COMMENT

Choosing drugs for UK COVID-19 treatment trials

*UK Covid Therapeutics Advisory Panel Due Diligence team**

In 2020, the UK Government funded a portfolio of platform trials to develop new treatments for COVID-19. A key feature was the independent prioritization of candidate drugs with central co-ordination to prevent duplication, accelerating recruitment to deliver definitive trial results. A similar approach could be used for non-communicable diseases where treatment advances have been limited.

In early 2020, SARS-CoV-2 led to an escalation of UK hospital admissions. The new virus had a poorly understood pathophysiology, leading to severe complications and high mortality in at-risk groups. At the time, no treatments were known to be effective at altering the disease course.

The UK government health research funders (National Institute for Health Research (NIHR) and UK Research Innovation (UKRI)) joined forces to fund research focused on COVID-19 and its complications. Recognising the importance of central coordination, NIHR put in place a prioritization process refocusing support from the Clinical Research Network (CRN) on clinical studies aimed at delivering clinical impact for COVID-19. These included a rationalized portfolio of national platform treatment trials, encompassing phase III studies in hospital (RECOVERY and REMAP-CAP) and the community (PRINCIPLE), phase II studies (ACCORD 2, CATALYST, TACTIC, DEFINE, RECOVERY+), and phase I (AGILE), post-hospitalization (HEAL-COVID), and prophylaxis (PROTECT-CH and PROTECT-V) trials, followed by Long-COVID in 2021.

A central tenet of the national platform trials was the coordinated identification of candidate drugs for testing in the different studies through an open and transparent process delivered by the newly assembled UK COVID-19 Therapeutics Advisory Panel (UK-CTAP, Supplementary Figure 1). UK-CTAP comprised ~~eight~~ seven clinical scientists and an independent chair not directly involved in the platform trials, ensuring independent and impartial recommendations. Potential treatments were nominated through an open web portal. An expert due diligence team established the knowledge base for a given candidate (Supplementary Figure 1), specialist subgroups then contextualized that knowledge with expert opinion, and UK-CTAP considered all of the information to create a balanced portfolio that did not err towards one particular class of drug or mechanism of action. These three layers mitigated against unconscious biases, including familiarity and specialist scientific expertise.

Key data informing decision making

From September 2020 to July 2021, UK-CTAP received 336 nominations and made 33 recommendations into trial (Supplementary Figure 2), based on the following principles.

Scientific rationale. Candidate drugs needed to have a well-defined mode of action relevant to the pathophysiology of COVID-19 based on in vitro, preclinical and clinical data. Important mechanisms of action included antiviral, anti-inflammatory, immunomodulatory, antithrombotic and antifibrotic activity. During the first year, our understanding of the pathophysiology of COVID-19 evolved substantially. This information was assimilated into the rationale for each candidate drug as it became available, and their likely impact at different stages of the disease. For example, antiviral activity would be most likely to be beneficial earlier in the disease course, but might benefit some patients with severe disease if there were a persistent viral burden. On the other hand, specific immunomodulatory drugs were theoretically detrimental during the early stages, but potentially beneficial at a later stage when patients were closely monitored in hospital and suffering from a pro-inflammatory 'cytokine storm'.

Both repurposed and new drugs were considered. Immuno-modulatory drugs with well-described mechanisms of action were repurposed when the same anti-inflammatory activity was likely to be relevant for COVID-19 immune pathology; and known antiviral drugs were repurposed based on preclinical evidence of anti-SARS-CoV-2 activity[1].

Pharmacokinetics and pharmacodynamics. Published and commercially privileged data were combined with in-house pharmacokinetic (PK) and pharmacodynamics modelling to predict whether a treatment was plausible and at what dose. A critical issue was whether therapeutically relevant drug concentrations would be achieved in the lung, and over what time period. For antiviral

drugs, the lung tissue concentration needed to exceed the levels reducing viral load by 90%. For targets on the cell surface (for example, umifenovir, which inhibits both viral entry and post-entry stages[2]), plasma concentrations served as a surrogate. For treatments with intracellular targets such as favipravir, the intracellular concentration was modelled to support the selection of a dosing regimen. For example, although the antimalarial atovaquone binds to the SARS-CoV-2 Mpro substrate-binding pocket and exhibits micromolar inhibition of viral growth[3], PK modelling predicted that plasma levels would be insufficient for standard oral doses due to its high plasma protein binding.

For anti-inflammatory therapies, a key issue was selecting a safe and efficacious dosing regimen. For example, modelling of glucocorticoid receptor occupancy by dexamethasone in pemphigus showed a linear relationship with interleukin 6 release in blood monocytes[4], informing the high dosage (20 mg) of dexamethasone for the RECOVERY trial over the previously adopted dosage (6 mg).

Safety and possible drug interactions. The safety profile was considered in healthy volunteers and other relevant diseases such as adult respiratory distress syndrome, when COVID-19 data was not available. Higher safety standards were required for community trial platforms, particularly prophylaxis studies where the risks of severe COVID-19 were low. For example, although antifibrotics were proposed in a post-hospital discharge setting for lung fibrosis patients, the side effect profile of licenced antifibrotic drugs was considered too high for use in COVID-19 patients, particularly given reports of the spontaneous resolution of the radiological features.

Availability and supply. These were key considerations in partnership with the Department of Health and Social Care Therapeutic Task Force and NHS procurement teams. For example, inhibition of the C5 complement cascade was recognised as a potential target for COVID-19 but there was no scientific rationale to prioritize one complement C5 inhibitor over another, so the prioritization was based on availability and supply for UK trials, including cost.

Human studies in COVID-19 patients. The due diligence team continuously surveyed emerging information for efficacy in COVID-19, including global monitoring of live clinical trials, and shared with other regulatory intelligence sources such as the RAPID C19 oversight group hosted by the National Institute for Heath and Care Excellence. One of the most challenging issues was whether or not to begin a trial in the UK because of uncertainties about the delivery of similar trials elsewhere in the world.

Prioritisation decisions

UK-CTAP made recommendations based on several factors, including the practicalities of giving the treatment (for example, intravenous drugs potentially useful in the community but impractical at scale), adverse side-effect profile in standard clinical settings (for example, a high likelihood of exacerbating renal dysfunction in patients already severely ill with COVID-19, who were known to have a high incidence of renal failure), drug supply issues (for example, the inability to manufacture at a sufficient scale for national roll-out), or because the mechanism of action was potentially dangerous. In this way, UK-CTAP assembled a live list of prioritized agents where the ranking was reordered over time based on new knowledge.

Conclusions

UK-CTAP provided an independent rigorous model for prioritizing the best possible candidates into clinical trials based on available data in a rapidly evolving landscape. The open web portal ensured any individual or organization could propose a new treatment for a trial through the nationally funded platforms. Prioritization decisions were made through an open, transparent process based solely on the available scientific data and the logistics of giving the treatment in the NHS. The recommendations are published online. Importantly UK-CTAP's ethos was to prioritize promising drugs based on the best information available at the time, rather than outright acceptance or rejection of candidates.

Since August 2020, UK-CTAP has met 16 times, informed by 47 expert subgroup meetings, all conducted virtually (Supplementary Figure 2). Meetings were often scheduled at very short notice and outside office hours in response to new data or the need for a new trial candidate. The work was only possible because of the commitment of the panel and subgroup membership, often meeting through video links at unsociable hours because of their additional responsibilities, including frontline NHS clinical duties. The model of decision-making shows what can be done during a pandemic. A similar independent and evidence-based approach could be used to evaluate and prioritize therapeutic candidates for nationally coordinated trials in other disease areas.

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Competing interests

The authors declare no competing interests.

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Supplementary information

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UK Research and Innovation, London, UK.

e-mail; patrick.chinnery@mrc.ukri.org

Patrick F. Chinnery, Department of Clinical Neurosciences and MRC Mitochondrial Biology Unit, University of Cambridge, Cambridge, UK

Marion Bonnet

Alison Cave

Matthias Hofer

Glenn A. McConkey

Nicholas Medcalf

Stephen Smith

Teresa Tsakok

Robert Watson

Steven Webster

Tao You