MINI-REVIEW ARTICLE

Current Advances in Novel SARS-CoV-2 Disease (COVID-19) Treatment and Intervention Strategies

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Abstract: Background: During the eleven months of the novel SARS-CoV-2 disease (COVID-19) outbreak in China and its global spread, there is a remarkable understanding of its epidemiology, pathobiology, and clinical management strategies. While countering a heavy toll on health and the economy, world’s regional authorities are enforcing safety guidelines and providing patient care. Currently, there is no globally approved treatment or intervention for COVID-19.

Methods: A structured online literature search for peer-reviewed articles was conducted on PubMed, Europe PMC, Google, WHO, CDC, FDA, and ClinicalTrials portals, using phrases such as COVID-19 treatment and intervention, COVID-19 drugs and COVID-19 vaccines.

Results: Analysis of the retrieved data showed that as a part of ‘Solidarity Clinical Trials’, hundreds of treatment and intervention strategies, including antiviral drugs, cytokine antagonists, convalescent plasma therapy, and vaccine candidates, have been registered worldwide. While remdesivir, the anti-Ebola virus drug, has been approved as an ‘emergency use’ drug in the USA, favipiravir, the anti-flu drug, has been recently approved in Russia. Tocilizumab and sarilumab, the cytokine (IL-6) antagonists, have entered Phase-II/III clinical trials in hospitalized COVID-19 patients. Among the leading vaccine candidates, Phase-III clinical trial results of Moderna, Pfizer and Oxford vaccines seem to be game changers for COVID19.

Conclusion: The world health authorities have strongly and quickly responded to the COVID-19 pandemic. Nonetheless, world bodies must unite in combating this health crisis by developing cost-effective drugs and vaccines and making them accessible to resource-poor countries.

Keywords: SARS-CoV-2, COVID-19, antiviral, chloroquine, remdesivir, vaccine.

1. INTRODUCTION

The global crisis of COVID-19 pandemic, caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has exerted a great toll on human health and economy [1, 2]. Currently, over 54.7 million people are infected with SARS-CoV-2, with > 13.3 million deaths in about 200 countries [1]. The SARS-CoV-2 originated in Dec 2019 in Wuhan, China, is the seventh human CoV and third highly pathogenic CoV after the 2002-03 SARS-CoV-1 and the 2012-13 Middle-East respiratory syndrome CoV (MERS-CoV). The origin of SARS-CoV-2 and its first source of human transmission still remains debated. Nonetheless, the genetic analysis of SARS-CoV-2 showed its very close similarity (~96%) with bat SARS-like CoV (Bat-SL-CoV), indicating its natural zoonosis in bats [3]. Very likely, it jumped into other mammals, like Malayan pangolin or civet cats, and then to its handler in Wuhan’s wet market. The human-to-human direct transmission of COVID-19 has been confirmed through multiple modes, such as nasal droplets, aerosols, and oral mucus [4].

During the eleven months of the COVID-19 crisis, we have developed a growing understanding of the epidemiology, pathobiology and clinical management strategies. Currently, viral RNA-based RT-qPCR and antibody-based test-kits are routinely used to identify infected people. Over 500 clinical trials of potential COVID-19 treatments and interventions have been registered worldwide, including those from the Chinese Clinical Trial Registry, ClinicalTrials.gov, Korean Clinical Research Information Service, EU Clinical Trials Register, ISRCTN, Iranian Registry of Clinical Trials, Japan Primary Registries Network, and German Clinical Trials Register [5]. Of these, few repurposed drugs and leading vaccine candidates are under Phase-I/II/III clinical trials. Meanwhile, worldwide, local government authorities and health care providers are enforcing safety guidelines and providing available patient care.

2. SARS-CoV-2 BIOLOGY

The SARS-CoV-2 is a plus-sense single-strand RNA virus that is classified into SARS-CoV-1, MERS-CoV, and...
other human CoV within the genus Betacoronavirus [6]. The viral 5′-capped mRNA (~30 kb) encodes several non-structural, structural, and accessory proteins [7]. Like other CoV, the SARS-CoV-2 encodes four typical structural proteins - spike (S), envelope (E), membrane (M) and nucleocapsid (N) (Fig. 1). The ‘S’ glycoprotein’s subunit ‘S1’ contains the human cell-receptor Angiotensin-Converting Enzyme-2 (ACE-2) receptor-binding domain, whereas the subunit ‘S2’ contains the structural elements required for membrane fusion [8, 9].

The ‘M’ glycoprotein is crucial for formation of the viral envelope and virion assembly, whereas the ‘E’ protein is necessary for the assembly and morphogenesis of nascent virions [10]. Though hitherto unproven in SARS-CoV-2 infected patients, the SARS-COV-1 ‘N’ protein is highly antigenic that triggers the production of neutralizing antibodies in about 90% of patients and is used as a serological marker [11]. Since the ‘S’ protein is expressed on the surface of the SARS-CoV-2, it is the major target for neutralization by the host antibodies. Two-third of the genomic RNA encodes for a polyprotein that is further cleaved into sixteen replicase and protease non-structural and six accessory proteins necessary for the viral life cycle as well as modulating host-innate immune system [6].

3. CLINICAL MANIFESTATIONS OF COVID-19

SARS-CoV-2 has an incubation period of 2-14 days with symptoms of fever, cough, headache, and breathlessness, manifesting from mild pneumonia to severe illness and death. In addition, some patients may also experience rashes on toes, discoloration of skin, dizziness, fizzing, burning sensation, and loss of taste or smell. COVID-19 patients mostly in old age or with pre-existing chronic conditions like respiratory, cardiac, renal, and hepatic disorders have shown a higher mortality rate. While nearly 80% of patients remain asymptomatic or show very mild flu-like symptoms and can recover at home, about 15% of severe cases require hospitalization, and 5% develop respiratory failure, septic shock, and even multi-organ failure [12]. In addition to pharyngeal-pulmonary symptoms and etiology, a good proportion of COVID-19 patients have also shown evidence of gastrointestinal and hepato-biliary symptoms where viral RNA has been detected in rectal swabs and stool samples [13-17]. Moreover, arrhythmia, hypertension and cardiac co-morbidity have been observed among critical cases compared to non-critical COVID-19 patients [15, 18, 19]. These clinical observations highlight the importance to correct and timely diagnosis and treatment of non-respiratory symptoms along with pneumonia to reduce the case fatality rate.

4. COVID-19 IMMUNOPATHOGENESIS

Clinical studies have shown that COVID-19 patients with severe pneumonia may rapidly progress to ARDS, septic shock or multiple organ failure and deaths [20]. Because ACE-2 is abundantly present on ciliated cells of the airway epithelium and lungs alveolar type-2 cells, ARDS progression and extensive lung damage in COVID-19 patients are inevitable. It is however, still unclear how SARS-CoV-2 is able to inhibit or evade host-innate immune responses to initiate severe pathogenesis. SARS-CoV encoded nonstructural and accessory proteins are suggested to modulate induction of cellular IFNs and cytokines (e.g., IL), which could enable the virus to evade antiviral mechanism of ISGs [21]. High plasma levels of IP-10, MCP-3, HGF, MIG and MIP-1α have been reported to be associated with disease severity in COVID19 patients [22]. Notably, considerable

![Fig. (1). A schematic representation of viral and cellular targets of various COVID19 drugs under clinical trials.](A higher resolution / colour version of this figure is available in the electronic copy of the article).
release of IL-6 has been previously reported in SARS and MERS patients, and suggested to play a role in disease progression [14, 22]. In COVID-19 patients, a large number of T lymphocytes and mononuclear macrophages are activated, producing IL-6, which bind to the IL-6 receptor on the target cells, leading to the cytokine-storm and severe inflammatory responses in lungs and other organs [23]. In addition, the host-immune responses through inflammatory and CTL activities play critical roles in inhibiting viral replication and dissemination. Therefore, the immune overdrive along with cytolytic effects, results in disease severity.

In a recent study of COVID-19 patients during recovery stage, the high ratio of classical CD14++ cells with elevated cytolytic effects, results in disease severity. dissemination. Therefore, the immune overdrive along with host-immune responses through inflammatory and CTL activities play critical roles in inhibiting viral replication and dissemination. Therefore, the immune overdrive along with cytolytic effects, results in disease severity.

As part of broader patient care, SARS-CoV-2 specific antibody-rich plasma (i.e., plasma therapy) from fully recovered patients when transfused to hospitalized COVID-19 patients has shown encouraging results in many countries. The Regeneron and Eli Lilly initiatives on SARS-CoV-2 monoclonal antibodies are now in Phase-III clinical trials [27]. Although the duration of acquired immunity against COVID-19 still remains poorly understood, the plasma therapy might give healthcare workers and first responders at least a temporary vaccine-like protection.

**6. COVID-19 VACCINE DEVELOPMENT**

Developing a vaccine is always the best preventive measure, but it is also the most complicated process requiring a period of at least 24-30 months. As a quick initiative, several countries including US, China, Canada, UK, Australia and Italy have already developed COVID-19 vaccines, which are in the last stage of clinical trials. Though public information on the specific SARS-CoV-2 antigen(s) as vaccine candidate is limited, most of them have used the viral ‘S’ protein as a potent inducer of neutralizing antibodies against the ACE-2 receptors. However, the clinical correlation between different molecular forms and/or variants of ‘S’ protein used in developing different vaccines with regard to the genomic epidemiology of SARS-CoV-2, still remains unclear. Nonetheless, previous experiences with SARS-CoV-1 vaccine development have indicated the effectiveness of different viral antigens that could be also potentially relevant to SARS-CoV-2 vaccine development.

As a fact, an estimated 77% of vaccine candidates make it through Phase-I human trials, and of which only 33% make it through Phase-II and III before it successfully gets marketed. The Coalition for Epidemic Preparedness Innovations (CEPI) has been working with global health authorities and pharma companies to support the development of COVID-19 vaccines. The first COVID-19 vaccine candidate entered human clinical testing in the USA with unprecedented rapidity in March 2020, following the WHO announcement of a second from the USA, one from the UK, and two from China. In April 2020, the global COVID-19 vaccine R&D landscape has included 115 vaccine candidates, of which seventy three active candidates are currently at exploratory or preclinical stages [36]. A month later, about 10 most advanced SARS-CoV-2 vaccines that entered the
Table 1. Various classes of leading COVID-19 therapeutics under clinical trials.

<table>
<thead>
<tr>
<th>Antivirals</th>
<th>Antibiotic</th>
<th>Immune Modulator</th>
<th>Interleukin Antagonist</th>
<th>Antibody Therapy</th>
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<tbody>
<tr>
<td>Remdesivir</td>
<td>Azithromycin</td>
<td>Dexamethasone</td>
<td>Tocilizumab</td>
<td>Convalescent plasma</td>
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<td>Hydroxychloroquine</td>
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<td>Liponavir</td>
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<td>Ritonavir</td>
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Phase-I clinical trials, included mRNA-1273 (LNP-encapsulated messenger RNA vaccine encoding ‘S’ protein; Moderna, USA), Ad5-nCoV (Adenovirus type 5 vector expressing ‘S’ protein; CanSino Biologicals, China), ChAdOx1 nCoV-19 (Adenovirus vector expressing ‘S’ protein; Oxford vaccine Group, UK); INO-4800 (DNA plasmid encoding ‘S’ protein; Inovio Pharmaceuticals, USA), and LV-SMENP-DC (DC modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTL; Shenzhen Geno-Immune Medical Institute, China). Phase-I/II trials results from Oxford ChAdOx1, Pfizer-BioNTech mRNA and Moderna mRNA 1273 have shown promising outcomes in terms of the generation of neutralizing antibodies which are comparable to or higher than the level in convalescent sera [37, 38]. These pharma companies have recently released their Phase-III trial results in which Pfizer-BioNTech (~95% efficacy), Moderna-NIH (~94.5% efficacy) and Oxford-AstraZeneca (~70% efficacy) vaccines seem to be game changers for COVID19. Nonetheless, large-scale Phase-III trials of leading vaccine candidates are warranted to ensure minimal side-effects in some population before final approval and licensing.

There are however, unique and unknown risks associated with the mRNA vaccines, such as the possibility of inducing strong type-I IFN responses that could cause tissue inflammation and autoimmune conditions [39]. And, the fact remains that mRNA vaccines have never been successfully launched for human infectious diseases. The Oxford vaccine works via engineered adenovirus, a common cold virus that elicits strong immune response in addition to expressing the SARS-CoV-2 ‘S’ protein. Unlike the Moderna mRNA vaccine, the Oxford vaccine does not need to hijack cellular machinery and rather uses the adenovirus’s machinery to produce the ‘S’ protein in the body. Therefore, from a biological and clinical perspective, there is less risk of generating a type-I IFN response and autoimmunity. In the meantime, results from Phase-I trial of CanSino Biologics Ad5 vectored COVID-19 vaccine has shown a yield of peak T cell response at day 14 and peak antibody response at day 28 post-vaccination [40].

Notably, the Coalition for Epidemic Preparedness Innovations (SEPI) in April 2020 had speculated that a COVID-19 vaccine might be available under ‘emergency use protocols’ by early 2021. On the other hand, the organizers of the United States push called ‘Operation wrap Speed’ has recommended for picking a diverse set of vaccine candidates, their unprecedented comparative studies in animals, fast-track human trials, and production of 300 million shots by January 2021 for American people [41].

CONCLUSION

The ongoing COVID-19 pandemic has forced several countries to resort to extreme public health measures. Amid the advances in the understanding of COVID-19 pathobiology and clinical intervention strategies, several antiviral drugs and vaccine candidates are under final stages of clinical trials. In the USA, while remdesivir has been granted approval as emergency drug, the Moderna, Oxford and Pfizer vaccines has shown very promising results in Phase-III trials. Importantly, the regulatory authorities or agencies must ensure that the preset standard protocols and guidelines are being strictly followed amid the ‘gold rush’ of drug or vaccine trials. Nonetheless, world bodies must unite in combating this health crisis by developing cost-effective diagnostics and therapeutics and making them available to resource-poor countries.

LIST OF ABBREVIATIONS

WHO = World Health Organization
CDC = Center for Disease Control and Prevention
FDA = Food and Drug Authority
CoV = Coronavirus
COVID-19 = SARS-CoV-2 Disease 2019
ARDS = Acute Respiratory Distress Syndrome
IP-10 = Interferon-inducible protein-10
IL = Interleukin
IFN = Interferon
IFG = IFN-stimulated Genes
HGF = Hepatocyte Growth Factor
MCP-3 = Monocyte Chemotactic Protein-3
MIG = Monokine Induced Gamma Interferon
MIP-1α = Macrophage Inflammatory Protein 1 Alpha
CTL = Cytotoxic T Cell
CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors thankfully acknowledge their mentor Dr. Shahid Jameel (Director, Trivedi school of Biosciences, Ashoka University, India), for motivating and guiding in the field.

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