

Prevention of neurological complications during COVID-19: protocol for a retrospective analysis of the ISARIC4C national cohort

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ABSTRACT

Neurological complications such as stroke and encephalopathies affect 4% of adults with acute COVID-19 infection, causing significant morbidity with long term health and economic consequences. Dexamethasone reduces the 28-day mortality in hospitalised patients requiring supplemental oxygen, while remdesivir has antiviral action against SARS-CoV-2 and reduces the severity of COVID-19 in these patients. We hypothesise that adding either remdesivir, dexamethasone or both to standard of care in patients hospitalised with COVID-19 may reduce the incidence of COVID-19-associated neurological complications. This retrospective analysis of the ISARIC4C cohort will analyse data from patients aged 18 years and older admitted to hospital with COVID-19 between 31 Jan 2020 and 29 Jun 2021. The incidence of neurological complications following COVID-19 in patients receiving standard of care and either remdesivir, dexamethasone or both will be compared against the standard of care using propensity scoring methodology. The effect of neurological complications on markers of disease severity, as well as clinical outcome, will be assessed using multivariable linear and logistic regression.

INTRODUCTION

COVID-19 is associated with a range of multi-system complications, causing significant morbidity which may overshadow the acute illness¹, especially in younger and less clinically vulnerable patients. While existing therapeutics may reduce the severity of COVID-19, their effects on functional outcomes, including a return to pre-morbid level of functioning, are less well-defined than for mortality and acute disease severity^{2,3}. A renewed emphasis on reducing long-term morbidity due to systemic complications of COVID-19 is therefore needed.

Neurological complications following COVID-19 are associated with the worst functional outcomes¹ of all systemic complications, and include stroke, encephalopathies, neuropsychiatric and inflammatory syndromes⁴⁻⁶. Stroke is the most common and best described, with an incidence of 1-2% in all hospitalised patients. The cost of care following acute stroke is estimated at between £6840 – 37,800 per annum⁷, mostly due to prolonged rehabilitation. Meanwhile, neurological conditions of any type are the leading global cause of disability-adjusted life years (DALYs)⁸. As COVID-19 is projected to become a seasonal infection^{9,10}, the incidence, severity and demographics of neurological complications may translate into a significant socioeconomic burden of care, in terms of physical and cognitive disability, across multiple decades. As a result, evidence-based treatment strategies aiming to reduce the morbidity arising from neurological complications of COVID-19 are of urgent public health importance.

The disease processes leading to neurological complications may occur during or following infection with SARS-CoV-2. Proposed mechanisms include viral-driven endotheliitis, systemic inflammation leading to coagulopathy, cytokine toxicity, blood brain barrier disruption, antibody and cell-mediated autoimmunity, as well as the consequences of severe prolonged illness^{6,11-13}. Neurological complications increase with the severity of COVID-19⁶, which is in turn associated with a higher viral load in the upper respiratory tract¹⁴. Uncontrolled viraemia is related to a stronger immune response which may facilitate bystander neurological autoimmunity^{15,16}. Existing treatments licensed for COVID-19 may prevent or lessen the impact of neurological complications through reducing viral replication and the severity of inflammation, although this has not been investigated.

Remdesivir is a repurposed antiviral medication approved in the UK for the treatment of COVID-19 on 30 July 2020, and has shown broad antiviral action *in vitro* against emerging coronaviruses, including MERS-CoV, SARS-CoV-1 and SARS-CoV-2¹⁷. In the ACTT-1 trial remdesivir demonstrated a 50% greater chance of clinical improvement in adults hospitalised with COVID-19 and requiring supplemental oxygen¹⁸. While the SOLIDARITY trial found no significant effect for remdesivir on time to recovery, patients in the remdesivir group were admitted for a longer period to receive their treatment, potentially confounding these results¹⁹. More recently, in the PINETREE study²⁰, remdesivir reduced COVID-19-related hospitalisation by 87% in patients at high risk of disease progression²¹ and was shown to reduce the time to clinical improvement by 2 days in a separate retrospective analysis of hospitalised COVID-19 patients²². Taken together these results show remdesivir may reduce the severity of COVID-19, likely through inhibiting viral replication. Dexamethasone is another treatment approved in the UK on 16 Jun 2020 for use in COVID-19, after the RECOVERY trial reported a reduction in 28-day mortality in hospitalised COVID-19 patients receiving either invasive ventilation or supplemental oxygen². Rather than affect viral replication, it is thought to work by mitigating hyper-inflammatory organ injury². This study will therefore assess whether adding remdesivir, dexamethasone or both to standard of care reduces the incidence of inpatient neurological complications associated with COVID-19, and whether this effect is maintained at different degrees of respiratory disease severity.

As part of the research response to the COVID-19 pandemic, the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) WHO Clinical Characterisation Protocol for the UK (CCP-UK) developed in the UK in 2012 was reactivated on 17th January 2020²⁸. This was used by the ISARIC Coronavirus Clinical Characterisation Consortium (ISARIC4C), to establish an open-access analysis platform containing data on the clinical course, treatments and outcomes of over 250,000 patients who were hospitalised in the UK with COVID-19. ISARIC4C has been used to describe the clinical characteristics, risk factors, and complications of severe COVID-19^{1,3,29,30}, as well as assess the impact of medications on patient outcomes^{3,31}. As a result, it presents a suitable framework for causal analysis in relation to remdesivir, dexamethasone and neurological complications.

In view of these considerations, we outline a protocol for a retrospective cohort study within the ISARIC4C platform assessing whether treatment with either remdesivir, dexamethasone

or both prevents the occurrence of neurological complications in patients hospitalised with COVID-19 who required supplemental oxygen at any point (the primary analysis). A secondary analysis will be performed to assess whether: 1) treatment with dexamethasone, remdesivir or both is associated with more severe disease and worse clinical outcomes; and 2) the presence of neurological complications is associated with more severe disease and worse clinical outcomes compared to cases without neurological complications. Finally, an additional analysis will be performed on the effect of dexamethasone, remdesivir or both on neurological complications in inpatient cases of 'non-hypoxic' COVID-19, defined as not requiring supplemental oxygen at any point.

Primary objective

The primary objective is to assess whether treatment with either remdesivir, dexamethasone or both, along with standard of care, prevents the occurrence of neurological complications in patients who are hospitalised with COVID-19 and required supplemental oxygen at any point during their admission, compared to standard of care alone.

Secondary objectives

The secondary objectives are to assess whether: (1) treatment with either remdesivir, dexamethasone or both, along with standard of care, reduces severity and improves clinical outcome, compared to standard of care alone; (2) cases with neurological complications have more severe disease and worse clinical outcome compared to cases without neurological complications. Severity will be assessed using length of inpatient stay and need for intensive care admission, while clinical outcome will be assessed using mortality and the ability of patients to self-care at the end of their care episode relating to COVID-19. 'Non-hypoxic' is defined as not requiring supplemental oxygen at any point.

Additional objective

The additional objective is to whether treatment with either remdesivir, dexamethasone or both, along with standard of care, prevents the occurrence of neurological complications in patients who are hospitalised with COVID-19 and who remain 'non-hypoxic' during their admission, compared to standard of care alone.

STUDY DESIGN

This is a retrospective, non-interventional cohort study of hospitalised adults with COVID-19, conducted within the ISARIC4C platform. This platform contains data that has already been collected for other purposes and will be used to explore hypotheses regarding outcomes of interest. While the overall sample size is large, circa 85000, sample sizes across different treatments are expected to be asymmetrical. As smaller sample sizes increase the likelihood of a Type II error, sample sizes will be reported alongside all analyses. The study will be performed and reported in accordance with STROBE and DEBATE guidelines^{32,33}

Materials relating to ISARIC4C including protocol, revision history, case report forms (CRFs), study information, and consent forms are available online²⁸. Only patients who provided biological samples were required to provide informed, written consent. All other patients had routinely collected clinical data collated for which written consent was not required under UK health research regulations. ISARIC WHO CCP-UK received ethical approval from the South Central—Oxford C Research Ethics Committee in England (13/SC/0149) and by the Scotland A Research Ethics Committee in Scotland (20/SS/0028).

Setting

The duration of this study is from the day of admission to the point of death, discharge, or resolution of the COVID-19 clinical episode. Information was collected between 31 Jan 2020 and 29 Jun 2021.

Inclusion criteria

Adult patients, aged 18 years and older, admitted to hospital between 31 Jan 2020 and 29 Jun 2021 with laboratory confirmed SARS-CoV-2 infection will be eligible for inclusion in this study.

Exclusion criteria

Patients missing all data in the case report forms for the admission day, or the discharge will be excluded, as will those with missing data for neurological outcomes, except when at least one complication is confirmed. Patients who received a dose of any COVID-19 vaccine will be excluded, in addition to those enrolled in clinical trials for COVID-19 vaccines. Patients

who contracted COVID-19 in hospital, evidenced by symptom onset occurring after hospitalisation, will also be excluded.

Blinding

Since this is a retrospective study patients, clinicians and researchers cannot be blinded to treatment allocation.

Sequence and duration of study periods

All patients are followed up until the point of discharge from hospital, death, or continued hospitalisation without ongoing care needs related to COVID-19, at which time any neurological complication will be recorded.

Treatments

Remdesivir

Remdesivir (Gilead Sciences, Inc.) is given early in the clinical course. To maximise the number of patients included in the analysis, we will use two definitions of treatment exposure. The first definition will be treatment with remdesivir on the day of admission. The second definition will be treatment with remdesivir at any point during admission. In both cases, non-exposure will be defined as standard of care with no remdesivir prescription at any point. It is expected that the standard of care will not vary significantly between the two groups.

Remdesivir was approved by the UK's Medicines and Healthcare products Regulatory Agency (MHRA) under the Early Access to Medicines Scheme (EAMS) for people aged 12 years and older affected with severe COVID-19. EAMS ran from 26th May 2020 until July 2020 when it was withdrawn and remdesivir was commissioned by NICE for routine use in severe COVID-19³⁶. UK guidelines recommended use in newly hospitalised patients, within 10 days of symptom onset and only in non-ventilated patients³⁷. Remdesivir is not recommended for use in patients with an eGFR < 30 and in pregnant patients³⁷.

Treatment was allocated locally by treating clinicians and as such there was no control over treatment allocation by the research team. The treatment course used for severe COVID-19 was a 200mg intravenous loading dose on day one followed by a 100mg intravenous

maintenance dose on days two to five with an optional additional five-day course of 100mg intravenous maintenance doses. The guidance regarding this additional course changed over time:

- 26th May 2020 – 2nd Jun 2020: “If a patient does not demonstrate clinical improvement”
- 3rd Jun 2020 – 28th Sep 2020: “If a patient deteriorates and progresses to ventilation and/or ECMO treatment”
- 28th Sep 2020 – 22nd Mar 2021: “Ensure that clinicians prescribe a maximum treatment course of 5 days” – this was due to a disruption in supply of the drug. It is stated that some exceptions may receive additional doses, but these were undefined by the guidelines
- 23rd Mar 2021 – present: “Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen.” – therefore no additional course was recommended.

Dexamethasone

Dexamethasone was commissioned for use in COVID-19 by NICE on 16 Jun 2020 in patients requiring supplemental oxygen to meet prescribed oxygen saturation levels, or those with a level of hypoxia requiring supplemental oxygen but who are unable to receive or tolerate it. Treatment is with 6mg once daily, administered as an oral or intravenous preparation according to clinical circumstances. The duration of treatment is 10 days, unless there is a clear indication to stop early such as discharge from hospital. Treatment was allocated locally by treating clinicians so there was no control over treatment allocation by the research team.

Analyses

Primary analysis

The primary analysis will assess whether treatment with either dexamethasone, remdesivir or both is associated with a reduction in the incidence of neurological complications (the

primary study outcome). Since it is anticipated that patients may be treated with either or both treatments of interest, in addition to standard of care, the following treatment group comparisons will be made:

1. Remdesivir alone versus standard of care
2. Dexamethasone alone versus standard of care
3. Remdesivir and dexamethasone versus standard of care

For each comparison, treatment exposure with remdesivir will be considered as either starting on the day of admission or at any point during admission.

The primary analysis will be conducted amongst patients who required supplemental oxygen (most often for O₂ saturations <94%) at any point during their admission. Such cases are defined as severe COVID-19 by WHO.

Secondary analyses

The secondary analyses will include only severe COVID-19 patients meeting criteria for inclusion in the primary analysis. The secondary outcomes are disease severity and markers of clinical outcome, and these will be assessed across:

- A. The treatment groups outlined in the primary analysis
- B. Patients who developed neurological complications compared to those who did not develop neurological complications.

Additional analysis

An additional analysis will be undertaken on patients who did not require supplemental oxygen at any point during their admission (termed 'non-hypoxic'), otherwise meeting criteria for inclusion in the primary analysis. This analysis will assess whether the treatment groups outlined above are associated with a reduction in neurological complications in these patients.

Study outcomes

Primary outcome

The primary outcome will be a neurological complication at the point of death, discharge, or resolution of the COVID-19 clinical episode. This will be a binary variable, i.e., either present or absent, and will be defined as any one of the following: stroke, seizure, meningitis/encephalitis, or any other neurological complication. The ISARIC CCP UK CRF version 10.1 does not provide a definition for the outcome of other neurological complication⁴⁵.

Secondary outcomes

Secondary outcomes will be length of inpatient stay and admission to intensive or high-dependency care (to assess severity) and mortality and self-care (to assess clinical outcome). These are defined as the following:

1. Length of inpatient stay will be scalar, defined as the time in days from admission to discharge, or until continued hospitalisation without ongoing care needs related to COVID-19. This variable will not be assessed in patients who have an outcome of death or palliative discharge.
2. Admission to intensive or high dependency care will be a binary variable, i.e. admitted or not admitted, defined as admission to either intensive or high dependency care at any point during the admission.
3. Mortality will be binary i.e., dead or alive at the time of resolution of the COVID-19 related clinical episode.
4. Self-care will be a binary variable (same/better or worse), reported at the time of resolution of the COVID-19 related clinical episode, in relation to the patients' baseline at admission. This will be assessed only in patients who are discharged or have no ongoing healthcare needs related to COVID-19. Patients requiring ongoing hospital care at the resolution of the care episode relating to COVID-19 were defined as having a worse ability to self-care relative to pre-admission baseline. Neurological complications often have a significant impact on patients' ability to self-care, so a difference between the treatment groups is important.

Confounding variables

Confounders will include sex, age, ethnicity, comorbidities, clinical frailty score, smoking status, severity of pulmonary infection, time in days from symptom onset to hospital admission and eligibility for remdesivir. The definitions of all covariates are set out below:

1. Sex at birth will be dichotomous i.e., male or female. Outcomes for males admitted to hospital with COVID-19 are known to be worse than for females³⁸
2. Age in years on the date of admission to hospital will be a scalar variable. A consistent observation throughout the COVID-19 pandemic has been that as age increases so too does mortality³⁸.
3. Ethnicity will be categorical (White, BAME, other, not available). Mortality for Black, Asian and other ethnic minority patients has been demonstrated to be higher than for white patients. As there is not a significant difference between them, they have been merged into one ethnicity variable state (BAME) for the purpose of analysis³⁰.
4. The number of comorbidities present has been shown to be a positive predictor of mortality³⁸. While some co-morbidities are not independent from each other, a combined comorbidities score will be derived. A maximum of one point will be allocated for the presence of a clinically significant comorbidity, resulting in a scalar variable from 0-14. Each comorbidity will be considered as either present or absent, and will include: cardiac disease, inclusive of congenital heart disease, not including hypertension; hypertension; any chronic pulmonary disease, including asthma; chronic kidney disease; any rheumatologic disorder; any moderate or severe liver disease; any chronic haematological disease; any chronic neurological disorder including dementia; type 1 or 2 diabetes; any malignant neoplasm; patients on immunosuppression therapies; obesity; solid organ transplant recipients; patients with rare diseases and inborn errors of metabolism that significantly increase the risk of infections such as severe combined immunodeficiency (SCID).

5. Clinical frailty score is an ordinal scale (1-9). The Rockwood clinical frailty score is a good predictor of patient mortality from COVID-19³⁹ and may also have impacted on clinical decisions made regarding active treatment for patients.
6. Smoking status will be ordinal (current, former, never). Current or former smoking is associated with higher risk of infection, hospitalisation and mortality from COVID-19⁴².
7. Ventilation will be binary, i.e., ventilation of any type, or no assistance with ventilation at all. More severe COVID-19 requiring ventilation is associated with a higher risk of mortality that did not alter as the pandemic progressed⁴⁰, though the proportion of patients ventilated did decrease. The use of invasive or non-invasive ventilation, at any point throughout admission is therefore used to assess disease severity.
8. Time in days from symptom onset to hospital admission will be a scalar variable. Delayed presentation to hospital after symptom onset is associated with more severe COVID-19⁴³.
9. Patients with clinical features that would render them ineligible for remdesivir according to the Summary for Product Characteristics⁴⁴ (e.g. chronic kidney disease, pregnancy). This will be a binary variable.

Statistical analysis

In an observational study, covariates are usually not balanced between groups, hence confounding will be controlled for by covariate adjustment using a propensity score methodology (PS)³⁴ when comparing groups. PS methodology, in comparison to multivariable adjustment, separates confounding factor adjustment and analysis of the group difference. The PS will be determined by logistic regression, with each group comparison pair of interest as the dependent variable, and the relevant covariates as the independent variables. The PS will subsequently be used as a covariate in the final regressions described below. This PS approach has the advantage of retaining the available sample size, when compared with PS matching, as matching is not always possible.

Primary analysis:

To assess whether treatment groups are associated with a reduction in the incidence of neurological complications in patients who required supplemental oxygen at any point during admission:

- A logistic regression will be used to analyse the association between the treatment and the binary outcome of neurological complication, adjusting for the PS (calculated using the nine covariates).

Secondary analyses:

To assess disease severity and markers of clinical outcome across treatment groups outlined in the primary analysis:

- A linear regression will be used to analyse the association between the treatment and the scalar outcome of length of in-patient stay, adjusting for the PS (calculated using the nine covariates).
- A logistic regression will be used to analyse the association between the treatment and the binary outcome of admission to intensive or high dependency care, adjusting for the PS (calculated using the nine covariates).
- A logistic regression will be used to analyse the association between the treatment and the binary outcome of mortality, adjusting for the PS (calculated using the nine covariates).
- A logistic regression will be used to analyse the association between the treatment and the binary outcome of self-care, adjusting for the PS (calculated using the nine covariates).

To assess disease severity and markers of clinical outcome in patients who developed neurological complications compared to those who did not develop neurological complications:

- A multivariable linear regression will be used to analyse the association between neurological complications and the scalar outcome of length of in-patient stay, adjusting for the PS (calculated using the nine covariates and the treatment groups).
- A multivariable logistic regression will be used to analyse the association between the treatment and the binary outcome of admission to intensive or high dependency care, adjusting for the PS (calculated using the nine covariates and the treatment groups).
- A multivariable logistic regression will be used to analyse the association between the treatment and the binary outcome of mortality, adjusting for the PS (calculated using the nine covariates and the treatment groups).
- A multivariable logistic regression will be used to analyse the association between the treatment and the binary outcome of self-care, adjusting for the PS (calculated using the nine covariates and the treatment groups).

Additional analysis

An additional analysis, similar to the above, will be performed in 'non-hypoxic' cases, to assess whether:

- treatment groups are associated with a reduction in the incidence of neurological complications, compared to control – in 'non-hypoxic' patients.
- disease severity and markers of clinical outcome in patients who developed neurological complications compared to those who did not develop neurological complications - 'non-hypoxic' patients.

Exploratory analyses

Any analyses performed outside the protocolled analysis detailed above will be considered entirely exploratory and hypothesis-generating in nature.

Missing data

A complete case analysis will be conducted. Patients who have missing data in the values used to calculate the primary outcome will be excluded, unless any neurological complication

is recorded. For comorbidities, failure to mention a comorbidity is assumed to indicate its absence. Accounting for the underlying causes of missingness (e.g. missing systematically, missing at random) is beyond the scope of this analysis.

DECLARATIONS

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