AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

MINIREVIEW

Updated Approaches against SARS-CoV-2

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ABSTRACT Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lies behind the ongoing outbreak of coronavirus disease 2019 (COVID-19). There is a growing understanding of SARS-CoV-2 in virology, epidemiology, and clinical management strategies. However, no anti-SARS-CoV-2 drug or vaccine has been officially approved due to the absence of adequate evidence. Scientists are racing to develop a treatment for COVID-19. Recent studies have revealed many attractive therapeutic options, even if some of them remain to be further confirmed in rigorous preclinical models and clinical trials. In this minireview, we aim to summarize the updated potential approaches against SARS-CoV-2. We emphasize that further efforts are warranted to develop the safest and most effective approach.

KEYWORDS COVID-19, SARS-CoV-2, antiviral drugs, treatment, vaccines

Since December 2019, coronavirus disease 2019 (COVID-19) has been spreading around the world, with over 130,000 confirmed cases (as of 13 March 2020) (1, 2). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel betacoronavirus, is the causative agent of this global health threat (3). Like other coronavirus strains, SARS-CoV-2 is characterized by a spherical morphology with spike projections on the surface. It was demonstrated that SARS-CoV-2 shared high sequence identity with SARS-CoV and bat SARS-like coronavirus (SL-CoV) (4). Notably, SARS-CoV-2 has lower pathogenicity than SARS-CoV but higher transmissibility from human to human (5). Cell entry is the first step of cross-species transmission. SARS-CoV-2 is more likely to infect lung type II alveolar cells, which may explain the severe alveolar damage after infection (6).

The rapid spread of COVID-19 has resulted in an urgent requirement for effective therapeutic strategies against SARS-CoV-2. Initially, without licensed vaccines or approved antiviral drugs, COVID-19 treatment was mainly based on the experience of clinicians. The newest guideline published by National Health Commission (NHC) of the People's Republic of China recommends alpha interferon (IFN-α), lopinavir/ritonavir, ribavirin, chloroquine phosphate, and arbidol as antiviral therapy (7). To date, many potential approaches have been revealed based on the progress of SARS-CoV-2 research, including inhibition of SARS-CoV-2 fusion/entry, disruption of SARS-CoV-2 replication, suppression of excessive inflammatory response, convalescent plasma (CP) treatment, and the use of vaccines as well as the combination of traditional Chinese medicine (TCM) and Western medicine (as summarized in Fig. 1). Additionally, a number of clinical trials are in progress to test the safety and effectiveness of candidate drugs. In this review, we summarize the current knowledge on the potential treatment against SARS-CoV-2 based on the emerging basic and clinical data.

UPDATED ATTRACTIVE APPROACHES AGAINST SARS-CoV-2

Inhibition of SARS-CoV-2 fusion/entry. Similarly to SARS-CoV, SARS-CoV-2 uses spike (S) protein to gain entry into host cells (8). It was shown that the S protein on the surface of SARS-CoV-2 cell bound the entry receptor angiotensin-converting enzyme 2

Citation Li H, Zhou Y, Zhang M, Wang H, Zhao Q, Liu J. 2020. Updated approaches against SARS-CoV-2. Antimicrob Agents Chemother 64:e00483-20. https://doi.org/10.1128/AAC.00483-20.

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Accepted manuscript posted online 23 March 2020
Published 21 May 2020

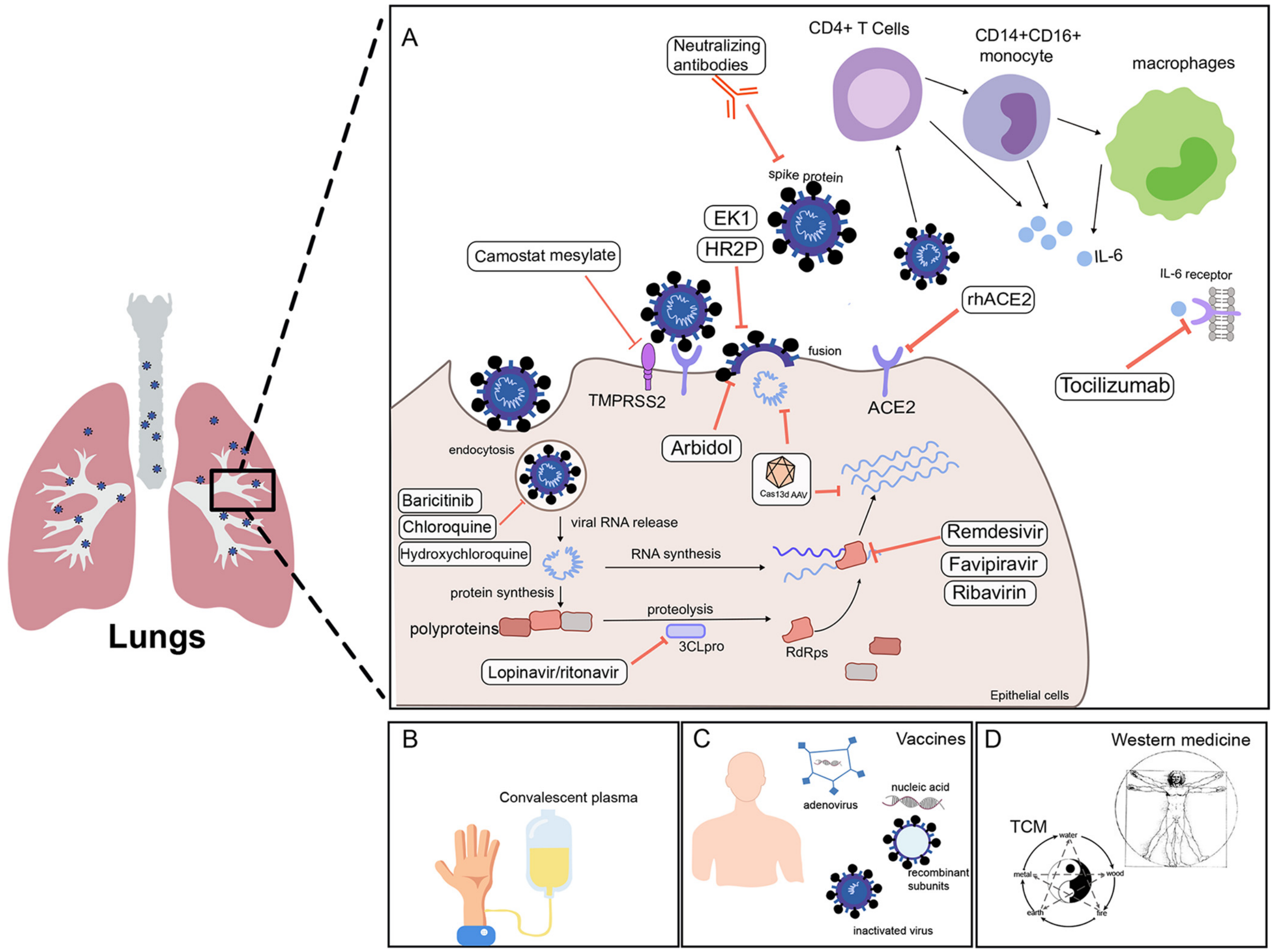

FIG 1 Updated potential approaches against SARS-CoV-2. (A) Dampening of SARS-CoV-2 fusion/entry; disruption of SARS-CoV-2 replication; inhibition of excessive inflammatory response. (B) Convalescent plasma treatment. (C) Vaccines. (D) Combinations of traditional Chinese and Western medicine. ACE2, angiotensin-converting enzyme 2; rhACE2, recombinant human ACE2; HR2P, heptad repeat 2-derived peptides; EK1, a modified OC43-HR2P peptide; 3CLpro, 3C-like protease; RdRps, RNA-dependent RNA polymerases; AAV, adeno-associated virus; IL-6, interleukin-6; TCM, traditional Chinese medicine.

(ACE2) on infected cells (9). SARS-CoV-2 was predicted to recognize human ACE2 more efficiently than SARS-CoV (10). Thus, targeting the interactions between ACE2 and S protein may be a potential approach. Specifically, a receptor binding domain (RBD) within the S protein is the critical target for neutralizing antibodies. Since SARS-CoV-2 S protein displayed high homology to that of SARS-CoV, the available neutralizing antibody of SARS-CoV CR3022 was found to bind potently with SARS-CoV-2 RBD (4). Nevertheless, Zheng and Song recently reported that more than 85% of the RBD antibody epitopes in SARS-CoV-2 showed remarkable alterations compared with SARS-CoV, indicating the necessity to develop new monoclonal antibodies for SARS-CoV-2 (11). In addition, the rationale for the choice of the ACE2 receptor as a specific target has been reviewed elsewhere (12, 13). Notably, an open-label, randomized, controlled, pilot clinical trial is in progress, further investigating the effect of recombinant human ACE2 (rhACE2; GSK2586881) in patients with severe COVID-19 (ClinicalTrials registration no. NCT04287686). It was suggested that S protein-derived cell entry depended on not only ACE2 but also on the host cellular serine protease TMPRSS2 (14). Camostat mesylate, a clinically proven inhibitor of TMPRSS2, significantly reduced lung cell line infection with SARS-CoV-2 and could be considered for COVID-19 treatment (14). In addition, heptad repeat 1 (HR1) and heptad repeat 2 (HR2) on SARS-CoV-2 involved viral and cell membrane fusion (15). Xia et al. reported that HR2-derived peptides

(HR2P) and EK1 (a modified OC43-HR2P peptide) exhibited effective fusion inhibitory activity toward SARS-CoV-2 and would act as fusion/entry inhibitors to treat SARS-CoV-2 infection. Further studies are warranted to substantiate these concepts.

Moreover, it was suggested that coronavirus entry also involved pH- and receptor-dependent endocytosis (16, 17). Targeting endocytosis may be another option for fighting SARS-CoV-2. AP-2-associated protein kinase 1 (AAK1) is a host kinase that regulates clathrin-mediated endocytosis (18). A group of approved drugs targeting AAK1 were searched out based on artificial intelligence (AI) technology (19). Among them, the Janus kinase inhibitor baricitinib, an AAK1-binding drug, was expected to be a suitable candidate drug for COVID-19 because the standard treatment doses of baricitinib were sufficient to inhibit AAK1 (19).

Arbidol and chloroquine phosphate have been added to the list of potential treatment options in the NHC guideline for COVID-19 treatment (7). Arbidol was shown to inhibit multiple enveloped viruses by inhibiting virus entry/fusion of viral membranes with cellular membranes (20). Chloroquine, a traditional antimalarial drug, was shown to be effective against SARS-CoV-2 infection *in vitro* (21). Several clinical trials are in progress to test the efficacy and safety of chloroquine phosphate against COVID-19 (22). Results from more than 100 patients provided the first evidence that chloroquine phosphate was more effective in inhibiting the exacerbation of pneumonia than control treatment (22). Additionally, Yao et al. found that hydroxychloroquine (50% effective concentration [EC_{50}] = 0.72 μM) was more potent with respect to inhibiting SARS-CoV-2 than chloroquine (EC_{50} = 5.47 μM) *in vitro* (23). Most importantly, the molecular mechanism of chloroquine phosphate in the treatment of COVID-19 remains elusive. It has been reported that chloroquine could impair endosome-mediated viral entry or the late stages of viral replication (24). More efforts are needed to pin down the exact mechanism.

Disruption of SARS-CoV-2 replication. Many antiviral agents have been developed against viral proteases, polymerases, MTases, and entry proteins. Clinical trials are currently in progress to test a number of antiviral drugs, such as remdesivir (ClinicalTrials registration no. NCT04252664 and NCT04257656), favipiravir (Chinese Clinical Trial registration no. ChiCTR2000029600 and ChiCTR2000029544), ASC09 (ChiCTR2000029603), lopinavir/ritonavir (ChiCTR2000029387, ChiCTR2000029468, and ChiCTR2000029539), and arbidol (ChiCTR2000029621). Martinez reported that the most promising antiviral for fighting SARS-CoV-2 was remdesivir (25). Remdesivir is a monophosphoramidate prodrug of an adenosine analog. Its active form can incorporate into nascent viral RNA by the activity of RNA-dependent RNA polymerases (RdRps), which then causes RNA synthesis arrest (26). Wang et al. demonstrated that remdesivir effectively inhibited SARS-CoV-2 *in vitro* (21). The clinical condition of the patient with the first case of COVID-19 confirmed in the United States improved following intravenous remdesivir administration (27). Similarly, favipiravir and ribavirin are monophosphoramidate prodrugs of guanine analogues and have been approved for treatment of infections by some other viruses (28). However, their antiviral effect in patients with COVID-19 needs rigorous data to support their use. Lopinavir and ritonavir are protease inhibitors targeting the coronavirus main proteinase (3C-like protease; 3CLpro). 3CLpro is responsible for processing the polypeptide translation product from the genomic RNA into the protein components (29). High-throughput screening was also used to screen small-molecule drugs targeting the viral main protease in clinical drug libraries (30). Four molecules, including prulifloxacin, tegobuvir, bictegravir, and nelfinavir, showed reasonable binding conformations with the viral main protease (30).

Targeting the RNA genome of SARS-CoV-2 may be another approach. Nguyen et al. showed the application of the novel CRISPR/Cas13 RNA knockdown system in cleaving the SARS-CoV-2 RNA genome (31). This CRISPR/Cas13d system was composed of a Cas13d protein and guide RNA-containing spacer sequences specifically complementary to the virus RNA genome. It was suggested that the Cas13d effector could be delivered via an adeno-associated virus (AAV) to the lung infected with SARS-CoV-2 (31).

Suppression of excessive inflammatory response. A coordinated cytokine response is essential for the host immune response. However, a dysregulated response leads to a hyperinflammatory condition in some patients infected with SARS-CoV-2. It was reported that patients in intensive care units (ICUs) had higher concentration of cytokines in plasma than non-ICU patients with COVID-19, suggesting that the cytokine storm was associated with disease severity (32). Besides, higher percentages of granulocyte-macrophage colony-stimulating factor-positive (GM-CSF$^+$) and interleukin-6-positive (IL-6$^+$) CD4$^+$ T cells were isolated from ICU patients infected with SARS-CoV-2 than from non-ICU patients (33). In view of this, inhibition of excessive inflammatory response may represent an adjunct therapy for COVID-19. Nevertheless, the therapeutic use of corticosteroids, which has shown excellent pharmacological effects with respect to suppressing exuberant and dysfunctional systematic inflammation, is still controversial (25, 32). The current NHC guideline emphasizes that the routine use of systematic corticosteroids is not recommended unless indicated for another reason. In line, there were no available data showing that patients benefited from corticosteroid treatment in SARS-CoV or Middle East respiratory syndrome coronavirus (MERS-CoV) infection, which might be attributable to the suppression of immune response against virus (34). Notably, a recent retrospective study showed the potential benefits accruing from low-dose corticosteroid treatment in a subset of critically ill patients with SARS-CoV-2 (35). More studies are needed to find out how and when to use corticosteroids properly.

At the cellular level, Zhou et al. demonstrated that CD4$^+$ T cells were rapidly activated to produce GM-CSF and other inflammatory cytokines after SARS-CoV-2 infection, which further induced CD14$^+$ CD16$^+$ monocyte activation with high levels of expression of interleukin 6 (IL-6) (33). Thus, blocking GM-CSF or IL-6 receptor would potentially reduce immunopathology caused by SARS-CoV-2. In line, a multicenter, randomized, controlled clinical trial is under way to examine the efficacy and safety of tocilizumab (an IL-6 receptor-specific antibody) in patients with COVID-19 (Chinese Clinical Trial registration no. ChiCTR2000029765). Moreover, Fu et al. mentioned possible mechanisms of SARS-CoV-2-mediated inflammatory responses in which the neutralizing antibodies triggered Fc receptor (FcR)-mediated inflammatory responses and acute lung injury (36). Various options to block FcR activation might reduce SARS-CoV-2-induced inflammatory responses (36).

Convalescent plasma treatment. With infections for which there is no specific therapy available, therapy with convalescent plasma (CP) has been proposed as a principal treatment (37). The CP is obtained from a donor who has recovered from infection by developing humoral immunity against the SARS-CoV-2 (38). The protective and therapeutic benefit of CP was attributed to the possible source of specific antibodies of human origin (39). However, evaluation of the efficacy of CP treatment is still difficult because of the lack of high-quality randomized clinical trials and of knowledge of the precise mechanism of action of plasma therapy. According to the NHC guideline, the CP of recovered patients is mainly used for patients in rapid disease progression or in a severe or critical condition (40). Several clinical trials investigating the efficacy and safety of convalescent plasma transfusion in patients with COVID-19 are in progress (Chinese Clinical Trial registration no. ChiCTR2000030010, ChiCTR2000030179, and ChiCTR2000030381).

Vaccines. With the global spread of SARS-CoV-2, vaccination must be the most efficient and cost-effective means to prevent and control COVID-19 (41). Robust research efforts are under way to facilitate the development of vaccines against SARS-CoV-2. Specifically, the S protein of SARS-CoV-2 remains a key target for vaccine development. Recently, Wrapp et al. reported and shared the cryo-electron microscopy (cryo-EM) structure of SARS-CoV-2 S trimer, which enabled additional protein engineering efforts and speeded up the process of vaccine development (42). In addition, Lucchese searched the pentapeptides unique to SARS-CoV-2 by comparing the viral and the human proteomes and found that 107 human-foreign pentapeptides were embedded in S protein (43). Further, these S protein pentapeptides yielded 66 candidate epitopes for vaccine development (43). Moreover, since there were few available immunological studies related to SARS-CoV-2, Ahmed et al. screened the SARS-CoV-derived epitopes due to its high level of genetic similarity with SARS-CoV-2 (44). A screened set of SARS-CoV-derived B cell and T cell epitopes that mapped identically to SARS-CoV-2 proteins were identified, which would help the initial phase of vaccine development (44).

More than 15 potential vaccine candidates for treatment of COVID-19 infection are being developed around the world, including inactivated vaccine, recombinant subunits vaccine, nucleic acid-based vaccine, adenoviral vector vaccine, recombinant influenza viral vector vaccine, etc. (45). On 23 January 2020, the Coalition for Epidemic Preparedness Innovations (CEPI) announced the finding on DNA, mRNA, and "molecular clamp" vaccine platforms (46). There was no existing literature on SARS-CoV-2 vaccine trials as of 13 March 2020. The safety of vaccine remains a top priority for vaccine development.

Combination of traditional Chinese and Western medicine. It was reported that the Chinese medicine products that were used to treat respiratory tract infectious diseases might be helpful for SARS-CoV-2 treatment (47, 48). Among these products, Lianhua Qingwen capsules and ShuFeng JieDu capsules were shown to exert independent antiviral effects and synergistic antiviral effects with Western medicine products on influenza viruses, respectively (49, 50). The latest treatment guideline in China added traditional Chinese medicine (TCM) as one of the treatment options for COVID-19. Wang et al. reported four cases with COVID-19 which showed improvement after the patients were given combined Chinese and Western medicine treatment (51). However, there are few published studies on Chinese medicine products in the treatment of COVID-19 and, in particular, a dearth of high-quality research. Additional prospective, rigorous population studies are urgently required to confirm the therapeutic effect of TCM. The mechanism of their antiviral action needs to be further illuminated.

CONCLUSIONS

The potential therapeutic strategies mentioned above are based on the updated research data for SARS-CoV-2. Among those options, we anticipate that the therapeutic drugs that directly target SARS-CoV-2 will be most effective. Besides, vaccines are critical for the prevention and limitation of COVID-19 transmission. Notably, the encouraging advances in deciphering SARS-Cov-2 will lead to additional potential therapeutic targets. Further, strong preclinical and clinical studies are needed to determine the safe and effective treatment for COVID-19.

ACKNOWLEDGMENTS

All of us declare that we have no conflict of interest.

The work was supported by the National Natural Science Foundation of China (J.L., no. 81472735) and by the National Basic Research Program of China (973 program, J.L., grant no. 2015CB932600).

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