Commentary

Clinical trials for coronavirus disease 2019: What is being evaluated and what is not

Yaseen M. Arabi[1,2,3], Ayed Asseri[4], Steve Webb[5], John Marshall[6], Mohamed S. Al Moamary[7,8]

[1]Intensive Care Department, Ministry of National Guard Health Affairs, [2]King Abdullah International Medical Research Center, [3]Intensive Care Department, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, [4]Intensive Care Department, Prince Mohammed Bin Abdulaziz Hospital - Ministry of Health, [7]College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, [8]Department of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [5]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia, [6]Interdepartmental Division of Critical Care Medicine, Keenan Research Centre for Biomedical Science, St. Michael's Hospital, University of Toronto, Toronto, Canada

Address for correspondence:
Prof. Yaseen M. Arabi, Intensive Care Department, Respiratory Services, College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, King Abdulaziz Medical City, P.O. Box 22490 Riyadh 11426, Kingdom of Saudi Arabia.
E-mail: yaseenarabi@yahoo.com

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Abstract:

Since the report of the first case of coronavirus disease 2019 (COVID-19) in China in late December 2019, there have been 204 610 cases worldwide as of 18 March, 2020. As part of the response to this outbreak, there has been an impressive amount of research undertaken to better characterize the disease and to evaluate therapeutic options. By March 12, 2020, there are more than 382 studies registered in the clinical trials databases addressing COVID-19 including more than 80 randomized controlled trials.

Keywords:

Clinical trials, coronavirus disease 2019, outbreak response

Since the report of the first cases of coronavirus disease 2019 (COVID-19) in China in late December 2019, there have been 204 610 cases worldwide as of March 18 2020. While cases are declining in China, there has been a sharp increase in the number of cases across more than 120 countries outside China. The reported case fatality rate of COVID-19 is approximately 1%–4%.[1] A study from China classified COVID-19 patients into nonsevere cases constituting 80% and severe cases constituting 20% of patients.[2] In total, 5% of COVID-19 patients were critically ill and were admitted to the intensive care units, with a mortality rate of 49%–62%.[2,3] This high mortality rate among critically ill COVID-19 patients is reminiscent of what was observed among critically ill patients with Middle East respiratory syndrome (MERS).[4,5] The disease affects different age groups; with older patients being at the highest risk.[2]

As part of the response to this outbreak, there has been an impressive amount of research undertaken to better characterize the disease and to evaluate therapeutic options. By March 12, 2020, there are more than 382 studies registered in the clinical trial databases addressing COVID-19 including more than 80 randomized controlled trials.[6,7]

Currently registered clinical trials are evaluating a wide variety of interventions[6,7] [Table 1]. Antiviral agents under study include remdesivir, lopinavir/ritonavir, and other antiretroviral agents, chloroquine, and several anti-influenza antiviral agents. Several interferons including interferons alpha-1b, alpha-2b, beta-1a, and beta-1b are also being examined. A host of biological therapeutics including mesenchymal stem cells, immunoglobulin, and convalescent plasma are being tested as well. Different immunomodulators are also being evaluated.

What appears to be missing from the list of the ongoing clinical trials are the

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Table 1: Interventions being evaluated for coronavirus disease 2019 based on registered trials

Category	Scientific title
Antivirals	Remdesivir
	Antiretrovirals: Lopinavir-ritonavir, darunavir and cobicistat, ASC09/ritonavir
	Anti-influenza antivirals: Arbidol, baloxavir, favipiravir
	Azvudine
	Chloroquine phosphate
	Hydroxycholoroquine
	rhACE2
	Ribavirin
Interferons	Interferon α-1b
	Interferon α-2b
	Interferon β 1-a
	Interferon β-1b
Biological therapies	Mesenchymal stem cell
	Type I macrophages therapy
	Umbilical cord blood mononuclear cells
	NK cells treatment
	Immunoglobulin
	Umbilical cord blood plasma
	Convalescent plasma
Chinese medicine and natural products	Xue-Bi-Jing injection and others
Immunomodulators	Corticosteroid
	Thymosin
	Tocilizumab
	Ruxolitinib
	Eculizumab
	Thalidomide
	Fingolimod
	PD-1 blocking antibody
	Bevacizumab
	Vitamin C
Macrolides	Carrimycin
Others	Washed microbiota transplantation
	Recombinant cytokine gene-derived protein injection
	Nasal high-flow preoxygenation-assisted fiber-optic bronchoscope intubation
	Hydrogen-oxygen nebulizer
	Antiaging-active freeze-dried powder granules

rhACE2=Recombinant human angiotensin-converting enzyme 2, NK=Natural killer, PD-1=Programmed cell death-1

interventions related to supportive care, which arguably are very important in determining patient outcomes. For example, noninvasive ventilation and high-flow nasal cannula have been widely used in the ongoing COVID-19 outbreak, but data about efficacy and safety are lacking.[3] In critically ill patients with MERS, 35% of patients received noninvasive ventilation; however, this use was associated with high failure rate reaching 92%.[8] Importantly, patients intubated after failed noninvasive ventilation were more likely to require oxygen rescue therapy than those who were intubated without noninvasive ventilation.[8] Although all the studies showed that noninvasive ventilation was not associated with different mortality, these findings raise concern about the efficacy of noninvasive ventilation; therefore, these important therapeutics should be considered as high research priority.[8] The use of extracorporeal membrane oxygenation in the current COVID-19 outbreak has been reported in several centers, but data are needed. Studies on COVID-19 reported high incidence of arrhythmias reaching 41% in one report among critically ill patients with COVID-19.[9] The extent of cardiac involvement is unknown at present; however, myocardium involvement is not uncommon with influenza virus infection and myocarditis in this context is well known.[10] Therefore, more data about the clinical involvement of the myocardium are needed. The implications on the management in terms of fluid therapeutics and type of inotropes required need to be further studied.

What is needed is a research agendum that addresses different questions related to the management of COVID-19. The World Health Organization (WHO) in collaboration with the Global Research Collaboration for Infectious Disease Preparedness has held the Global Research and Innovation Forum on February 11–12, 2020, to identify the urgent priorities for COVID-19 research. The domains that were addressed included the natural history of the virus, transmission and diagnosis, animal and environmental research, epidemiological studies, clinical characterization and management, infection prevention and control, therapeutics and vaccines, ethical considerations for research, and integration of social sciences into the outbreak response.[11] Informal consultation on research prioritization of candidate therapeutic agents by the WHO has prioritized remdesivir for clinical trials followed by lopinavir/ritonavir and interferon beta-1b combination.[12] The WHO Master Protocol for multicenter, adaptive, randomized controlled trial addresses several therapeutics in hospitalized patients with COVID-19.[13] Prioritization of questions related to support care is urgently needed. Several questions may be addressed in adaptive design trials. The randomized, embedded, multifactorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP) is designed as an adaptive preplanned, preapproved platform trial for ICU patients with severe community-acquired pneumonia.[14] The trial evaluates multiple interventions and their interactions.[14] The REMAP-CAP has now been adjusted to include domains related to the COVID-19. This design increases the efficiency of the research process and helps addressing important questions related to COVID-19 on an urgent basis.

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Conflicts of interest

Dr. Arabi is the principal investigator on a clinical trial for lopinavir/ritonavir and interferon in Middle East respiratory syndrome (MERS) and that he was a nonpaid consultant on antivirals for MERS-coronavirus (CoV) for Gilead Sciences and SAB Biotherapeutics. He is a co-investigator on REMAP-CAP. Dr Arabi and Dr Webb are investigators on REMAP-CAP and Board Members of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). Dr. Marshall is the Chair of the International Forum for Acute Care Trialists (InFACT), and co-chair of the WHO working group on clinical characterization; he has no relevant commercial conflicts to disclose.

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