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Biologics and Small Molecules in the Treatment of COVID-19

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INTRODUCTION

The novel corona virus disease (COVID-19) is caused by a virus belonging to the betacorona virus family.[1] The highly infectious nature of the disease, ability to spread through asymptomatic carriers, as well as the lack of a vaccine, have led to its uncontrolled spread worldwide since its inception in Wuhan, China in December 2019. The current reported number of cases is 613,882 worldwide with a death toll of 28,231 as of March 28, 2020. Hence, our immediate urgent challenge is to find effective drugs for the management of this disease.[1-4]

The National Health Commission of China issued pharmaceutical guidelines for the management of COVID-19, which has since undergone 5 rounds of modification. Currently, anti-viral drugs including protease inhibitors and nucleoside reverse transcriptase inhibitors, Interferon (IFN)-alfa, chloroquine, and arbidol are being used for a duration of 10 days. Newer drugs including Favirapir and Remdisavir have shown good results.[5]

The pathogenesis of COVID-19 involves binding to its receptor, ACE2 (angiotensin converting enzyme-2) protein, and using the cellular protease TMPRSS2 to enter target cells.[6] Therefore, a TMPRSS2 inhibitor would block entry of the virus and thus constitute a valuable treatment option. Imatinib, a BCR-ABL kinase inhibitor, inhibits the fusion of virions with the endosomal membrane.[7] Patients taking drugs that upregulate ACE2 receptors (including ACE inhibitors and ARB blockers) should have these ceased or other drug classes substituted. As these ACE2 receptors are expressed not only in the alveolar tissue of the lungs but also the eyes, oral mucosa, and intestine, and endothelial cells in blood vessels, contamination of broken skin such as atopic dermatitis, blistering diseases, and psoriasis, if allowed to relapse or be unprotected, could be dangerous.[8]

Given the routes of transmission of this coronavirus, it is imperative that health care workers are provided with adequate personal protective clothing – N95 masks (which can be re-sterilized using a protocol recently developed at Duke University if in short supply, by research labs),[9] goggles without ventilation, and complete gowning; those in lower risk areas of hospitals need patients wearing masks and health care workers at the least in N95 masks and goggles because humans can be asymptomatic for at least 5 days while spreading the virus and because it persists in the air and ventilation system on droplets and surfaces and gloves if sampling broken skin and mucosae.[10]

Cytokine involvement in the pathogenesis of COVID-19 infection is diverse. In particular, IFN-1 production is dysregulated. cGAS, ALK, and STING cytokines are suggested as potential therapeutic targets to prevent the cytokine storm. Cytokine directed antagonists, such as adalimumab (TNF-α) and CMAB806 (IL-6) are currently under clinical trials against COVID-19.[11,12]

Sorafenib is a potent inhibitor of the STING pathway, and hence a potential candidate in trials.[13]

Anaplastic lymphoma kinase (ALK) inhibitors were reported to be effective STING antagonists both in vitro and in vivo. Thus, ALK-targeted drugs have great potential in treating moderate to severe lung inflammation in COVID-19.[14]

Suramin, an effective cGAS antagonist acts as an entry inhibitor for different type of viruses.[15] Clinical trial of Suramin for COVID-19 is already underway.[16]

In another study, clinical data of COVID-19 positive patients showed a rise in IL-6, which reduced with treatment. Hence, it is hypothesized that antibodies targeting IL-6 or IL-6R may be a novel treatment option, especially in those with severe symptoms.[17] The humanized anti-human IL-6 receptor monoclonal antibody, tocilizumab, can specifically bind sIL-6R and mIL-6R

TABLE 1.

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Drug Name	**Drug Class/Mechanism**	**Reference/Clinical Trial Registration**
Imatinib	BCR-ABL kinase inhibitor	Coleman et al.
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Camrelizumab	PD-1 receptor antagonist	COVID-19 registered trials—an analysis (1)
Eculizumab	Targeted against C5 complement	COVID-19 registered trials—an analysis (1)
Mepolizumab	IL-5 antagonist	COVID-19 registered trials—an analysis (1)
PD-1 mAb	Monoclonal antibody against PD-1	COVID-19 registered trials—an analysis (1)
Sorafenib	STING pathway inhibitor	Deng et al.
Suramin	cGAS antagonist	COVID-19 registered trials—an analysis (1)
Toclizumab	IL-6 antagonist	Xu et al.
Siltuximab	Chimeric monoclonal antibody against IL-6	https://www.clinicaltrialsarena.com/news/eusa-pharma-siltuximab-study-covid-19/
Sarilumab	Fully humanized monoclonal antibody against IL-6	https://www.clinicaltrialsarena.com/news/sanofi-regeneron-trial-kevzara-covid-19/
	IL-6 antagonist	Xu et al.
Siltuximab	Chimeric monoclonal antibody against IL-6	https://www.clinicaltrialsarena.com/news/eusa-pharma-siltuximab-study-covid-19/
Sarilumab	Fully humanized monoclonal antibody against IL-6	https://www.clinicaltrialsarena.com/news/sanofi-regeneron-trial-kevzara-covid-19/

and inhibit signal transduction. It was found to be effective in managing critically ill COVID-19 patients in China, when combined with the regular treatment.[18]

Siltuximab, another chimeric monoclonal antibody against IL-6, is also under clinical trials at present.[15]

One of the major causes of death in COVID-19 is the unpredictable development of ARDS, as with SARS and MERS. After each of these epidemics, no funding was continued to investigate the causes and risk factors for the development of ARDS. It is imperative that teams taking care of these patients prospectively store samples of their serum and genomic DNA samples from both patients and controls who are infected but not as symptomatic, so that afterwards, genome-wide association studies (GWAS) and other techniques can be adopted to investigate what genetic acytokine response factors are involved in the development of SARS or myocarditis, another major cause of death in COVID-19 patients. Experts in conducting such case-control studies in multifactorial diseases are already among the field in dermatology.[19] A team of such talent could work in the background against this virus, just as the codebreakers did during World War II.

Taking a closer look at our toolbox in medicine is worthwhile when new diseases such as COVID-19 arise. We need to draw on the experience of every specialty when developing treatments for new, challenging illnesses. Biologics and small molecules offer a promising role in management of severe cases of COVID-19.

DISCLOSURE

Prof. Dedee Murrell is an investigator and on the advisory board for: Principiabio; Sanofi; Roche; Menlo; Janssen; Sun Pharma; Pfizer.

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