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EDITORIAL

A call for the appropriate application of clinical pharmacological principles in the search for safe and efficacious COVID-19 (SARS-COV-2) treatments

1 | ASCEPT-BPS STATEMENT ON COVID-19 (SARS-COV-2)

The rapid emergence of coronavirus disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has led to remarkable efforts by the scientific communities internationally to identify potential pharmacological treatments through the rapid initiation of clinical trials of novel and/or repurposed regulatory authority-approved therapies. We greatly welcome the significant global effort to safely expedite trials. However, we are concerned that many studies have not been of high quality to generate clinically meaningful data to enable effective translation to clinical practice. Identifying the "right" drug (or drug combinations) is only the first step. Applying core clinical pharmacology principles at all stages of research will help identify the right dose, the right patient, and the right treatment protocol. We hope that by setting out the principles outlined in this statement, efforts to find a safe and efficacious treatment for COVID-19 will have the best chance of success.

At the time of writing (dated 20/5/2020), over 1,000 clinical trials are underway for the successful treatment of COVID-19 infections, with most trials testing remdesivir, hydroxychloroquine, lopinavir/ritonavir and azithromycin separately or in combination. Drug development to treat COVID-19 has mainly focused on antivirals and immune modulators, with the logic that the early stages of the disease are characterised by the viral infection/replication stage, whereas the later, severe stage is characterised by the so-called 'cytokine storm'. The later phase is experienced by a subset of patients but is the major cause of fatalities.

The enthusiasm for antiviral agents has been driven by the successful demonstration of *in vitro* antiviral efficacy using cell culture experiments, often without concomitant studies in appropriate preclinical species and at doses that may be unsafe or unachievable in humans. Further, *in vitro* efficacy does not guarantee that a drug will be efficacious and safe in humans using doses required to achieve free drug concentrations at the sites of infection, even for those agents already marketed for other indications. The repurposing and trialling of immune modulatory agents, such as those targeting IL6, TNF-α, IL1 and JAK, is because over-production of pro-inflammatory cytokines has been implicated in tissue injury (especially in the lungs), leading to multi-organ failure and death. However, at this stage of the disease, we cannot exclude that the virus itself is also responsible, either partly or wholly, for the organ manifestations observed in COVID-19. It is therefore important that treatment choice must be connected to understanding of disease mechanism.

An understanding and application of the core principles of clinical pharmacology can help researchers navigate the known challenges of drug discovery and development. These principles are vital to support medication choice, clinical trial design, dose selection and dose individualisation, relative to the stage of viral infection. In this statement, we outline five core principles (Figure 1) to ensure safety and efficacy of proposed treatments, some of which are relevant to antiviral drug development only (principles 1 and 3), while others apply to both antivirals and immune modulators (principles 2, 4 and 5). The aim of this statement is to provide benchmark recommendations for those publishing results, reporting results or developing clinical trials for the treatment of COVID-19. This is essential to understand the public health impact of potential COVID-19 treatments.

We suggest that alignment with the outlined principles should be considered and reported when:

- Planning and communicating research studies including clinical trials and non-interventional studies
- Reviewing and accepting manuscripts in scientific journals
- Making funding decisions related to COVID-19 research
- Interpreting and reporting research findings with all forms of media
- Producing patient and consumer information
- Developing and implementing policies by Governments and related bodies to inform COVID-19 guideline recommendations and medication purchasing

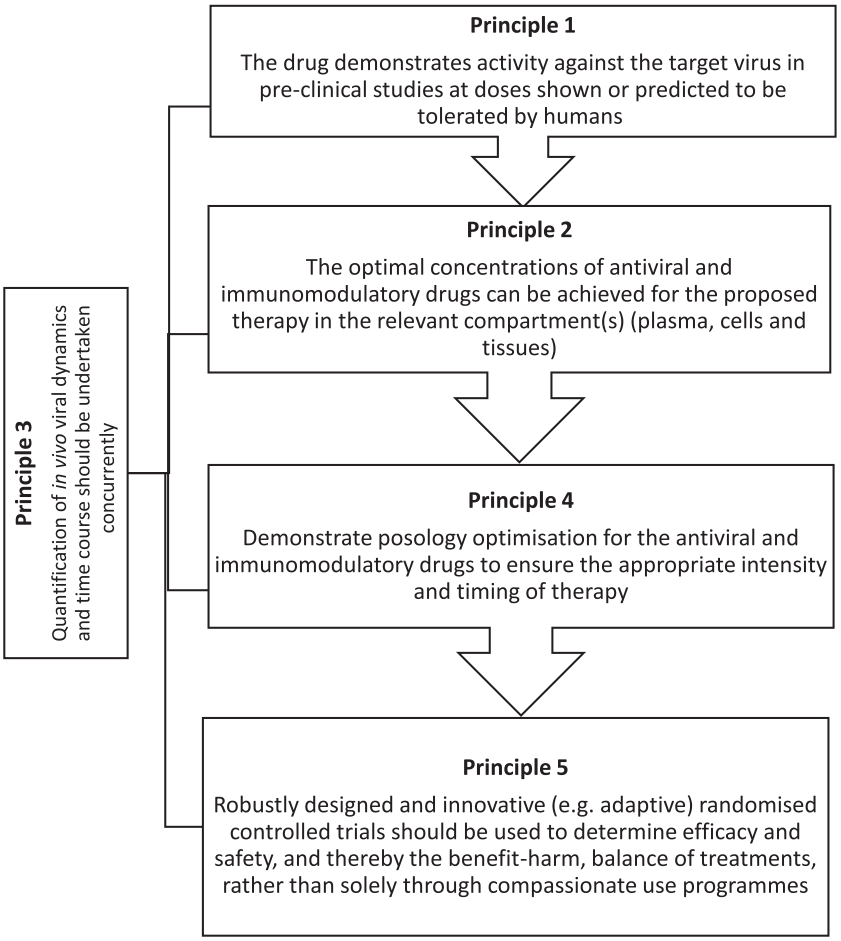

FIGURE 1 The core principles and recommendations to ensure that the safety and efficacy of COVID-19 treatments is optimised. In a pandemic situation, some of these activities may need to be undertaken in parallel

2 | CORE CLINICAL PHARMACOLOGY PRINCIPLES AND RECOMMENDATIONS TO OPTIMISE SAFETY AND EFFICACY OF COVID-19 TREATMENTS

Principle 1

The drug demonstrates activity against the target virus in pre-clinical studies at doses shown or predicted to be tolerated by humans.

Recommendations:

i The EC_{50} and/or EC_{90} (if available) for the target virus is reported and standardised to molar units

ii Differences between cell culture system(s) relative to human physiology are reported and critically evaluated. Two key issues need to be addressed: a) the protein and its concentration in assays is compared to circulating proteins *in vivo* (human) or pre-clinical species, and, b) the type and function of cells utilised in assays relative to the molecular target(s) that are key determinants of viral ingress and replication, in particular, angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2)

iii A proposed mechanism of action to inhibit viral replication is reported which is biologically plausible while not causing apoptosis or an innate immune activation

iv Where an appropriate animal model is available, the activity of the antiviral drug is shown *in vivo* in the model, even if this is done in parallel with planning (and execution) of human studies. At present, non-human animal models have been used for investigating viral dynamics and immunity, but do not necessarily replicate all the features of COVID-19 infection in humans such as the inflammatory processes

Principle 2

The optimal concentrations of antiviral and immunomodulatory drugs can be achieved for the proposed therapy in the relevant compartment(s) (plasma, cells and tissues).

Recommendations:

i Human Plasma: demonstrate that the target unbound antiviral drug concentration is achievable by:

- Comparing the *in-vivo* EC_{50} and/or EC_{90} of the registered primary indication to the *in-vitro* viral EC_{50} and/or EC_{90} standardised to molar units
- Comparing the measured free antiviral drug concentration at the regulatory approved dose and frequency to *in-vitro* viral EC_{50} and/or EC_{90} standardised to molar units. This may also be obtained from population pharmacokinetic (PopPK) or Physiologically Based Pharmacokinetic (PBPK) models available from regulatory approvals or scientific publications

ii Target Human Tissue: demonstrate that the unbound antiviral drug concentration is achievable in the target human tissue by:
- Comparing the measured tissue drug concentration at the regulatory approved dose and frequency to the *in-vitro* viral EC_{50} and/or EC_{90} standardised to molar units
- Comparing the predicted drug concentration in tissues using PBPK models at the regulatory approved dose and frequency to *in-vitro* viral EC_{50} and/or EC_{90} standardised to molar units

iii Use *in-silico* quantitative pharmacology methods to simulate unbound plasma and, where appropriate, tissue concentration profiles of antivirals and immune modulators, including understanding the likely differences in key special populations where further dose individualisation may be needed (e.g. pregnant women, children, people with immunosuppression or chronic diseases, older adults)
- For antivirals, quantitation of the time at, or above, the reported EC_{50} or EC_{90} for the SARS-CoV-2 virus should be defined
- For drugs targeting the 'cytokine storm', quantitation of binding to either the unbound circulating cytokine and/or soluble receptor must be understood and defined

iv Measure total (and if practical unbound) concentrations in blood (and if practical tissue) of the proposed treatment during clinical trials. These can be used to develop PK models of the time course of drug concentrations in patients who have COVID-19

Principle 3

Quantification of *in vivo* viral dynamics and time course should be undertaken concurrently (Figure 1).

***Recommendations*:**

i Quantitate the viral life cycle using appropriate assays to understand:
- Time of infection
- Time to symptom onset
- Time-course of viral load using a validated method (VK model)
- Time-course of viral shedding
- Time-course for increases in cytokines and other inflammatory markers
- Time-course of disease progression during hospitalisation using ordinal clinical scales such as SOFA and NEWS II
- Rates of hospitalisation
- Rates of ICU admissions
- Rates of mortality
- Rates of infection and time-course in different high-risk target populations e.g. paediatrics, pregnancy, older people, the critically unwell.
- Likely isolation times and cross infection rates
- Time course to return to baseline physical and cognitive function

ii Use data in step 3i, to develop quantitative viral kinetic (VK) models using previously established regulatory approved methodologies for influenza and respiratory syncytial virus (RSV)

iii Link VK models to PK models obtained *in vivo* in patients with COVID-19 (see 2iv) or if these clinical studies are not available in patients with another disease with a registered indication to produce PK-VK models to understand the key windows for treatment (or prophylaxis) between infection and/or clinical symptom development relative to the known biology of the proposed drug. If clinical PK models are not available then *in-silico* quantitative simulations may need to be used (see 2iii)

Principle 4

Demonstrate posology optimisation for antiviral and immunomodulatory drugs to ensure the appropriate intensity and timing of therapy.

***Recommendations*:**

i Define the optimal drug dose(s) and frequency to achieve unbound concentrations in plasma and tissue to maximise antiviral and/or disease suppressing activity.
- For antivirals, this will require that the time course of unbound drug concentration accumulation at the site of infection is optimised using quantitative pharmacology methods to obtain optimal inhibition of viral growth relative to the stage of viral infection
- For disease suppressing agents, this will require that the time course of unbound drug concentration at the site of production or action of the cytokine combined with known quantitation of binding to either the unbound circulating cytokine and/or soluble receptor to optimise dosing

ii Ensure the proposed drug exposure in plasma (unbound or total) and where appropriate, tissues, is below the minimum toxic concentrations for humans
- Optimised dosing schedules which exceed current regulatory approved doses or frequencies will require a full safety assessment
- The likelihood of concentration-related adverse effects which may be detrimental to the patient are understood, e.g. cardiac toxicity such as QT prolongation, and appropriate monitoring, dose adjustment recommendations and other risk mitigation procedures are developed

iii Define the likelihood and extent of drug–drug PK and/or PD interactions with concomitant medications used for treatment or

support of the patient, and develop appropriate risk mitigation procedures to minimise risk

iv Define dose adjustment for special populations to ensure safety and efficacy

v Model informed simulations for the dose and dose frequency linked to viral kinetics (PK-VK), or target mediated drug disposition for cytokine antibodies are essential for the development of treatment arms within clinical trials to ensure the highest likelihood of efficacy and safety

Principle 5

Robustly designed and innovative (e.g. adaptive) randomised controlled trials should be used to determine efficacy and safety so that the benefit-harm balance of treatments are identified, rather than treatments being made solely available through compassionate use programmes.

Recommendations:

i Leveraging prior knowledge from Phase I-II studies for the primary (or related) indications of the medication, it may be appropriate to progress directly to phase III trials. However, where this information is not available, for example a new formulation of a known drug, early Phase trials (I and II) should be undertaken so that they form a pipeline of products to be tested in Phase III

ii Treatments should be compared to standard of care (preferably with placebo) in a randomised double-blind trial setting, even if multiple doses are being trialled

iii Trials should be adequately powered taking into account the stage and biology of the disease, and feasibility of undertaking the trial, particularly in the context of an epidemic where numbers may be changing rapidly because of concurrent social control measures

iv Inclusion criteria should not be too broad within particular trial to better define the populations in which the treatment will be most suitable

v Core clinical outcome criteria such as those proposed by the COMET initiative should be used in Phase III trials to enable comparisons between different trials and act as an enabler for meta-analyses. For earlier phase trials, the use of surrogate measures may be appropriate, but these should be rigorously justified

vi Given the complexity of COVID-19, it is likely that combination therapies will be needed, at least in some patients. Thus, for trials involving combination therapies, there should be clear justification for the choice and doses of the drugs used based on disease biology, when they are started (simultaneously or sequentially), and whether the combination is likely to be superior to each of the monotherapies

vii There should be thorough assessment of safety end-points in all trials, including those due to drug–drug and drug-disease interactions, to ensure there is a complete profile of the hazards of the medicine, in relation to the benefits, at different stages of the disease

viii Clinical trials should be undertaken within the appropriate regional or national ethical and regulatory frameworks.

3 | OTHER POTENTIAL THERAPIES

A number of potential therapies are emerging (e.g. anticoagulants, fibrinolytic agent, and agents that work on the renin angiotensin system) as our understanding of the pathophysiology of COVID-19 and the host response expands. The principles of rigorous scientific assessment described above apply equally to these potential therapies.

4 | CONCLUSIONS

COVID-19 is having such an enormous impact on individuals, populations, and on the economy. There is urgent need to develop safe and efficacious treatments that can reduce morbidity and mortality, and restore societal norms. However, this should not come at the expense of the quality of science and clinical medicine. In many instances, the adoption of un-trialled and potentially dangerous treatments (and combinations) has dominated the discourse and caused patient harm. To better understand the scope of potential therapies, we advocate that these five key clinical pharmacological principles should be adopted by the scientific and clinical communities to improve the development of safe and efficacious treatments for SARS-CoV-2.

COMPETING INTERESTS

There are no competing interests to declare.

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