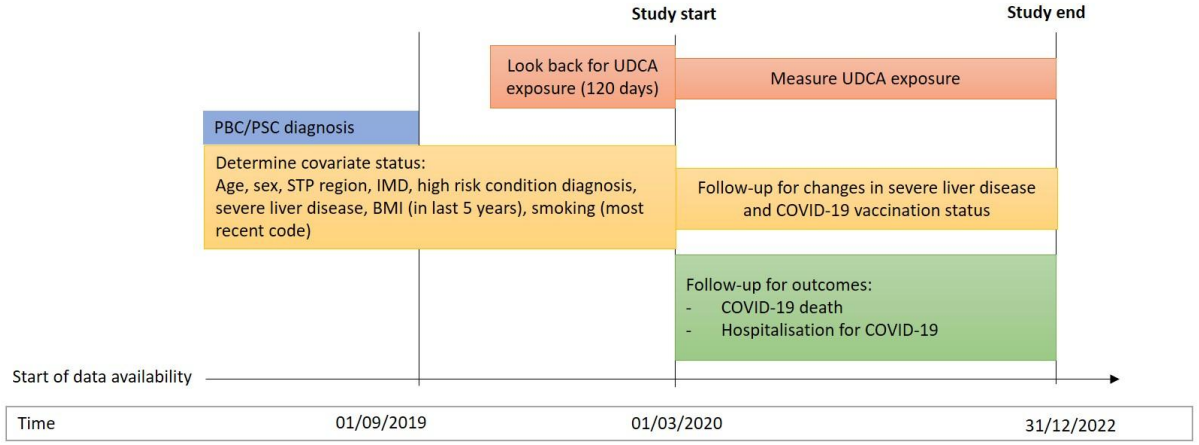
Exclusion Criteria

1. Less than 6 months of registration in a TPP practice as of study start, which could preclude adequate ascertainment of key covariates.
2. Missing sex or index of multiple deprivation (IMD) as this may indicate poor data quality.
3. Liver transplant prior to study start.

Follow-up

People will be followed from study start (1st March 2020) until the outcome, death, deregistration from their GP or the end of the study period (31st December 2022).

Figure 1: Study design



Study measures

Exposure

Primary exposure is time-varying UDCA status. We will identify all UDCA prescriptions from 120 days prior to 1st March 2020 and throughout follow-up to determine periods of exposure. As we only have the date of prescription we will assume that the prescription lasts 120 days (this assumes prescriptions are likely to be for up to 90 days, and allows for an additional 30 days between prescriptions). If the prescription overlaps the next prescription we will assume continuous exposure. Overlapping days will not be added to exposure time. If there is more than one prescription on the same day only one prescription will be included. We will have a 120 day look back at baseline to determine exposure at baseline.

Outcomes

The primary outcome will be a composite of COVID-19 death and hospitalisation for COVID-19. The secondary outcomes will investigate these individually.

These will be defined as follows:

COVID-19 death: Death due to COVID-19 during the study period will be identified through linked ONS death registration data. This will be defined as a death with COVID-19 reported as an underlying or contributory cause on the death certificate (ICD-10 codes U07.1 and U07.2).

Hospitalisation for COVID-19: Hospitalisations with COVID-19 diagnosis listed in any position (ICD-10 codes U07.1 and U07.2), during the study period, will be identified from linked secondary care data.

For the composite outcome, if a person is hospitalised before death, the date of hospitalisation will be used.

Full potential list of covariates collated through literature review and discussions with domain experts

Time-varying covariates will be assessed 6-monthly and at exposure switching (12).

- Age (time-varying).
- Sex.
- Geographic region (STP, n~35).
- Having a COVID-19 high risk condition at baseline:
    - Learning difficulties any time before study start
    - A solid cancer: up to 6 months prior to study start,
    - A haematological disease in 12 months prior to study start or stem cell transplant any time before study start
    - Renal disease any time before study start
    - Immune-mediated inflammatory disorders identified through immunosuppressant drugs and glucocorticoid prescribing in previous 12 months prior to study start
    - Primary immune deficiencies any time before study start
    - HIV/AIDS any time before study start
    - Solid organ transplant any time before study start
    - Rare neurological conditions (multiple sclerosis, motor neurone disease, myasthenia gravis or huntington's disease) any time before study start
- Indicators of PBC/PSC disease severity :this will include: cholestasis, ascites, portal hypertension, hepatic decompensated cirrhosis, esophageal varices, hepatic failure, hepatocellular carcinoma. We chose a wide range of terms to ensure we captured severe disease, as it may not be well coded (time-varying).
- Second-line therapies:
    - OCA at baseline: OCA could be a confounder as it works in the opposite way to UDCA, potentially increasing the likelihood of COVID-19 infection. OCA can be determined from high cost drugs data only which is only available up to March 2020.
    - Budesonide. Budesonide has been associated with improved recovery from COVID-19 infection (13) so could be a confounder.
- Additional prescribing:
    - Glucocorticoids

    - Biologics at baseline (specifically Rituximab in PSC) - only available in high-cost drug data so only available up to March 2020.
- Ethnicity - identified from primary care records and supplemented by hospital records.
- Index of Multiple Deprivation (quintiles).
- BMI at baseline, ascertained from weight measurements within the 10 years prior to study start, restricted to those taken when the patient was over 16 years old.
- Smoking, most recent code prior to study start.
- COVID-19 vaccination (time-varying): considered vaccinated from the date of 1st vaccination (to be included if study follow-up extended).
- Liver transplant (time-varying)
- COVID-19 variants (time-varying)

Table 1: Codelists

Criteria	Codelist link
PBC diagnosis	https://www.opencodelists.org/codelist/user/ruthcostello/primary_biliary_cirrhosis/00438120/#full-list
PSC diagnosis	https://www.opencodelists.org/codelist/user/ruthcostello/primary-sclerosing-cholangitis/2dba3230/
UDCA	https://www.opencodelists.org/codelist/user/ruthcostello/udca/23020452/
COVID-19 High risk conditions (listed above)	Codelists available based on NHS digital code lists to identify high-risk patients eligible for new COVID-19 treatments.
Budenoside	https://www.opencodelists.org/codelist/user/ruthcostello/budesonide/090fa297/
Disease severity:	These codelists for decompensated liver cirrhosis are available in Snomed and ICD-10.
Ethnicity	https://www.opencodelists.org/codelist/opensafely/ethnicity-snomed-0removed/2e641f61/
Smoking	https://www.opencodelists.org/codelist/opensafely/smoking-clear/2020-04-29/

Missing data

In the primary analysis, those with missing BMI will be assumed non-obese and those with missing smoking information will be assumed to be non-smokers on the assumption that both obesity and smoking would be more likely to be recorded if present. A missing category will be used where ethnicity is not recorded.

Statistical analysis

As a first step, flowcharts showing the number of patients meeting each inclusion and exclusion criteria will be generated.The characteristics of the population will be summarised using descriptive statistics, stratified by UDCA exposure status at baseline.

For each outcome (death due to COVID-19 and composite death and hospitalisation for COVID-19), time to the outcome will be displayed in Kaplan-Meier plots and adjusted cumulative incidence plots with time in study as the timescale. Cox proportional hazards regression will be used to estimate hazard ratios and 95% confidence intervals for the association between UDCA exposure and each outcome stratified by STP region and 1) unadjusted, 2) adjusted for covariates listed above. Robust standard errors will be applied.

Sensitivity analyses

To test the robustness of our results the following sensitivity analyses will be explored:

1. **UDCA exposure**:
    a. We have made assumptions when preparing the prescription data, we will test whether these made a difference to the association by updating prescription length to 90 days.
    b. We will add on overlapping days to the next unexposed period up to 120 days.
2. **Outcomes:**
    a. We will limit deaths and hospitalisations to those with the primary cause/reason of COVID-19.
3. **Second line therapies:** Second line therapies are broadly likely indicate a lack of response to UDCA, if this relates to the mechanism that UDCA may work against severe COVID-19 could be an indirect effect modifier, therefore an interaction term between UDCA exposure status and second-line therapy, will be fitted.
4. **Quantitative bias analysis.** Given the potential for unmeasured confounding by disease severity, we will apply quantitative bias analysis (QBA) to obtain bias-adjusted hazard ratios for this potential binary confounder (14). This QBA analysis requires the specification of several parameters that will be derived based on clinical input: prevalence of the confounder in the treated (assumed X or Y), prevalence of the confounder in the untreated (assumed Z) and estimated hazard ratio for the relationship between the unmeasured confounder and outcome (assumed HR: A, B,C) .

Table shells

Figure 1: Flowchart of Patients

Table 1: Descriptive Characteristics

		Total	No UDCA	UDCA
Total				
Age	18-<40			
	40-<50			
	50-<60			
	60-<70			
	70-<80			
	80+			
Gender	Female			
	Male			
BMI	<18.5			
	18.5-24.9			
	25-29.9			
	30-34.9			
	35-39.9			
	Missing			
Ethnicity	White			

	Mixed			
	Asian or Asian British			
	Black			
	Other			
	Missing			
IMD	1 (least deprived)			
	2			
	3			
	4			
	5 (most deprived)			
Smoking	Never			
	Current			
	Former			
	Missing			
High risk of COVID-19 condition				
Severe liver disease				
Exposure to other medications	Obeticholic acid			
	Budesonide			

Figure 2: Kaplan-Meier Plot of Time to COVID-19 hospitalisation/death, stratified by exposure group

[Note: Including number under follow-up at each time-point, for each treatment category]

Table 2: Hazard Ratios (HRs) and 95% confidence intervals (CI) for COVID-19 hospitalisation/death

			Crude	DAG Adjusted	Fully adjusted
	Events	**Rate per 1000 PY**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
No UDCA			1.00	1.00	1.00
UDCA					

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