Cost-effectiveness of therapeutics for COVID-19 patients: a rapid review and economic analysis

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Primary conflicts of interest: Paul Dark is the National Deputy Medical Director of the National Institute for Health and Care Research Clinical Research Network. He is a Local Principal Investigator for both the RECOVERY and REMAP-CAP platform trials, NIHR Urgent Public Health (UPH) pandemic research Advisory Group Lead Link for REMAP-CAP and specialist member of NIHR UPH Advisory Group. His NHS host hospital Research and Innovation Department has been contracted and paid to provide advice on the use of tocilizumab for Roche and sotrovimab for GlaxoSmithKline both in COVID-19. He supported the activity as a named NHS expert employed by the Northern Care Alliance NHS Foundation Trust (Salford Care Organisation) but received no personal payments. Ronan McMullan received grants or had contracts with NIHR HTA programme, NIHR Efficacy and Mechanisms Evaluation Programme, Medical Research Council (MRC) and Invest Northern Ireland (with Randox Lab Ltd). He was also paid honorarium for giving a lecture from Gilead Sciences Ltd in the past 36 months. Matt Stevenson provided advice to AstraZeneca Rare Disease regarding an unrelated intervention in an unrelated disease area. There are no other conflicts of interest within this project team.

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Scientific summary

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Scientific summary

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19). At the time of writing (January 2023) there had been over 620 million confirmed cases and over six-and-a-half million deaths worldwide associated with COVID-19. For the UK, these values are more than 24 million cases and nearly 200,000 deaths.

In addition to the widespread vaccination programme, treatments exist that can help people who have been hospitalised due to COVID-19 (casirivimab and imdevimab (henceforth casirivimab/imdevimab), tocilizumab, remdesivir, baricitinib, and baricitinib with remdesivir) or be used in patients who have COVID-19 and are at high risk of needing hospitalisation [casirivimab/imdevimab, molnupiravir, nirmatrelvir and ritonavir (henceforth nirmatrelvir/ritonavir), remdesivir, sotrovimab, and tixagevimab and cilgavimab (henceforth tixagevimab/cilgavimab)]. For reasons related to urgency, these treatments, unlike interventions in other disease areas, have not received positive guidance from the National Institute of Health and Care Excellence (NICE) before being routinely used. As the pandemic subsides there is more need for a formal evaluation of the clinical and cost-effectiveness of these treatments.

Objectives

The objective of this study is to summarise the current knowledge related to the clinical efficacy of the interventions and to conduct an economic evaluation that estimates the cost-effectiveness of each intervention against standard of care (SoC), as of January 2023. A full incremental analysis is performed while noting the caveats in the comparison of all interventions simultaneously.

Methods

Given the timescale of the project, where there were < 3 months between the publication of the final scope and the deadline of a report for NICE and the consultation process, a literature review following best practice was not possible. Instead, a pragmatic, alternative approach was undertaken where evidence was taken from two living systematic reviews (supported by the COVID-network meta-analyses (NMA) initiative and the metaEvidence initiative) in line with current best practice guidelines. For interventions related to use in hospitals, data were extracted on time to death, clinical improvement and time to discharge. For interventions that are used in the community for patients at high risk of hospitalisation, data were extracted on the risks of hospitalisation or death, and the risks of death. These measures of efficacy were assumed generalisable to January 2023 despite changes in background conditions which include the SoC, the percentage of people who have been vaccinated and a change in the dominant SARS-CoV-2 variant. This is noted as a very large limitation as drugs that have looked effective in previous variants have not worked as well in later variants and sensitivity analysis on the efficacy of the interventions has been conducted.

A mathematical model was constructed that used the data from the living systematic reviews to simulate the experiences of patients in hospital, and requirement for supplemental oxygen, until discharge or death in hospital. Due to the (conditional) marketing authorisations of the interventions, the model was developed such that results could be produced for the supplemental oxygen group and the non-supplemental oxygen group separately. The model structure used an eight-point ordinal scale that was used in clinical trials to categorise patients during their admissions. Outputs from this model included the costs associated with interventions and care, and the quality-adjusted life-years (QALYs) gained by

the patient both within the hospital episode and after discharge, incorporating decrements in health-related quality of life associated with the lasting impact of COVID-19. For interventions used in the hospital, these values allowed a cost per QALY gained to be calculated for each treatment compared with SoC, and for completeness, a full incremental analysis to be conducted although the External Assessment Group (EAG) cautions against comparisons between treatments due to the heterogenous conditions when pivotal studies were undertaken.

The costs of each intervention were taken from public sources where available. However, baricitinib, sotrovimab and tocilizumab have confidential patient access schemes agreed, which discount the price of the intervention, and are not considered in this document, but were provided to the NICE Appraisal Committee in a separate confidential appendix. The price of three treatments (casirivimab/imdevimab, molnupiravir and tixagevimab/cilgavimab) were not publicly available at the time of writing and the cost-effectiveness results for these three drugs are contained in a confidential appendix.

For patients at high risk of hospitalisation treated in the community, a decision tree was put before the hospital model, which simulated the reduced need for hospitalisation associated with early treatment. The total costs and QALYs associated with treatment options were estimated to allow an evaluation of the cost per QALY of each treatment against SoC and for completeness, a full incremental analysis to be undertaken, noting the same caveat as for interventions used in hospital when comparing treatments. The modelling did not assess the logistical aspects of treatment in the community, but the EAG notes that this could be a large factor in deciding which treatments could be preferred, as oral treatments could be more acceptable to patients and healthcare systems than treatments that are given intravenously or subcutaneously. The costs of providing treatment within the community were provided by National Health Service (NHS) England.

Three scenarios were run changing the efficacy of interventions. The 'mean efficacy' estimate used the mean of each distribution extracted from the living systematic reviews, the 'high efficacy' estimate used the most favourable limits of the 95% confidence intervals (CIs) and the 'low efficacy' estimate used the least favourable limits of the 95% CIs. The EAG has acknowledged a limitation that the CI is influenced by the number of observed events and the sample size, such that two identical treatments could have markedly different confident intervals purely due to the size of the pivotal study.

Seven scenario analyses were performed, explored the impact of changing: (1) the duration of long COVID (ranging from half to double that of the base case); (2) changing the rate of hospital admission in the community with people being at 'high risk' of hospitalisation from a value of 2.79% to 1.00%, 5.00% and 10.00%; (3) changing the average age of patients at high risk of hospitalisation in the community from 55 years to 50 and 60 years; (4) using a hazard ratio (HR) of unity for all interventions in relation to time to hospital discharge and time to clinical improvement; (5) changing the baseline distribution of supplemental oxygen requirements from that associated with SoC (19% no supplemental oxygen, 55% high-flow oxygen, 16% non-invasive ventilation and 10% invasive ventilation) to an arbitrarily less severe baseline distribution (25% no supplemental oxygen, 60% high-flow oxygen, 10% non-invasive ventilation and 5% invasive ventilation) for patients who have received an intervention in the community; (6) assuming a utility decrement of 0.02 per day for patients receiving intravenous (i.v.) treatment in the community; and (7) changing the standardised mortality ratio for people during the period of long COVID from 7.7 to 5.0 and 10.0. Two scenario analyses were conducted that explored the use of different efficacy measures based on the Solidarity study for remdesivir and the 'Efficacy and safety of intramuscular administration of tixagevimab–cilgavimab for early outpatient treatment of COVID-19' (TACKLE) study for tixagevimab/cilgavimab.

Results were presented in terms of incremental cost-effectiveness ratios (ICERs) measured in cost per QALYs gained and also using incremental net monetary benefit (NMB). An advantage of NMB is that interventions can be compared using different assumptions on efficacy for different interventions, and interventions can be omitted without the need to recalculate efficiency frontiers.

Results

Due to changes between the conditions when the pivotal studies were undertaken and the current conditions in terms of the SoC, the percentage of people who have been vaccinated and a change in the dominant SARS-CoV-2 variant all results should be treated with caution. Caution should also be applied when comparing between interventions. The results also do not incorporate confidential price discounts for baricitinib, sotrovimab and tocilizumab, nor were any cost-effectiveness results presented for casirivimab/imdevimab, molnupiravir and tixagevimab/cilgavimab which had confidential list prices. These analyses were seen by the NICE appraisal committee in a confidential appendix.

All treatments used for hospitalised patients, had a median HR for death below one, indicating a benefit, although all CIs crossed unity apart from those for baricitinib, casirivimab/imdevimab and tocilizumab. The overlapping CIs and heterogeneous studies meant that no firm conclusions could be made regarding the relative efficacy of these treatments. There was less data relating to the relative risks (RRs) of clinical improvement at 28 days and the HRs for the time to discharge, although these were generally close to unity and had CIs that crossed unity. No clear conclusions could be made on the relative efficacy of treatments for these two measures compared with SoC.

All treatments used in the community had favourable median RRs for hospitalisation and death at 28 days with the upper limit of the CI being below 1 for all drugs except molnupiravir. The median RRs associated with death at 28 days were favourable for all interventions, except for remdesivir where the median estimate was unity as no deaths were observed in the study within COVID-NMA. The CIs were wide and spanned one for all treatments except for molnupiravir and nirmatrelvir/ritonavir.

For hospitalised patients requiring supplemental oxygen, all treatments had estimated ICERs compared with SoC below £12,000 in both the mean efficacy and high efficacy scenarios. However, in the low efficacy scenario only baricitinib and tocilizumab generated more QALYs than SoC. Baricitinib had an estimated ICER under £9000, while tocilizumab had an estimated ICER under £29,000. For hospitalised patients not requiring supplemental oxygen, all treatments had estimated ICERs compared with SoC below £12,000 in both the mean efficacy and high efficacy scenarios. However, in the low efficacy scenario, only baricitinib generated more QALYs than SoC with an estimated ICER below £6000.

For interventions used in the community, the estimated ICERs compared with SoC were more varied. In the mean efficacy scenario, the estimated ICERs were below £7000 for nirmatrelvir/ritonavir, below £35,000 for sotrovimab and below £91,000 for remdesivir. In the high efficacy scenario, the estimated ICERs were below £5000 for nirmatrelvir/ritonavir, below £19,000 for sotrovimab and below £25,000 for remdesivir. In the low efficacy scenario, the estimated ICER was below £12,000 for nirmatrelvir/ritonavir, with remdesivir and sotrovimab having ICERs in excess of £10,000.

Only one of the scenario analyses noticeably changed the ICERs for all interventions, which was changing the proportion of people with COVID-19 in the community at high risk of hospitalisation who are hospitalised when treated with SoC. Treatments became more cost-effective as the admission proportion increased at the mean and high efficacy scenarios. The ranges in the ICERs assuming mean efficacy for the drugs, when using 1%, 10% and 20%, rather than 2.82% as assumed in the base case, were: nirmatrelvir/ritonavir (£25,544, dominant and dominant), remdesivir (£280,819, £16,170 and £1512) and sotrovimab (£111,318, £4870 and dominant). If data from Solidarity are included, the low efficacy scenarios for remdesivir had a positive NMB regardless of the willingness-to-pay threshold and oxygen status assumed. For patients requiring supplemental oxygen the ICER was £25,903; the corresponding ICER was £34,550 for those not requiring supplementary oxygen.

Conclusions

There is considerable uncertainty in the efficacy of treatments compared to SoC observed in the studies due to the small number of events, which results in wide CIs for HRs and RRs. Some treatments (baricitinib and tocilizumab in the hospitalised setting and casirivimab/imdevimab, molnupiravir and nirmatrelvir/ritonavir in the community setting) were estimated to have a statistically significant benefit related to death due to COVID-19, however, this may also have been shown for other treatments if the pivotal studies had had larger sample sizes. However, the dominant SARS-CoV-2 variant, the SoC and the percentage of people who have had a vaccination, have all changed since the pivotal studies were undertaken meaning that the efficacies for treatments are highly uncertain. This is demonstrated by sotrovimab having favourable median and mean efficacies in prevention hospitalisation, but this drug is not authorised in the USA, as it is unlikely to be effective against the Omicron BA.2 subvariant. Further the World Health Organization has made strong recommendations against the use of sotrovimab. Given potential further changes in the variant, the results presented in this report, and within the confidential appendix, should be treated with caution.

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This report

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