Updated approaches against SARS-CoV-2

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Abstract

The 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 the 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 towards the development of treatment for COVID-19. Recent studies have revealed many attractive threptic 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: SARS-CoV-2; COVID-19; treatment; anti-viral drugs; vaccines

1. Introduction

Since December 2019, coronavirus disease 2019 (COVID-19) has been spreading around the world with over 130,000 confirmed cases (as time of March 13, 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, 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 that of SARS-CoV and bat SARS-like coronavirus (SL-CoV) (4). Notably, SARS-CoV-2 has lower pathogenicity but higher transmissibility from human to human compared with SARS-CoV (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 raises an urgently requirement for effective therapeutic strategies against SARS-CoV-2. Initially, without licensed vaccines or approved anti-viral drugs, COVID-19 treatment was mainly based on the experience of clinicians. The newest guideline published by National Health Commission (NHC)

46 recommends IFN-α, lopinavir/ritonavir, ribavirin, chloroquine phosphate and arbidol
47 as anti-viral therapy (7). To date, many potential approaches have been revealed
48 based on the research progress of SARS-CoV-2, including the inhibition of
49 SARS-CoV-2 fusion/entry, disruption of SARS-CoV-2 replication, suppression of
50 excessive inflammatory response, convalescent plasma treatment, vaccines as well as
51 the combination of Traditional Chinese and Western medicine (as summarized in
52 figure 1). Additionally, a number of clinical trials are in progress to test the safety and
53 effectiveness of candidate drugs. In this review, we summarize the current knowledge
54 on the potential treatment against SARS-CoV-2 based on the emerging basic and
55 clinical data.
56

57 **2. Updated attractive approaches against SARS-CoV-2**

58 **2.1 Inhibition of SARS-CoV-2 fusion/entry**

59 Similar to SARS-CoV, SARS-CoV-2 uses spike (S) protein to gain entry into host
60 cells (8). It was shown that the spike (S) protein on the surface of SARS-CoV-2 cell
61 bound the entry receptor angiotensin-converting enzyme 2 (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, receptor binding domain (RBD) within the S protein is the critical target for neutralizing antibodies. Since SARS-CoV-2 S protein displayed high homology toward 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 et al. recently reported that more than 85% of the RBD antibody epitopes in SARS-CoV-2 implied remarkable alterations when compared with SARS-CoV, indicating the necessity to develop new monoclone antibodies for SARS-CoV-2 (11). In addition, the rationale for 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 (NCT04287686). It was suggested that S protein-derived cell entry depended on not only ACE2 but also the host cellular serine protease TMPRSS2 (14). Camostat mesylate, a clinically proven inhibitor of TMPRSS2, significantly reduced lung cell line infection with

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78 SARS-CoV-2 and could be considered for COVID-19 treatment (14). In addition, the
79 heptad repeat 1 (HR1) and heptad repeat 2 (HR2) on SARS-CoV-2 involved viral and
80 cell membrane fusion (15). Xia et al. reported that HR2-derived peptides (HR2P) and
81 EK1 (a modified OC43-HR2P peptide) exhibited effective fusion inhibitory activity
82 towards SARS-CoV-2, which would act as fusion/entry inhibitors to treat
83 SARS-CoV-2 infection. Further studies are warranted to substantiate these concepts.

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

92 Arbidol and chloroquine phosphate have been added into the NHC guideline of
93 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 SRAS-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). More than 100 patients provided the first evidence that chloroquine phosphate was more effective in inhibiting the exacerbation of pneumonia compared with control treatment (22). Additionally, Yao et al. found that hydroxychloroquine (EC50=0.72 μM) was more potent to inhibit SARS-CoV-2 than chloroquine (EC50=5.47 μM) in vitro (23). Most importantly, the molecular mechanism of chloroquine phosphate in the treatment of COVID-19 remains elusive. It was reported that chloroquine could impair the endosome-mediated viral entry or the late stages of viral replication (24). More efforts are needed to pin down the exact mechanism.

2.2 Disruption of SARS-CoV-2 replication

A lot of anti-viral agents have been developed against viral proteases, polymerases, MTases, and entry proteins. A number of clinical trials of antiviral drugs are currently

in progress, such as remdesivir (NCT04252664, NCT04257656), favipiravir (ChiCTR2000029600, ChiCTR2000029544), ASC09 (ChiCTR2000029603), lopinavir/ritonavir (ChiCTR2000029387, ChiCTR2000029468, ChiCTR2000029539), 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 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 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 some other viruses treatment (28). However, their antiviral effect in patients with COVID-19 needs rigorous data to support. 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 molecular drugs targeting the viral main protease in clinical drug libraries (30). Four molecules were showed reasonable binding conformations with the viral main protease, including prulifloxacin, tegobuvir, bictegravir and nelfinavir (30).

Targeting the RNA genome of SARS-CoV-2 may be another way. 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 RNAs-containing spacer sequences specifically complementary to the virus RNA genome. It was supposed that the Cas13d effector could be delivered by adeno-associated virus (AAV) to the lung infected with SARS-CoV-2 (31).

2.3 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 the patients in intensive care unit

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(ICU) had higher concentration of cytokines in plasma compared with non-ICU patients with COVID-19, suggesting that the cytokine storm was associated with disease severity (32). Besides, higher percentage of GM-CSF^{+} and IL-6^{+}CD4^{+} T cells was found from ICU patients infected with SARS-CoV-2 compared with non-ICU patients (33). In view of this, inhibition of excessive inflammatory response may be an adjunct for treating COVID-19. Nevertheless, the therapeutic use of corticosteroids that has excellent pharmacological effects to suppress exuberant and dysfunctional systematic inflammation is still controversy (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 was no available data showing that the patients benefited from corticosteroid treatment in SRAS-CoV or MERS infection, which might be attributed to the suppression of immune response against virus (34). Notably, a recent retrospective study showed the potential benefits from low-dose corticosteroids treatment in a subset of critically ill patients with SRAS-CoV-2 (35). More studies are needed to find out how and when to use corticosteroids properly.

157 At the cellular level, Zhou et al. demonstrated that the $CD4^+$T cells were rapidly
158 activated to produce GM-CSF and other inflammatory cytokines after SARS-CoV-2
159 infection, which further induced $CD14^+CD16^+$ monocytes activation with high
160 expression of interleukin 6 (IL-6) (33). Thus, blocking GM-CSF or IL-6 receptor
161 would potentially reduce immunopathology caused by SARS-CoV-2. In line, a
162 multicenter, randomized, controlled clinical trial is under way to examine the efficacy
163 and safety of tocilizumab (an IL-6 receptor-specific antibody) in patients with
164 COVID-19 (ChiCTR2000029765). Moreover, Fu et al. mentioned the possible
165 mechanisms of SARS-CoV-2-mediated inflammatory responses, in which the
166 neutralizing antibodies triggered Fc receptors (FcR)-mediated inflammatory responses
167 and acute lung injury (36). Various options to block FcR activation might reduce
168 SARS-CoV-2-induced inflammatory responses (36).

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170 **2.4 Convalescent plasma treatment**

With infections wherein there is no specific therapy available, the therapy with convalescent plasma (CP) has been proposed as 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, the efficacy of CP treatment is still difficult to be evaluated because of the lack of high-quality randomized clinical trials and precise action mechanism of plasma therapy. According to the NHC guideline, the CP of recovered patients is mainly used for patients in rapid disease progression, 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 (ChiCTR2000030010, ChiCTR2000030179, ChiCTR2000030381).

2.5 Vaccines

With the global spread of SARS-CoV-2, vaccination must be the most efficient and cost-effective mean to prevent and control COVID-19 (41). The robust researches are currently 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, Daniel et al. reported and shared the cryo-EM structure of SARS-CoV-2 S trimer, which allowed for additional protein engineering efforts and speeded up the process of vaccine development (42). Besides, Lucchese et al. 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 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 of COVID-19 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 to DNA, mRNA, and "molecular clamp" vaccine platforms (46). There was no existing literature search on SARS-CoV-2 vaccine trials as time of March 13, 2020. The safety of vaccine remains a top priority for vaccine development.

2.6 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, Lianhuaqingwen capsules and ShuFeng JieDu capsules were shown to exert independent anti-viral effect and synergistic antiviral effect 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 gained improvement after taking combined Chinese and western medicine treatment (51). However, there are rarely published studies on Chinese medicine products in the treatment of COVID-19, especially the dearth of high-quality research. More 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.

3 Conclusions

The potential therapeutic strategies mentioned above are based on the updated research data for SARS-CoV-2. Among these options, we suppose 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 SRAS-Cov-2 will lead to additional potential

231 therapeutic targets. Further, strong pre-clinical and clinical studies are needed to

232 determine the safe and effective treatment for COVID-19.

Conflict of interest

All authors have no conflict of interest.

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426 Figure legend

427 Figure1: The updated potential approach against SARS-CoV-2. (A) Dampening of
428 SARS-CoV-2 fusion/entry; Disruption of SARS-CoV-2 replication; Inhibition of
429 excessive inflammatory response. (B) Convalescent plasma treatment. (C) Vaccines.
430 (D) Combination of Chinese traditional and Western medicine. ACE2;
431 angiotensin-converting enzyme 2; rhACE2, recombinant human ACE2; HR2P, heptad
432 repeat 2-derived peptides; EK1, a modified OC43-HR2P peptide; 3CLpro; 3C-like
433 protease; RdRps, RNA-dependent RNA polymerases; AAV, adeno-associated virus;
434 IL-6, interleukin-6; TCM, Traditional Chinese Medicine.

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