Challenges of drug development during the COVID-19 pandemic: key considerations for clinical trial designs

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Abstract

There is an urgent need for targeted and effective COVID-19 treatment. A number of medications, including hydroxychloroquine, remdesivir, lopinavir-ritonavir, fapiravir, and tocilizumab, have been identified as potential treatments for COVID-19. Bringing these repurposed medications to the public for COVID-19 will require robust and high-quality clinical trials. This article reviews translational science principles and strategies for conducting clinical trials in a pandemic and evaluates recent trials for each drug candidate. We hope that this knowledge will help focus efforts during this crisis and lead to the expedited development and approval of COVID-19 therapy.

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Running head Clinical trial design for COVID-19 drug therapies

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ABSTRACTThere is an urgent need for targeted and effective COVID-19 treatment. A number of medications, including hydroxychloroquine, remdesivir, lopinavir-ritonavir, fapiravir, and tocilizumab, have been identified as potential treatments for COVID-19. Bringing these repurposed medications to the public for COVID-19 will require robust and high-quality clinical trials. This article reviews translational science principles and strategies for conducting clinical trials in a pandemic and evaluates recent trials for each drug candidate. We hope that this knowledge will help focus efforts during this crisis and lead to the expedited development and approval of COVID-19 therapy.

Introduction

Identification of the 2019 novel coronavirus (SARS-CoV-2) and the associated coronavirus disease (COVID-19) global pandemic is the foremost human tragedy affecting our life today. This disease has reached nearly every country, causing significant morbidity and mortality as it continues to spread. The development of drugs and vaccines is critical to win the battle against the SARS-CoV-2 virus. At present, although different countries have employed different methods of controlling COVID-19 based on their national conditions and health-care systems, the general strategy is consistent: 1) flatten the growth curve of COVID-19 infections by public health measures while reducing their mortality by supportive care, and 2) accelerate the development of drugs and vaccines. This article summarizes the challenges of conducting clinical trials under pandemic conditions; describes potential options to develop drugs for COVID-19 rapidly; discusses how to improve the likelihood of trial successes; and reviews currently registered clinical trials for the treatment and prevention of COVID-19 by analysing available initial data and assessing the potential success of upcoming trials.

Challenges in conducting clinical trials in a pandemic

Humans have experienced pandemics before, like the 1918 Spanish Influenza pandemic, but the present COVID-19 pandemic is perhaps unique due to modern trends of globalization and changing healthcare practices. However, we have a limited understanding of the SARS-CoV-2 pathogen and currently few ways to treat its victims. There is enormous pressure on our healthcare institutions to preserve the lives of the infected while finding effective treatments *ab nihilo* . We have long understood that the safety and efficacy of new medical treatments can only be evaluated through carefully and systematically designed clinical trials. How can we preserve this requirement while finding new treatments in the shortest possible time under conditions of intense crisis?

Time pressure : Conventional drug research and discovery can easily take a decade from target identification to pivotal phase III clinical trials. This approach cannot be used for COVID-19. There is simply not enough time. Instead, we must focus on identifying existing drugs or drug candidates intended for other indications that may have efficacy against COVID-19 and put them into accelerated clinical trials. By leveraging pre-existing drugs with known pharmacological data, we can reduce the need for dose-finding and toxicologic assessments. Further dose evaluations can be integrated into an expanded phase III trial using a combination of clinical, viral load reduction and immune response as endpoints. This kind of acceleration will place a substantial burden on regulatory agencies that only the pandemic itself can justify.

Repurposing drugs: Our current knowledge of the molecular and biochemical features of the SARS-CoV-2 virus suggest that drugs produced for related RNA viruses (e.g. Ebola) may also be effective for treating COVID-19.[1,2] The clinical development pathway for an existing drug proposed for a new indication is well understood by regulatory agencies and is relatively brief. However, because SARS-CoV-2 is new, the repurposed drugs will not have undergone research and early development optimization for COVID-19.

Lack of information: Once a drug candidate is selected, the greatest unknowns are the dose, dosing regimen and treatment duration to be used. Conventionally these are determined in phase II trials with objectives of proof of concept (PoC) and dose ranging through studying a drug's pharmacokinetics (PK) and pharmacodynamics (PD). This process may be compressed or even eliminated through the use of existing therapeutic dosing guidelines for established indications or acceptance of a near maximum tolerated dose. Alternatively, two or more dose levels may be tested in an expanded pivotal safety/efficacy trial. The absence of an optimal therapeutic dosing regimen for COVID-19 may lead to false negatives (lack of observed efficacy for an efficacious drug). In addition, the lack of knowledge about the viral dynamics of SARS-CoV-2 and disease progression means that the therapeutic dosing time window for treatment is not well defined, potentially leading to misleading conclusions.

Operational challenges : Epidemiological shifts in disease burden across the global also complicate clinical trials. COVID-19 was first observed in the Chinese city of Wuhan. Many clinical trials of repurposed drugs were performed there.[3,4] However, strict public health efforts reduced the number of new cases from hundreds each day to only a few in a matter of months. As a result, Wuhan is an unfavourable site for future clinical

trials. After the Wuhan outbreak, COVID-19 cases spiked in Europe, especially Italy and Spain. At the time of this writing, the nation with the largest disease burden is the United States, which has the greatest number of total cases recorded. Clinical trial design needs to take this dynamic into consideration. It is likely that future clinical trials will have to be designed as global trials for this reason. Clinical operations can also be an issue as routine evaluations requiring close patient observations can't be conducted in settings of home quarantine. There are also ethical considerations and resource competition between clinical trials at play that will limit trial conduct or feasibility. Factors include immense pressure on clinical staff, equipment shortages, and patient desperation for effective treatment. At present most clinical staff are almost exclusively focused on the preservation of patient lives. Diversion of their efforts toward patient selection and treatment changes necessary for clinical trial conduct could meet serious resistance. Next, it will be difficult to define appropriate patient populations for trials. The availability of reverse transcription polymerase chain reaction (RT-PCR) testing to define SARS-CoV-2 infection is very limited and unequally distributed. A large fraction of patients with COVID-19 symptoms do not actually know if they are infected with SARS-CoV-2 virus and the time between symptom onset and confirmation of infection will vary widely. Furthermore, there is no well-established standard of care (SOC) on a global level. This will complicate construction of multinational control groups. Patient selection also needs to take into account the major differences in fatality between different age groups and patients with different co-morbidities. It is also important to consider patient concerns with respect to their likely enrolment into a clinical trial. In the context of potentially fatal disease, many patients may withdraw their participation in trials, especially if they are blinded to their treatment and they don't know what the treatment they are receiving. Despite the need for expedited trials, all these issues must be taken into account for actionable results.

Regulation and approval : Clinical trials need to be reviewed on scientific and ethical grounds before they can take place. The requirements for review and approval are well established with relatively minor national differences. The IND review and approval process is the standard pathway for drugs entering the clinical phase. The review process usually takes a few months and involves national regulatory bodies. Due to time pressure and fast changing disease incidence, accelerated regulatory review and approval for IND are required. Some COVID-19 drugs qualify for so called "investigator- initiated trials" which only require local IRB/EC approval. This is a fast process for initiating clinical trials that will be critical in this crisis. In investigator-initiated trials, pre-existing drugs are repurposed for COVID-19 treatment. Because the drugs in these trials have already undergone review for other indications, less regulatory oversight is needed for their use in COVID-19.

We present three key ideas for trial design to emphasize high quality patient selection, study conduct, dose identification, and endpoint evaluation to produce meaningful results.

Key 1 – Adhere to translational science principles

To design a robust clinical trial for an anti-infection drug, we usually need to know three sets of information: a) the disease symptomatology and progression; b) the underlying mechanism of disease periods, i.e., dynamics of viral load and immune response; and c) host-virus-drug interactions. We must have clear objective definitions of disease progression and improvement. Objectively, this may be reflected by viral load and host immune response. Viral load can be quantified through RT-PCR while immune response can be tracked through inflammatory markers and antibody production. By studying drug PK and PD, maybe indirectly from previous programs, we can optimize the dosage regimen (dosage, dosing interval and treatment duration) to maximize the cure rate, reduce toxicity and avoid drug resistance. The information obtained is critical in understanding trial results, as drugs will have different effects depending on disease progression. For example, a drug may be falsely dismissed as ineffective if it is given too late in the disease course. We must go beyond standard clinical evaluations and leverage basic science measures to enrich trial outcomes.

Key 2 – Leverage Innovative trial designs

Traditional Phase II studies on COVID-19 are largely missing due to the time pressure to produce clinically relevant results. Instead, many teams have progressed directly to exploratory, open-labelled studies, but

these were often underpowered and led to inconclusive results. The few robust Phase III trials that exist lack COVID-19 applicable Phase II data and producing them may not be feasible under pandemic conditions. Instead, simultaneous combination of supportive care and RCTs (Randomized Clinical Trials) has been recommended as the way to find effective and safe treatments for COVID-19 and any other future outbreak.[5] In addition, there are two types of trial designs, particularly useful in infectious diseases, that all parties involved in planning, designing and conducting COVID-19 like trials should be aware of through educational programs:

Adaptive platform (multi-arm, multi-stage) design.

This approach studies multiple targeted therapies in the context of a single disease in a continuous manner utilizing a shared control arm. Individual investigational therapies are allowed to enter or leave the platform on the basis of a decision algorithm (see Figure 1).[6] The advantages to this approach include its flexible design, which allows for multiple drugs to be evaluated, reduced control population and potential for international deployment. However, international deployment would require a high degree of regulatory coordination and normalization of clinical operations across many different settings.

2) Prophylactic design: These studies focus on a less-studied population in the COVID-19 pandemic; the close contacts (household or healthcare workers) of COVID-19 patients. These individuals have a high likelihood of contracting disease and limiting spread of disease is critical for managing this crisis. Prospective, cluster-randomized, double-blind, placebo-controlled studies designed to investigate the efficacy of anti-viral drugs in prevention of the secondary spread of disease to close contacts have gained popularity through anti-influenza trials.[7] We designed a post exposure prophylaxis (PEP) trial in Wuhan, China using hydroxychloroquine in mid-February 2020 (see Figure 2), but it didn't proceed due to the dwindling number of patients in Wuhan. Scientifically, it would be better if hydroxychloroquine's antiviral effect toward SARS-CoV-2 was confirmed prior to a PEP trial. Similarly designed trials and its variations, including pre-exposure prophylaxis (PrEP) and progression prevention trial in diagnosed patients using HCQ, are on-going in the US/UK (see Table 4).

Key 3 – Implement 4R standards (right patient, right drug, right dosage, right timing)

1. Right patient

The idea of matching drugs to patients is a widely accepted paradigm in pharmacology. This personalized medicine approach emphasizes the numerous patient-level factors that can affect therapeutic targets, a medication's PK, as well as the overall burden of disease.

Patient selection is complicated by heterogeneity in the clinical manifestations of COVID-19. About 80% of patients will only have mild/moderate flu-like or pneumonia symptoms.[8] The majority of COVID-19 cases are self-limited and not life-threatening. A considerable portion of patients, up to 17.9% of RT-PCR-confirmed cases in some models,[9] may be completely asymptomatic for the entire duration of infection, though some may have objective subclinical manifestations of disease[10]. However, around 20% of patients are deemed severe cases with significant dyspnea, hypoxia, or lung imaging findings that require supplemental oxygen or intensive care and current estimates of COVID-19 case fatality rates vary from 2-7%,[8,11,12] though this figure varies by location.

A number of factors contribute to the disparate manifestations of COVID-19; the most well-studied factor is age. It has been reported in China, Italy, South Korea and United States that elderly patients comprised approximately 60-83% of all COVID-19 fatalities.[13,14,15] A similar trend is seen with designation of "severe" cases as well as rates of hospitalization and ICU admission, all of which are more prevalent in older individuals.[15]

Another factor is cardiovascular disease (CVD). There is a high prevalence of CVD amongst severe COVID cases and COVID cases overall, with death rates of individuals with CVD reportedly over four times the overall mortality rate.[11] The leading hypothesis for this is suggested to involve SARS-COV-2's interaction with angiotensin-converting enzyme 2 (ACE2) and the renin-angiotensin-aldosterone axis. Chronic respiratory disease is also linked with severe and fatal COVID-19 cases,[15]potentially due to the decreased lung

pulmonary reserve, dysregulated immune system, and disrupted lung microbiome in these patients.[16,17] Diabetes is also a significant risk factor for severe COVID-19 infection, potentially due to similar mechanisms of immune dysregulation, alterations in ACE2 expression, and increased processing of the SARS-COV-2 spike protein.[18] In addition, it has been suggested that common therapies for these conditions, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and immunomodulators like inhaled steroids have an effect on COVID-19 pathophysiology.[19,20,21]

In designing therapeutic drug trials for COVID-19, we may have to control for not only age, CVD, pulmonary disease, diabetes, and other patient-level factors like immunodeficiency, but also control for the therapies patients have been given.

2. Right Drug

Two approaches for developing scientific treatments for COVID-19 exist:

1) a "bottom-up" approach by repurposing already approved drugs or molecules under clinical development for other indications

2) a "top-down" approach targeting at new molecules and vaccines specifically designed for SARS-COV-2 which can be time-consuming, but more effective and safer.

COVID-19 is caused by SARS-CoV-2 that is a single-stranded positive-sense RNA virus.[22] Since SARS-CoV-2 is a newly discovered pathogen, no specific drugs are currently available. Several existing drugs and new drugs that have potential therapeutic effects are summarized in Table 1. These therapeutics are divided into 4 categories: convalescent plasma or immunoglobulins; direct-acting antiviral agents (DAA); host cell internalization protein blockers; and anti-inflammatory drugs.

Convalescent Plasma or immunoglobulin fractions have been used for treatment of Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV infections.[23,24,25] A clinical study of 5 critically ill patients with COVID-19 and acute respiratory distress syndrome (ARDS) showed that administration of convalescent plasma containing neutralizing antibodies improved some patient's clinical status.[26] Issues associated with this approach include donner identification, elimination of residual SARS-CoV-2 risk, off-target immunoglobulin binding, and dose estimation. Of special concern is the ability to scale this approach to the level required.

The potential targets of DAA against non-structural proteins include RNA-dependent RNA polymerase (RdRp), coronavirus main protease (3CLpro), and papain-like protease (PLpro). A potential target for a DAA against a viral structural protein was the glycosylated spike (S) protein.[27] S protein mediates SARS-CoV-2 entry via binding to angiotensin-converting enzyme 2 (ACE2) located on the surface membrane of host cells following which host cell produced transmembrane protease serine 2 (TMPRSS2) was involved in S protein priming that facilitates the process of internalization.[28] Thus, both host cell membrane proteins ACE2 and TMPRSS2 have become potential therapeutic targets. In addition, some recent studies also reported that S protein can also bind to the host cell receptor CD147[29] and the glucose regulated protein 78 (GRP78)[30] that may also mediate internalization.

The protease inhibitor combination lopinavir and ritonavir (Aluvia®), and two viral polymerase inhibitors, favipiravir and remdesivir, are non-structural SARS-CoV-2 protein targets currently in clinical trials. Galidesivir (BCX4430) is an adenine analogue RdRp inhibitor originally developed for the treatment of hepatitis C virus. It is currently undergoing safety testing in early clinical studies and is being evaluated for its efficacy in treating yellow fever. In preclinical studies, it exhibits activity against a variety of RNA viruses, including SARS and MERS.

Both SARS-CoV, responsible for severe acute respiratory syndrome (SARS), and SARS-CoV-2, responsible for COVID-19, are beta-coronaviruses (CoV) that share a structurally similar spike glycoprotein (S) complex surrounding the spherical viral particle that is comprised of a receptor binding domain (RBD) S1 subunit

and a membrane fusion S2 subunit.[31] The S proteins of SARS-CoV-2 have about 76% homology to those of SARS-CoV and both recognize and bind to ACE2.[31]

While Abidol is mainly used for the prevention and treatment of influenza virus infections, it may disrupt the binding of S proteins to ACE2 to prevent viral internalization and is currently in clinical trials (see Table 1). Soluble recombinant human angiotensin converting enzyme-2 (srhACE2) was initially proposed as a treatment for general ARDS but its affinity for the SARS-CoV-2 spike protein could enable a neutralization with the virus preventing the viral internalization. It is possible for shrACE2 to treat COVID-19 through a combination of preventing lung injury by reducing local angiotensin-II levels and preventing lung epithelial internalization of the virus.

Nafamostat and Camostat are two TMPRSS2 inhibitors with similar molecular structure that could block the virus internalization process. Camostat is currently in clinical trials for COVID-19 Infection (see Table 1).

Hydroxychloroquine (HCQ) / chloroquine (CQ) are anti-malarial drugs used for treating Lupus and forms of arthritis. HCQ is a derivative of CQ with therapeutic effects similar to those of CQ, but with reduced toxic side effects. HCQ/ CQ can inhibit the in vitro replication of several coronaviruses. Recent publications support the hypothesis that CQ can improve the clinical outcome of patients infected by SARS-CoV-2. CQ may interfere with ACE2 receptor glycosylation to inhibit SARS-CoV-2 binding to target cells. It may also inhibit cleavage of S proteins by acidifying lysosomes and may inhibit cathepsin activity. HCQ activates CD8 + T-cells that reduces the production of pro-inflammatory cytokines[32,33,34] to limit lung inflammation.

SARS-CoV-2 may cause the rapid release of inflammatory cytokines resulting in ARDS and multiple organ failure. Anti-inflammatory drugs can relieve this response. IL-6, CCR5 and JAK kinase are potential targets for relieving SARS-CoV-2 caused inflammation.[35] Tocilizumab (ACTEMRA®) is a recombinant human monoclonal antibody that specifically binds to soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R) and inhibits inflammatory IL-6-mediated signal transduction. CytoDyn's humanized CCR5 antagonist leronlimab (PRO140) has applied for a phase II clinical trial for adult patients with mild to moderate respiratory disease after infection with SARS-CoV-2. The JAK kinase inhibitors baricitinib and ruxolitinib can inhibit JAK-mediated inflammatory processes and are currently in clinical trials for COVID-19 (see Table 1).

3. Right dosage

New drug development paradigm : Dose is an important issue for antiviral drug development requiring years of work. The process starts at the interface between preclinical and Phase I when the first in human dose is calculated. Under today's model-based drug development paradigm, this exercise is supported by translational PK-PD modelling using available data of nonclinical PK, drug metabolism and toxicology. Phase I dose escalation trials will then be conducted to examine safety, tolerability and PK in reference of in vitro susceptibility and in vivo animal data. Phase II studies will be further conducted in target patients to achieve goals of PoC and dose ranging using biomarkers for both efficacy such as viral load and safety. Dosage for Phase III trial will be optimized based on a target PK/PD metric (e.g., $C_{min,ss}$/EC90) and population PK of the drug. In addition, experimental medicine studies will be conducted to study tissue penetration, and a series of clinical pharmacology studies will be conducted to examine intrinsic and extrinsic factors including age, body weight, the stage of the disease, the presence of co-morbidities, patients' use of other medications for the purposes of adjusting dose in special populations.

Dose estimation for repurposed drugs : Drug development for COVID-19, thus far, is dependent on the indication extension of existing, approved drugs. These anti-viral drugs must have been through the full pre-clinical discovery and clinical development process with extensive pharmacological, PK, toxicology and manufacturing work done. It is essential that drug candidates for repurposing must have shown efficacy for their original intended indication such that regulatory approval is achieved or fully expected. Absent these requirements additional exploratory development work will be required prior to conduct of a pivotal efficacy trial for the new indication (e.g. COVID-19).

The only information that should be needed to extend an existing drug for use to the new indication is the characterization of its target interaction as nothing else should change. If the new viral target attacks a different tissue, then additional tissue distribution work may be required.

The need to characterize an existing drug's interaction at a different target in the same tissue such as the RdRp for SARS-CoV-2 versus that of another RNA virus in the lung can be done at the *in vitro* level. If the EC50 value in this case is different, as it is more likely that the drug will be less potent, then a proportional dose adjustment is a useful approximation. In this case, a much greater effort must be made to estimate the effect of increasing the dose for the new indication. Do the human PK findings support a simple proportional dose adjustment? Do the safety findings support a higher exposure level? Small differences in potency make it likely that the drug can be used for the new indication but larger ones may well preclude this use. This is especially true if significant new clinical development efforts must be made that will substantially increase the time required to get the drug into patients. Assuming that the outcome supports repurposing the existing drug for the new indication it still must be tested in an adequately powered clinical trial for an appropriate patient population.

In COVID-19 drug trials, we found only two trials intended to explore different dosage regimens, Gilead remdesivir trials examine treatment durations of 10 days vs 5 days [NCT04292730, NCT04292899], and the PrEP trial by Washington University School of Medicine on HCQ employ low, mid and high dose regimens [NCT04333732]. None tried a dosage higher than its approved level.

Clinical investigators should collaborate closely with the innovator company to understand the PK, PD, biomarker and safety of drugs repurposed for the new indication and propose a dosage with highest possibility of suppressing the virus within the exposure range known to be safe. In most cases, safety data for levels much higher the than approved dose may be present in the development data file (i.e., single or multiple ascending dose studies). However, there can be no justification for pushing the clinical dose beyond the drug's known therapeutic window.

The *in vitro-in vivo* translation of antiviral efficacy should be considered throughout the development process. There are many considerations when using *in vitro* derived EC50 or EC90 to predict an efficacious dose *in vivo* . For typical drugs, the free-drug hypothesis can be used to translate *in vitro* EC values to *in vivo* efficacious dose based on the theory that unbound drug in the circulation equilibrates with that at the target site under steady-state conditions. However, differences in metabolic activity, drug permeability or transporter expression between the model cell line and target tissue or organ can result in prediction inaccuracy. In addition, special attention should be paid for an anti-viral prodrug, as its active moiety is a metabolite which only stays intracellularly (e.g., remdesivir).[36,37] An investigator using a cultured cell model needs to convince themselves that any such differences were characterized during the model development and can be accounted for.

Remdesivir and CQ were found to be relatively more potent (EC50 reported to be 0.77 and 1.13 μM, respectively) compared to ribavirin, penciclovir, nitazoxanide, nafamostat and favipiravir against a clinical isolate of SARS-CoV-2 in vitro.[36] This study also demonstrated that remdesivir functioned at a stage after virus entry while CQ functioned at both entry, and at post entry stages of the SARS-CoV-2 infection in Vero E6 cells.[36] In another study, the EC50 of HCQ is reported to be 0.72 μM.[38]

Remdisivir is an example of a proposed "repurposed drug" that appears not to meet the key standard on clinical efficacy described previously. An efficacy trial for Ebola where the drug, when combined with the triple monoclonal antibody ZMapp, failed to show efficacy relative to ZMapp alone.[39] Remdisivir is active against SARS-CoV and MERS-CoV replication in cell models and shows efficacy against SARS-CoV infection in carboxylesterase 1c knockout mice[37] and MERS-CoV infection in rhesus monkeys[40].

CQ and HCQ act at both viral entry and post entry stages so that their in vitro and in vivo translation can be complicated by major differences in their lung to plasma concentration ratios. Both CQ and HCQ are highly distributed to the lung in male CD albino rats[41] and HCQ[42].

For srhACE2 to occupy viral S protein it must reach the interior of the lung where the virus is located. To block infection srhACE2 must be delivered to the site of infection in both the upper and lower respiratory track areas by inhalation therapy in an adequate amount to occupy S protein sites on the virus. Intravenous administration is unlikely to block infection since there is little virus in the blood but might serve to reduce lung injury though this was not demonstrated in ARDS patients.

4. Right timing

Timing is important to the administration of therapy during the COVID-19 disease course. While our understanding of the natural history of severe COVID-19 infection is incomplete, it is thought to progress from invasion of the respiratory tract and gastrointestinal mucosa, to dysregulation of the RAAS and immune systems, systemic spread to other organs, and then finally cytokine storm, sepsis, and acute respiratory distress syndrome.[43]

COVID-19 is best treated in its early stages when viral load is low and host physiology is relatively unperturbed. However, this is complicated by COVID-19's relatively mild onset, with many patients being asymptomatic. A study showed that virus shedding was very high during the first week of symptoms (peak at 7.11×10^8 RNA copies per throat swab, day 4).[44] Furthermore, once the disease has progressed to its end-stage and organ failure has occurred, the number of specific therapies available dwindles as drivers of pathology shift from direct viral effects to secondary systemic dysregulation of host physiology. Given that most of the trial drugs currently being studied act on the Sars-Cov-2 viral lifecycle, rather than the downstream manifestations of COVID-19, these medications may not have an effect later in illness. This can be seen in the treatment of influenza, where the anti-viral oseltamivir is only effective if given in the first 48 hours.[45] After this period, there are no specific therapies that have shown benefit, and supportive care is the standard. Thus, it is important to define patients' disease progression in clinical trials, as certain drugs may have different effects when given at different times.

Trial analysis

We focused our analysis on the most representative ones including HCQ, remdesivir, lopinavir/ritonavir, favipiravir and tocilizumab with the intent that this will clarify inconclusive results from inadequate designs and guide potential future strategies.

1) hydroxychloroquine (HCQ) trials

A search (until April 7th, 2020) was performed on clinical trial registries of privately and publicly funded clinical trials (https://clinicaltrials.gov/) focusing on HCQ and COVID-19. A total of 44 registered clinical trials of HCQ were retrieved. Thirty (30) of these were therapeutic trials for active infection and 21 were prophylactic trials, with several studies having multi-purpose designs. The prophylactic trials were separated into 15 pre-exposure (PrEP) and 6 post-exposure prophylaxis (PEP) trials. These trials have exploded in number over the past month (see Figure. 3), especially in preventative trials.

CQ was first discovered to have potential activity against COVID-19 in China[46] and Chinese experts recommended CQ to patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia[47]. A dose of 500 mg bid for 10 days is recommended for chloroquine phosphate. HCQ has emerged as a drug of interest due to its relatively good clinical safety. HCQ has had some promising preliminary results. Compared to standard care, HCQ treatment has been associated with increased symptomatic pneumonia improvement (80.6% vs. 54.8%)[4] and higher levels of viral clearance (70.0% vs 12.5%)[48] when compared to the standard of care, though only in relatively small studies. On the other hand, HCQ has not shown an effect in all studies, with Chen J et al. reporting no difference in HCQ-treated and control group patients' viral clearance[49]. These findings are summarized in Table 3.

HCQ is also being studied in prophylactic trials, both pre- and post- viral exposure with a much larger sample size in the former (see Table 4). Most of these use a regimen of 800 mg of HCQ sulfate for day 1 and 400 mg daily for the rest of the trial. Median trial duration is 7 days. These trials are still on-going, but it should be noted that in pre-exposure studies, the population is mostly healthcare workers who likely have

a disproportionately high amount of viral exposure, versus a more general lay population in post-exposure trials. Thus, some of these trials may not be generalizable to a larger population.

Due to the high transmission of SARS-Cov-2, close contacts in household setting (˜15%) and other high-risk close contacts (˜10%) have a high secondary infection rate.[51] A preventive strategy using antiviral drugs is being adopted aimed at reducing transmission and hospitalization. As an existing drug, HCQ has the advantages of sufficient drug stockpile, good drug safety and economic cost, which provide the rationale that HCQ is being widely used.[52]

In treatment or PEP purpose studies, the most common dosage regimen in these trials is 800 mg for the first day + 400 mg daily for maintenance dosing (HCQ sulfate), where the dose interval is mostly twice a day. In the treatment purpose study, the median treatment period was 7 days (range: 5-14 days); which is longer than the median treatment period in the PEP study (median: 5 days, range: 3-11 days). For PrEP study, designs mainly focused on healthcare workers who are at potential risk to exposure to the COVID-19 from patients and HCQ is given over a longer treatment duration by daily regimen or regimens with longer than 24 hour dosing interval.

Although these large scale prevention trials should only be conducted after clinical confirmation of anti-viral efficacy by HCQ, their data, if released, will confirm the efficacy and safety of HCQ against the COVID-19.

Remdesivir trials

Remdesivir was originally developed by Gilead Science for Ebola virus infections [39] and is still under investigation. After a case report of a severe case of COVID-19 in the US being cured by remdesivir[53], a number of clinical trials on remdesivir started worldwide.

These trials include the Chinese studies (NCT04252664, NCT04257656) initiated by Dr. Cao Bin, the global multicenter study initiated by NIAID in the US (NCT04280705), the solidarity study initiated by WHO (remdesivir as a group, NCT04330690, NCT04321616) and 2 studies initiated by Gilead Science (NCT04292730, NCT04292899). More details of these trials are summarized in Table 2. Since there is no documented clinical data so far, it is still unknown whether remdesivir is effective for COVID-19.

Remdesivir is an adenosine analogue that can incorporate into the nascent viral RNA chains and cause the termination of viral replication.[54] In a mouse model of SARS-CoV, remdesivir significantly reduced lung viral load, improved pulmonary function, and reduced clinical disease.[37] According to previous reports, remdesivir is a potent inhibitor of SARS-CoV-2 replication in infected cells suggesting potential therapeutic activity against COVID-19.[36]

The treatment protocol for these trials is 200 mg IV remdesivir on Day 1, followed by 100 mg IV remdesivir as a daily maintenance dose for the duration of hospitalization, up to 5 or 10 days maximum, depending on the trial. This is the dose of remdesivir used to treat Ebola virus. However, this may not be an optimized dose for treatment of COVID-19. Early studies on remdesivir's action on COVID-19 report a much higher EC50 and EC90 (0.77 and 1.76 μM) than that for remdesivir's action against Ebola (EC50 [?]0.1 μM). It should also be noted that the Ebola remdesivir trials from which this dosing regimen was borrowed showed negative results.[39]

These trials also use different dose timings, using both symptomatic disease and RT-PCR to define their therapeutic windows. For example, the Chinese trials give doses within 8 days of symptom onset for mild and moderate cases, or 12 days for severe cases while the NIAID trial uses a window of 3 days after PCR confirmation. The Gilead trials use a window of 4 days after PCR confirmation. It is unknown what therapeutic timing window will be most effective.

These trials also study slightly different populations. Only NCT04252664 assesses remdesivir in patients with mild COVID-19. All other studies are limited to moderate and severe cases.

A recent case series on 53 severe COVID-19 patients who received remdesivir in the context of compassionate care shows some encouraging results.[55] 36 patients (68%) had an improvement in oxygen requirement or

ventilatory support, 25 patients (47%) were stabilized and discharged, and 7 patients (13%) died. Although this trial was not conclusive and did not have a control group, historical comparisons with general care or other clinical trial, such as 22% mortality overall in 201 In Wuhan, China[56] and 22% mortality in a recent randomized, controlled trial of lopinavir–ritonavir[3]. The compassion-use data suggest that remdesivir may have clinical benefit in patients with severe COVID-19. This study is limited by the small size of the cohort, the relatively short duration of 28 days follow-up, potential missing data, and the lack of a randomized control group. However, these results are encouraging and open the door for future randomized, placebo-controlled trials of remdesivir therapy.

3) Lopinavir-ritonavir

Lopinavir-ritonavir is originally a medication used for HIV but has been used for other RNA viruses including SARS-CoV. An open-label study published in 2004 suggested, by comparison with a historical control group that received only ribavirin, that the addition of lopinavir–ritonavir (400 mg and 100 mg, respectively) to ribavirin reduced viral load, incidence of acute respiratory distress syndrome, and mortality among patients with SARS.[57] These results suggest potential activity for SARS-CoV-2 as well.

Compared to HCQ and remdesivir, fewer trials exist for lopinavir-ritonavir treatment of COVID-19. In the largest trial of lopinavir-ritonavir in 199 adult patients hospitalized for severe COVID-19, there was no difference in time to clinical improvement between patients given 400 mg lopinavir and 100 mg ritonavir twice daily for 14 days compared to those given standard care.[3]Given these weak results, there has been less interest in lopinavir-ritonavir as a treatment for COVID-19.

However, these discouraging results may partially be explained by SARS-CoV-2's viral dynamics. The peak of SARS-CoV-2 viral load is around the time of symptom onset[58], but the average time between symptom onset and randomization in this study was 13 days. At this time, the application of antiviral drugs may be too late to have significant effect. Indeed, subgroup analysis showed a minor acceleration of clinical recovery (16.0 days vs. 17.0 days) and a reduction in mortality (19.0% vs. 27.1%) in those treated within 12 days of symptom onset. In addition, this trial did not assess effect at different doses and there is no preliminary data to suggest that the trial dose is effective for COVID-19. Finally, the trial was not blinded and the authors acknowledge the potential for bias in the subjective criteria used[3]. Ultimately despite the negative results on lopinavir-ritonavir for COVID-19, it is still uncertain whether or not this drug combination is useful for COVID-19.

4) Favipiravir

Favipiravir is a purine nucleic acid analogue that is ribosylated and phosphorylated intracellularly into its active metabolite, which may interfere with viral replication by inhibiting RNA-dependent RNA polymerase. The EC_{50} of fapiravir against SARS-COV-2 in vitro is 62 μM (9.7 mg/L)[36], which is much higher than the EC_{50} for influenza A and B viruses (0.014 0.55 mg/L). The steady-state peak concentration of fapiravir in human plasma is 62 mg/L (600 mg, BID).[59] Its serum protein binding in the concentration range of 0.3˜30 mg/L is 54 % and radio-tracer studies in monkeys showed that labeled fapiravir in the lung was approximately 51% of that in plasma at 0.5 h after dosing. Assuming that the fapiravir EC_{50} concentration in vitro represents unbound drug and that the free concentration of fapiravir in the lung is equal to that in plasma (i.e. about 46%) then the free concentration of fapiravir in lung is about 14.5 mg/L or about 50% greater than the EC_{50} value.

An open-label, nonrandomized, controlled trial was conducted at the Third People's Hospital of Shenzhen to evaluate favipiravir in patients with COVID-19 pneumonia.[60] Patients with mild or moderate pneumonia within 7 days of onset were selected for this study, and they were more appropriate subjects for antiviral drug trials compared to the severe patients. A total of 80 patients with mild or moderate pneumonia treated within 7 days of symptom onset were assigned to the test group (35) to receive favipiravir (1600 mg twice daily on Day 1 or 600 mg twice daily on Days 2-14 orally) or to the active control group (45), to receive lopinavir-ritonavir (400 mg/100 mg twice daily orally), respectively. In addition, all subjects received aerosolized interferon-α1b (60μg twice daily). Treatment continued until viral clearance was confirmed or for

14 days. The results showed that the favipiravir arm had shorter viral clearance time (median (interquartile range, IQR), 4 (2.5 – 9) d versus 11 (8 – 13) d, $P < 0.001$) and higher radiographic improvement rate (91.43% versus 62.22%, $P = 0.004$) compared to the control arm. However, this trial also has some limitations, such as the small number of enrolments and like most trials, it is unblinded, which leads to inevitable selection bias in patient recruitment.

5) Tocilizumab

Cytokine release syndrome (CRS) occurs in many patients with severe COVID-19, which is also an important cause of death. Interleukin-6 (IL-6) plays an important role in CRS.[61] As an IL-6 receptor blocker, tocilizumab has been included as an immunotherapeutic agent for severe and critical patients in the "Novel Coronavirus Pneumonia Diagnosis and Treatment Protocol (Trial Seventh Edition)". At present, there are several registered clinical trials of tocilizumab in the treatment of patients with COVID-19. Most trials have targeted severe patients, and some trials include an increase of inflammatory factors such as IL-6, CRP or ferritin as one of their inclusion criteria.

Summary

There is an urgent need for effective anti-viral drugs to combat the COVID-19 crisis. The identification and development of these drugs depend on effective clinical trials. However, there are tremendous challenges for the development of drug therapies under pandemic conditions, even for drugs repurposed from other indications. Current barriers that have limited previous trials include lack of pathophysiologic understanding of disease, unoptimized dose, operational and regulatory difficulties, poorly defined therapeutic timing windows, broad non-specific outcome measures, non-randomized and underpowered trial designs. As a result, though the knowledge previous trials have provided has been invaluable, conclusive results are lacking. Despite crisis conditions, we cannot forsake the need for well-designed clinical trials. We present 3 key ideas, namely, adhering to translational science principles, leveraging innovative trial design and implementing 4R concept to increase likelihood of trial success and to produce high-quality data. Furthermore, we think it is particularly important to establish Global Clinical Trial models (e.g., adaptive platform trials) that can be implemented rapidly wherever a new pandemic breaks out. Conducting such trials is certainly a tremendous undertaking that will need significant resources and commitment. This will require international cooperation and a shift in the global pharmaceutics research landscape. Finally, we hope that this unprecedented pandemic will lead to development of more robust infectious disease research infrastructure and funding to help mitigate future pandemics.

COMPETING INTERESTS

Authors report no conflicts of interest.

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