PROTOCOL: A patient-level meta-analysis on SARS-CoV-2 viral dynamics to model response to antiviral therapies

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Background

A key strategy in the battle against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is antiviral drug therapy. Significant efforts are currently under way to establish whether currently available agents may be re-purposed to treat SARS-CoV-2, in addition to development of novel agents. In order to judge whether a drug is able to significantly disrupt viral load, it is important to understand the natural history of the viral trajectories and patient factors which may influence this. In addition, since data are now being published on re-purposed clinical drug activity, it is now possible to begin to assess the effect of these treatments.

The aim of this work is therefore to undertake a systematic literature review to extract and pool individual patient-level data on viral load with time in order to develop a viral kinetic model. This model will be used to identify covariates associated with inter-individual differences in viral load trajectory in patients who are and are not treated with antivirals.

Objectives

1. Systematically search for case reports, case series and clinical trials reporting serial patient level viral load from any sampling method
2. Undertake qualitative graphical analysis on overall viral load trajectories from all studies regardless of quality/missing covariates
3. Perform quality assessment of data in terms of both assay quality (conversion of PCR cycle threshold to viral load) and drug history (recording of days upon which antivirals were administered for each patient)
4. Undertake a Cox proportional hazard modelling analysis with the outcome of time to viral clearance to determine the main factors associated with viral clearance.
5. Fit a nonlinear mixed effects model to derive the following metrics: viral AUC, peak viral load, viral elimination rate)
6. For data meeting the accepted quality criteria with regard to drug history fit a nonlinear mixed effects viral kinetic model and estimate potency of antiviral drugs used in included studies
7. Publish the resulting patient level dataset to be used as a resource for antiviral researchers

Methods

Criteria for selecting studies for this review

Since time of infection is usually not known, and there are yet to be human challenge studies on SARS-CoV-2, we will search for reports of either viral load or PCR cycle threshold with time since symptom onset (or in asymptomatic subjects time since viral monitoring started) from any sampling site. In addition, and since it is anticipated that there will be heterogeneous rates of reporting, the following patient-level covariates will be extracted:

1. Presence of fever >37.5 C at any time (non-time varying covariate)
2. Age, where possible individual age but will accept population central measure (e.g. mean, median) if not reported
3. Sex (m/f) only if reported per individual
4. Need for and days of intensive care treatment
5. Need for and days of mechanical ventilation
6. Whether patient died and time to death from symptom onset

Using the above criteria and reporting in the paper a disease score will be derived as follows:

0 = Asymptomatic ; 1 = Mild (Fever, cough or other mild symptoms reported) ; 2 = Moderate (in addition to mild need for supplemental oxygen) ; 3 = Severe (requirement for mechanical ventilation)

The following information will also be extracted on the viral load measurement:

1. Site from which samples were taken
2. If viral load not reported in copies/mL the PCR primers used
3. Assay limit of quantification and limit of detection

Two quality assessments will be applied to each dataset. Firstly the quality of viral load reporting will be graded as follows:

1 = viral load reported in copies/mL or a calibration curve reported in the manuscript allowing conversion of PCR cycle threshold to copies/mL ; 2 = Viral load reported in PCR cycle threshold but primers reported and a calibration curve from another source will be used to convert to viral load in copies/mL ; 3 = Viral load reported in PCR cycle threshold but primers not reported so an assumed calibration curve from another source will be used to convert to viral load in copies/mL.

The second quality assessment relates to reporting of the antiviral drug therapy administered, which drug(s) at what dose(s) and upon which days did patients receive the drug(s). Scoring will be as follows:

NA = no reporting of antiviral therapy, unknown whether patients received antivirals or not ; 0 = patients are reported to have received antivirals but either drugs received are unknown or days upon which they were received is unknown ; 1 = either it is clear that no antiviral treatment was used or the day(s) that any antivirals are administered is reported.

Whilst the final analysis may include viral load quality 1-3 data any data that is not quality 1 regarding antiviral therapy will be excluded.

Search methods for identification of studies

PubMed, EMBASE, medRxiv and bioRxiv will be searched with a date range of 1/1/2020 to 31/5/2020. The following search terms will be used for PubMed and EMBASE:

(SARS-CoV-2 OR COVID OR coronavirus OR 2019-nCoV) AND (viral load OR cycle threshold OR rtPCR OR real-time PCR OR viral kinetics OR viral dynamics OR shedding OR detection OR clinical trial)

The search will be truncated (due to character limits in the search engine) for medRxiv and bioRxiv as follows:

(SARS-CoV-2 OR COVID-19 OR coronavirus) AND (viral load OR cycle threshold OR PCR OR viral dynamics OR clinical trial))

After removing duplicates two reviewers will independently extract papers for full text screening, with any discrepancies decided by a third reviewer.

Data collection

Viral load and covariate information will be extracted into .csv format datasheets either by digitising plotted data (Rohatgi 2019), or extracting numerical data directly from published or supplementary files. Where data are missing corresponding authors will be emailed and asked to provide this. These extracted data will be stored on a shared github repository, and for each paper two R-scripts will read in and reshape the data to a standard format. The first script will extract viral load assay and time data, whilst the second will add covariates.

A quality control (QC) check will be performed for each paper by an independent reviewer who was not responsible for extracting the raw data. A standardised dataset with common columns relating to the items listed above will be created for each paper, and these will be stacked upon one another to created the final dataset for meta analysis.

Data cleaning and QC will be undertaken with the aim to lock the database for final analysis within 1 week of the end of the search period.

Data analysis

The following analyses will be performed:

Cox proportional hazards survival analysis

The dependent variable will be time to viral clearance defined as the time of the first sample falling below the limit of quantification following the last above limit of quantification sample (i.e. if samples become positive after being negative the earlier negative sample will be discounted). If the final sample is above the limit of quantification the case will be treated as censored.

A multivariable analysis will be undertaken in R (R Core Team 2017) accounting for patient covariates, sampling site, viral load limit of quantification, and antiviral drugs. Where possible if combinations of drugs used exploring the addition of interaction terms. Missing covariate data may or ay not be handled using multiple imputation depending on the level of missingness.

Descriptive analysis of viral dynamics

The viral kinetic model described by Kim et al. (2020) will be fitted to data from each sampling site in turn in NONMEM (Beal et al. 2013) with, below limit of quantification data included using the "M3 Method". Viral AUC, peak viral load and terminal elimination rate will be plotted against patient covariates and antiviral drug regimens.

Quantitative analysis of antiviral clinical pharmacological effects

For drug quality 1 data the model described by Kim et al. (2020) will be fitted with an Emax model used to accelerate viral clearance. Model building will begin with drug-free data and each drug and if available drug combination added to estimate drug effect parameters.

Appendices

Authors

The following authors will contribute to this analysis:

Silke Gastine, Juanita Pang, Florencia Tettamanti Boshier, Simon Carter, Dagan Lonsdale, Mario Cortina Borja, Judy Breuer, Frank Kloprogge and Joe Standing

Should any authors of included papers provide a significant contribution in terms of unpublished data and are willing to contribute to data interpretation and writing, they may be added as an additional author.

Contributions of authors

Initial idea and framing data to be collected: JB, DL, FK, JS Systematic literature search: JP, FTB, SG, JS Data extraction: JP, FTB, SG, SC, JS Data QC: SG, FK, SC, JS Statistical analysis: SG, JP, FTB, MCB, JS Model-based analysis: SG, FK, JP, FTB, SC, JS Manuscript writing: SG, all

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