EDITORIAL

New and Emerging Therapeutic Agents for the Management of SARS-Cov-2 Coronavirus Infection COVID-19

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COVID-19 emerged as a new severe acute respiratory illness in Wuhan, China in December 2019 and rapidly spread worldwide to become a global pandemic.[1] Although the figures keep changing on daily basis, by the end of October 2020, over 44 million people have been diagnosed with COVID-19 worldwide, according to World Health Organization. The pandemic has claimed more than a million human lives so far and resurgence in the number of new cases and continued growth in some countries has threatened both high and low-resource countries alike.

In January 2020, the virus responsible for the Coronavirus Infectious Disease 2019 (abbreviated as COVID19) was isolated and its RNA genome sequenced and shared globally online.[2,3] From complete genome sequencing it transpired that the cause of the severe acute respiratory illness that became known as COVID-19 is in fact a novel coronavirus, named SARS-CoV-2. Since then every so often new information about the virus and the new infection is emerging and history is constantly being rewritten. Subsequent phylogenetic analysis of the viral genome sequence suggests that SARS-CoV-2 originated in animals, probably bats, and was transmitted to other animals before crossing the human species barrier at the Huanan wet market in Wuhan City.[4,5,6]

The search for specific therapeutic drugs to effectively treat COVID-19 commenced as early as the discovery of the virus itself. However, with many studies carried out independently in small numbers of patients, there is a risk that such trials may lack sufficient statistical power for clinical recommendations. In this editorial, we will describe selected agents which are under investigation in large scale studies and which are more likely to produce robust outcome data for the efficacy and safety of these agents in the management of COVID-19. These studies include the World Health Organisation (WHO) SOLIDARITY study and the French Discovery study.[7,8]

WHO Study, "SOLIDARITY"

This is an international clinical trial to help find out an effective treatment for COVID-19 which was launched by the World Health Organization (WHO) and partners. It is one of the largest international randomised trials for COVID-19 treatments, enrolling almost 12, 000 patients in 500 hospital sites in over 30 countries. This study is evaluating the effect of drugs on 3 important outcomes in COVID-19 patients: mortality, need for assisted ventilation and duration of hospital stay.[7,8]

The study compares treatment options against standard of care to assess their relative effectiveness against COVID-19. By enrolling patients in multiple countries, the Solidarity Trial aims to evaluate whether any of the drugs improve survival or reduce the need for ventilation or reduce the duration of hospital stay. The trial is open to adding other drugs based on emerging new evidence. However, until such time as there is sufficient evidence, WHO cautions physicians and medical associations against recommending or administering unproven treatments to patients with COVID-19 or people self-medicating with such agents. WHO guidance on compassionate use can be found on the following link: https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19.

The Solidarity Trial published interim results in October 2020 which indicate that all four treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalised patients. This study is considering evaluating other

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treatments, to continue the search for effective COVID-19 therapies. So far, only corticosteroids have been proven effective against severe and critical COVID-19 infection.[7,8] In July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's hydroxychloroquine and lopinavir/ritonavir arms.

The International Steering Committee formulated the recommendation in light of the evidence for hydroxychloroquine vs standard-of-care and for lopinavir/ritonavir vs standard-of-care from the Solidarity Trial interim results, and from a review of the evidence from all trials presented at the 1-2 July 2020 WHO Summit on COVID-19 research and innovation. These interim trial results demonstrated that hydroxychloroquine and lopinavir/ritonavir produce little or no reduction in the mortality of hospitalised COVID-19 patients when compared to standard of care. Consequently, Solidarity Trial investigators interrupted the trials with immediate effect.

It is noteworthy that this decision applies only to the conduct of the Solidarity Trial in hospitalised patients and does not affect the possible evaluation in other studies of hydroxychloroquine or lopinavir/ritonavir in non-hospitalised patients or as pre- or post-exposure prophylaxis for COVID-19.

French Study, "Discovery"

France is co-ordinating the Discovery trial to compare the same drugs with standard care in a network of 3,200 patients in Belgium, France, Germany, Luxembourg, the Netherlands, Spain, Sweden and the UK. This will be randomised but non-blinded and will assess outcomes at 15 days.[7,8]

This study is a multi-centre, adaptive, randomised, open clinical trial of the safety and efficacy of treatments of COVID-19 in hospitalised adults. The study is a multi-centre and multi-country trial that will be conducted in various sites in Europe. Adult patient (≥18 year-old) hospitalised for COVID-19 with SpO2 ≤ 94% on room air OR acute respiratory failure requiring supplemental oxygen or ventilatory support are randomised between 4 treatment arms, each to be given in addition to the usual standard of care (SoC) in the participating hospital: SoC alone versus SoC + Remdesivir versus SoC + Lopinavir/Ritonavir versus SoC (this treatment arm has been ceased since June 29, 2020) + Lopinavir/Ritonavir plus interferon ß-1a versus SoC (this treatment arm has been ceased since June 29, 2020) + Hydroxychloroquine (this treatment arm has been ceased since May 24, 2020).

The primary objective of the study is to evaluate the clinical efficacy and safety of different investigational therapeutic options relative to the control arm in patients hospitalised with COVID-19, the primary endpoint is subject clinical status (on a 7-point ordinal scale) at day 15. The secondary objectives of the study are to evaluate: 1) the clinical efficacy of different investigational therapeutic agents through 28 days of follow-up as compared to the control arm as assessed by clinical severity (7-point ordinal scale, national early warning score, oxygenation, mechanical ventilation), hospitalisation, mortality through 28 days of follow-up, in-hospital mortality and 90-day mortality, 2) the safety of different investigational therapeutic options through 28 days of follow-up as compared to the control arm as assessed by the cumulative incidence of serious adverse events (SAEs), the cumulative incidence of Grade 3 and 4 adverse events (AEs), the discontinuation or temporary suspension of antiviral drugs for any reason, and the changes in white blood cell count, haemoglobin, platelets, creatinine, blood electrolytes, prothrombin time and international normalised ratio (INR), glucose, total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) over time.[7,8]

Other agents that have shown potential for the treatment of earlier coronavirus infections SARS and MERS are also being evaluated on the basis that the viruses share structural similarities with SARS-CoV-2. These include novel agents in development and antivirals currently in use for other indications. In addition, several studies have evaluated potential treatments *in vitro*.[9,10,11] A number of these therapies appear to have been introduced in China but are not well reported in English language scientific literature. China, as the country with the longest experience of managing COVID-19, is likely to have valuable expertise to share with the rest of the world.

Following is a summary of various agents under investigation for the treatment of COVID-19 that have shown some promise.[7,8]

1. Chloroquine/hydroxychloroquine: This drug

impairs release of virus after cell entry and blocks virus binding to cell receptor. It modulates immune response. The Food and Drug Administration (FDA) has given emergency use authorisation in the USA, however, the UK Medicine and Healthcare products Regulatory Agency (MHRA) states that it should only be used within a clinical trial. It is being investigated in the WHO SOLIDARITY study. Hydroxychloroquine is the preferred choice as it is associated with fewer adverse effects than chloroquine.

2. Hydroxychloroquine + azithromycin: Hydroxychloroquine impairs release of virus after cell entry and block virus binding to cell receptor. It modulates immune response. Azithromycin possesses possible anti-inflammatory action and it prevents secondary bacterial infection. One trial suggests reduction in viral nasopharyngeal carriage at 6 days in 20 patients as compared with unmatched untreated cohort, with azithromycin reinforcing the effect of hydroxychloroquine.[12]
3. Lopinavir/ritonavir: These agents are viral protease inhibitors. The use of this combination may inhibit SARS-CoV-2 virus and thus reduce adverse outcomes of infection. A randomised controlled trial including 200 patients, suggested no benefit so far.[13] Another trial is now underway in combination with a steroid, dexamethasone. Lopinavir/ritonavir combination is also being investigated in the WHO SOLIDARITY study.
4. Remdesivir: This drug blocks viral RNA synthesis. It has a broad-spectrum of activity against many coronaviruses. It was given emergency use authorisation by the FDA in the USA. Clinical trials have reported preliminary results.[14,15,16] Data from a study called Adaptive COVID-19 Treatment Trial (ACTT) indicates beneficial effect on reduction of time to recovery. Remdesivir is included in the WHO SOLIDARITY study.
5. Tocilizumab: This agent blocks interleukin-6 signalling which may inhibit the cytokine release in cytokine storm during severe COVID-19 infection. COVACTA trial supported by the US FDA is currently studying the role of tocilizumab in patients with severe COVID-19 pneumonia and cytokine storm.[8]
6. Favipiravir + interferon alpha: In this combination, favipiravir blocks viral RNA synthesis and interferon alpha stimulates innate antiviral response. This combination is being studied in a number of trials in China.[10]
7. Favipiravir + baloxavir marboxil: This combination of two antiviral agents blocks viral RNA synthesis. The U.S. Food and Drug Administration has approved baloxavir marboxil for the treatment of acute uncomplicated influenza (flu) in patients 12 years of age and older who have been symptomatic for no more than 48 hours. Now it is being studied against COVID19 in combination with favipiravir.[11]
8. Ribavirin + interferon alpha+ Lopinavir/ritonavir: This is a triple therapy combination of antiviral agents. Ribavirin inhibits the activity of the enzyme RNA dependent RNA polymerase, due to its resemblance to building blocks of the RNA molecules. It may inhibit replication of SARS-CoV-2. Lopinavir/ritonavir combination is viral protease inhibitors which may also inhibit SARS-CoV-2 virus and thus reduce adverse outcomes of COVID-19 infection. Interferon alpha stimulates innate antiviral response. Triple therapy is recommended by National Health Commission of the People's Republic of China as per Guidelines for diagnosis and treatment of novel coronavirus pneumonia 2020 (Trial Version 5).[17]

A trial claiming to show efficacy with hydroxychloroquine plus azithromycin received wide coverage in the lay media.[12] This study had important methodological deficiencies and its conclusions have been disputed by expert reviewers.[18] In addition, this combination is associated with an increased risk of QT interval prolongation which may turn out to be fatal in some high risk patients. Another controlled trial indicated that the combined viral protease inhibitor formulation of lopinavir/ritonavir is ineffective.[13] However, an uncontrolled trial of remdesivir which has *in vitro* activity against SARS-CoV-2, demonstrated improvement in 36 of 53 (68%) COVID-19 patients who were severely ill and who had oxygen saturation at ≤94% or were receiving oxygen support.[14] More recently, a randomised

control study has been published from China including 237 patients,[15] and headline results released from a global phase 3 trial named Adaptive COVID-19 Treatment Trial (ACTT) including 1063 patients.[16] Both of these studies included significant numbers of hospitalised patients with COVID-19 pneumonia.

In the study from China, remdesivir did not reduce time to clinical improvement, however, there was a trend towards faster improvement in patients who had a duration of symptoms of 10 days or less. By contrast, the ACTT study suggested that treatment with remdesivir was associated with a more rapid recovery as compared with placebo.[16] Median time to recovery was 11 *vs* 15 days, p<0.001, and there was an overall trend towards improved mortality (8.0% *vs* 11.6%; p=0.059). More data is required to provide a clearer picture on the benefits of remdesivir in rapid recovery and improved mortality from COVID-19.

The role of adjunctive agents such aspirin in severe COVID-19 infection with pneumonia has also been evaluated. A recent study indicated that hospitalised patients with COVID-19 who received aspirin prior to hospital admission or within 24 hours of hospital admission had a significantly lower risk of complications and death compared with patients who did not receive aspirin. [19] Aspirin use had a crude association with less mechanical ventilation (35.7% vs 48.4%; P = .03) and reduced intensive care unit admission (38.8% vs 51.0%; P = .04), but no crude association with in-hospital mortality (26.5% vs 23.2%; P = .51). Two of the most significant events in the pathophysiology of SARS-CoV-2 virus infection are cytokine storm and micro clot formation. The beneficial effects of aspirin in severe COVID-19 infection are believed to be blood thinning action and prevention of micro clot formation. The conclusion of this study was that aspirin use may be associated with improved outcomes in hospitalised COVID-19 patients.[19] However, sufficiently powered randomised controlled trials are required to elucidate the causal relationship between aspirin use and reduced lung injury and mortality in COVID-19 patients.

Conflict of Interest

The authors confirm that they have no conflict of interest.

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