

VIEWPOINT

Treating COVID-19—Off-Label Drug Use, Compassionate Use, and Randomized Clinical Trials During Pandemics

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Viewpoint



Audio

In the 2014 Ebola outbreak, close to 30 000 individuals developed Ebola viral disease (EVD), and numerous therapies were tested against this virus, including chloroquine, hydroxychloroquine, favipiravir, brincidofovir, monoclonal antibodies, antisense RNA, and convalescent plasma, among many others. With such a large number of therapeutic interventions given to affected patients, the goal was to determine which was efficacious against Ebola. Ultimately, none proved to be efficacious or safe.

Why were new therapies not discovered? One reason is because virtually all studies were single-group interventions without concurrent controls, which led to no definitive conclusion related to efficacy or safety. Despite much resistance and controversy regarding asking patients with EVD to participate in a randomized clinical trial (RCT),¹ the National Institutes of Health (NIH) conducted the first and only RCT during that outbreak. It took several months to design the trial, but it was implemented and successfully launched during the outbreak; however, it was too late for the RCT to be completed.² This tragedy of not discovering new therapies during an outbreak cannot be repeated.

The rapid and simultaneous combination of supportive care and RCTs is the only way to find effective and safe treatments for COVID-19 and any other future outbreak.

The world is now facing a pandemic of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, the cause of COVID-19), for which no proven specific therapies are available, other than supportive care. In China, and now Italy, France, and Spain, a large number of patients have received off-label and compassionate use therapies such as chloroquine, hydroxychloroquine, azithromycin, lopinavir-ritonavir, favipiravir, remdesivir, ribavirin, interferon, convalescent plasma, steroids, and anti-IL-6 inhibitors, based on either their *in vitro* antiviral or anti-inflammatory properties. These therapies have been mostly given without controls, except for a few randomized trials started in China, and more recently in the US.³

Although many drugs have *in vitro* activity against different coronaviruses, no clinical evidence currently supports the efficacy and safety of any drug against any coronavirus in humans, including SARS-CoV-2. Numerous drugs that have been highly promising *in vitro* for other infectious diseases have failed in clinical studies.

If *in vitro* activity automatically translated into clinical activity, more antimicrobial drugs for all kinds of infectious diseases would be available. Yet, there are published case reports of old and new drugs with *in vitro* activity against SARS-CoV-2 that have been given to patients but without a comparison control group. The administration of any unproven drug as a “last resort” wrongly assumes that benefit will be more likely than harm. However, when a drug with unknown clinical effects is given to patients who have severe illness from a new disease (like COVID-19), there is no way to know whether the patients had benefited or were harmed if they were not compared to a concurrent control group. A common interpretation of off-label use and compassionate use of drugs is that is that if the patient died, they died from the disease, but if the patient survived, they survived because of the given drug. This is not true.

As a practical example, chloroquine/hydroxychloroquine, azithromycin, and lopinavir-ritonavir have a variety of adverse effects, including QT prolongation, torsades de pointes, hepatitis, acute pancreatitis, neutropenia, and anaphylaxis. Considering that most patients who have died from COVID-19 were elderly and had cardiovascular comorbidities and that affected patients frequently have cardiac arrhythmias,^{4,5} chloroquine/hydroxychloroquine, azithromycin, and lopinavir-ritonavir could potentially increase the risk of cardiac death. Additionally, hepatitis and neutropenia are clinical manifestations of COVID-19, and both hepatic and bone marrow dysfunction could be made worse by the off-

label use of these drugs; thus, it would be impossible to differentiate the drug-related adverse effects from the disease manifestations in the absence of a control group.

Compassionate use of drugs that have not been previously approved for clinical use (eg, remdesivir) could cause serious adverse effects that were not previously detected because of the very small number of exposed patients. With respect to anti-inflammatory therapy, the use of intravenous steroids has been associated with delayed coronavirus clearance in both blood and lungs with MERS-CoV⁶ and SARS-CoV,⁷ and steroids were associated with significantly increased risk of mortality and secondary infections in patients with influenza.⁸ Furthermore, even low-dose steroids have shown harm in patients with sepsis, and IL-6 inhibitors may cause even more profound immunosuppression than steroids, increasing the risk of sepsis, bacterial pneumonia, gastrointestinal perforation, and hepatotoxicity.^{9,10} Yet, despite substantial evidence of potential harm, steroids and IL-6 inhibitors are now being given to patients with

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COVID-19 in several countries. Accordingly, even for treatments previously utilized in other diseases, it is critical to evaluate these drugs in studies that have a concurrent control group.

A control group may be defined as the standard of care with or without placebo. One concern during epidemics, for example, during the 2014 Ebola outbreak (and the current COVID-19 pandemic), is whether it is ethical to give patients a placebo. If the disease is not 100% lethal and it is not known whether the experimental drug would help or harm a patient (ie, a situation with true equipoise), then it is ethical to conduct an RCT. Without a control group, it is not possible to accurately determine the harms of any experimental drug. In reality, the placebo group will always be safer (regarding adverse effects) than the experimental group because patients in the placebo group will receive the established standard of care. In contrast, compared with RCTs, the administration of old or new drugs (eg, off-label use, compassionate use, single-group cohorts, case-historical controls, clinical trials without controls) may be less safe, and moreover, will not lead to the discovery of any new therapy.

In addition to the risk of harming patients without the possibility to even detect the magnitude of harm, the administration of off-label drug use, compassionate drug use, and uncontrolled studies during a pandemic also could discourage patients and clinicians from participating in RCTs, hampering any knowledge that could be gained

about the effects of the drug being tested. More than 300 000 individuals have been diagnosed with COVID-19; however, just a few hundred have been offered participation in RCTs. Meanwhile, many more patients have been offered uncontrolled drugs.

It is imperative to discover new therapies, otherwise there will be no proven treatments for future coronavirus pandemics. By participating in an RCT, both patients and clinicians can benefit from the unique opportunity to directly contribute to the discovery of new therapies, and also from the safer monitoring process in the conduct of clinical trials compared with uncontrolled drug administration (whereby safety cannot be determined). Optimally, during an outbreak, the type of RCTs that should be prioritized are ones with an adaptive design, which are able to rapidly accept or reject multiple experimental therapies throughout the trial, while being adequately powered for meaningful clinical outcomes.

With the current COVID-19 pandemic, RCTs have been launched around the world, including an adaptive trial sponsored by the NIH.³ This unprecedented speed from concept to implementation in just a few weeks is noteworthy and provides proof that clinical trials can be promptly initiated even in the middle of a pandemic. The rapid and simultaneous combination of supportive care and RCTs is the only way to find effective and safe treatments for COVID-19 and any other future outbreak.

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