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Review

Potential Antiviral Drugs for SARS-Cov-2 Treatment: Preclinical Findings and Ongoing Clinical Research

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Abstract. *Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), initially termed 2019-new CoV (2019-nCoV), is a novel coronavirus responsible for the severe respiratory illness currently ongoing worldwide from the beginning of December 2019. This beta gene virus, very close to bat coronaviruses (bat-CoV-RaTG13) and bat-SL-CoVZC45, causes a severe disease, similar to those caused by Middle East respiratory syndrome (MERS)-CoV and SARS-CoV viruses, featured by low to moderate mortality rate. Unfortunately, the antiviral drugs commonly used in clinical practice to treat viral infections, are not applicable to SARS-Cov-2 and no vaccine is available. Thus, it is extremely necessary to identify new drugs suitable for the treatment of the 2019-nCoV outbreak. Different preclinical studies conducted on other coronaviruses suggested that promising clinical outcomes for 2019-nCoV should be obtained by using alpha-interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir, and anti-inflammatory drugs. Moreover, clinical trials with these suitable drugs should be performed on patients affected by SARS-Cov-2 to prove their efficacy and safety. Finally, a very promising therapeutic drug, tocilizumab, is discussed; it is currently used to treat patients presenting COVID-19 pneumonia. Herein, we recapitulate these experimental studies to highlight the use of antiviral drugs for the treatment of SARS-Cov-2 disease.*

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SARS-Cov-2, initially termed 2019-new CoV (2019-nCoV), is a novel coronavirus (CoV) responsible for the severe respiratory illness currently ongoing worldwide from the end of December 2019. This virus is the seventh coronavirus identified able to infect humans (1-3). Belonging to a family of single-stranded RNA viruses (+ssRNA), SARS-Cov-2 which is a beta gene virus genetically very closed to bat-CoV-RaTG13 and bat-SL-CoVZC45 Covs, can cause severe illness with still unknown dynamics. Similarly, to other human CoVs such as MERS-CoV and SARS-CoV, this virus can result in severe clinical pictures. In particular, the clinical conditions associated with SARS-Cov-2 – generally termed as COVID-19 which is the acronym of "coronavirus disease 2019" – may range from uncomplicated (mild) illness to moderate or severe pneumonia to Acute Respiratory Distress Syndrome (ARDS) involving sepsis, septic shock, and multiorgan failure.

Unfortunately, to date, no specific antiviral agent is recommended for use in clinical practice to treat this viral infection and no vaccine is available. Thus, it is extremely necessary to identify new drugs suitable for the treatment of the SARS-Cov-2 outbreak (4).

Different preclinical *in vitro* and *in vivo* studies on other CoV-induced diseases suggested that promising clinical outcomes for SARS-Cov-2 patients should be obtained by using alpha-interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir and anti-inflammatory drugs (5-10). Moreover, clinical trials with these suitable drugs should be performed on patients affected by SARS-CoV-2 to prove their efficacy and safety as recently proposed for tocilizumab (11). Herein, we review these experimental studies to shed light on the potential use of alternative antiviral drugs for the treatment of 2019-nCoV.

Epidemiology

The World Health Organization (WHO) on 13 April 2020 counted 1,773,086 confirmed cases of COVID-19, including 111,652 deaths worldwide (12-13). Europe has the highest number of confirmed cases; 913,349 followed by Americas with 610,744, Western Pacific with 121,426, Eastern Mediterranean with 99,713, South-East Asia with 16,883 and Africa with 10,259. In Italy, from Jan 29 to 13 April 2020, there have been 156,363 confirmed cases of COVID-19 with 19,901 deaths. Italy has been the second-largest outbreak of COVID-19 after China, but it occupies the first place in the number of deaths (14). Italy is living its worst health crisis of the last decades. The outbreak is spread differently across the country; in Northern Italy, the outbreak is tremendous: Lombardia has the highest number of infected coronavirus cases, recording 59,052 positive cases with 10,621 deaths. At the same time in Campania (Southern Italy) there are 6,604 cases and 242 deaths. In Campania, the Cotugno Hospital (Hospital for Infectious Disease) together with the National Cancer Institute of Naples proposed a drug commonly used for arthritis. The drug, tocilizumab, has been approved according to the national protocol AIFA11 to extend the use of tocilizumab in other Italian centres. The mortality in the North of Italy is correlated to elderly age, comorbidities (the risk of dying for COVID-19 changes for a patient with a given pre-existing condition), inadequate protection from infections and late access to medical care when infected (this is important in improving survival). Moreover, in Italy, intensive care units have not been enough. While it seems too late to contain the virus, an important effort should be made to develop the vaccine and to strengthen different treatments.

Antiviral Drugs Suitable for SARS-Cov-2 Treatment: Shreds of Evidence from Preclinical Studies on Another Similar Coronavirus

Currently, no vaccines or antiviral treatments drugs are available for SARS-Cov-2 infections (9). Since the production of safe and stable vaccines can take a long time and the epidemy is currently ongoing, it is extremely urgent to screen and identify the existing drugs already effective against SARS and MERS to see if they can be successfully applied to SARS-Cov-2. Different preclinical *in vitro* and *in vivo* studies on other CoVs genetically very close to SARS-Cov-2 suggested that promising clinical outcomes for COVID-19 patients should be obtained by using several drugs including alpha-interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir and anti-inflammatory medications. Moreover, very recently, through a large-scale drug screening, it was highlighted that nelfinavir has potent antiviral activity against SARS-Cov-2, as reported by Li *et al*. (10). Besides, praziquantel, pitavastatin, and perampanel might be effective against SARS-CoV-2. Moreover, the pharmacokinetic and the safety of all these potential anti-CoVs agents should be evaluated *in vivo* studies by using an animal models and in human clinical trials.

Lopinavir/Ritonavir. Lopinavir/ritonavir (LPV/r) is a combination antiviral drug commonly used in the treatment of human immunodeficiency virus (HIV), the causative virus for acquired immunodeficiency syndrome (AIDS) (15). It combines lopinavir with a low dose of ritonavir. Accumulated pieces of evidence showed that the combination of lopinavir/ritonavir could be considered a therapeutic approach for CoVs-induced infections. Particularly, it has been shown that lopinavir/ritonavir can ameliorate the outcome of MERS-CoV infection in a model of Marmoset (16). Moreover, based on clinical studies conducted on patients with SARS, lopinavir/ritonavir is assumed as a treatment option for COVID-19 (17). Again, this anti-HIV drug was currently suggested from the National Health Commission of the People's Republic of China as a therapeutic option for COVID-19 pneumonia (18). However, another Trial on Lopinavir–Ritonavir in adults hospitalized with severe Covid-19 reported that Lopinavir-Ritonavir offered no significant benefit (19). Thus, more well-designed clinical studies are necessary to identify their efficacy as therapeutic agents for COVID-19.

Ribavirin. Ribavirin is an antiviral drug approved by the Food and Drug Administration (FDA) used predominantly for the treatment of Hepatitis C Virus (HCV), generally combined with other drugs (peginterferon, sofosbuvir, simeprevir, alfa-2b or peginterferon alfa-2a). It is also used to treat viral hemorrhagic fevers and Respiratory syncytial virus (RSV) infection (20). Despite its mechanism of action not being completely clear, it is known to be a nucleoside inhibitor and can thus arrest the synthesis and capping of viral mRNA. Being classified as a prodrug, when it is metabolized as purine RNA nucleotides, it blocks RNA metabolism necessary for viral replication (21). Very recently, Elfiky suggested the use of a combined antiviral therapy against COVID-19 (22). Specifically, this model is targeted by the anti-RNA-dependent RNA polymerase (RdRp) drugs, sofosbuvir, ribavirin, sofosbuvir, remdisivir, and IDX-184. Findings emerged from this study indicated that these drugs could bind to the coronavirus-19 RdRp by inhibiting the protein function and finally leading to the elimination of the virus. Their safety profile and *in vivo* effects need to be further explored.

Chloroquine phosphate. Chloroquine phosphate, a phosphate salt of chloroquine, possesses anti-inflammatory and antimalarial features. Normally used to treat malaria, it is also successfully used for the prevention and treatment of rheumatoid arthritis and lupus erythematosus. This drug can regulate the biosynthesis of nucleic acids and to interfere with

the accumulation of toxic heme within the parasite. Moreover, chloroquine inhibits thiamine uptake by acting on the transporter solute carrier family 19 member 3 (SLC19A3) and by inhibiting lymphocyte proliferation, phospholipase A2, the release of enzymes from lysosomes and production of interleukin-1 (IL-1), in the treatment of rheumatoid arthritis. Moreover, it can act as antiviral against SARS-CoV. As reported by Wang *et al*., (23) this drug can block the COVID-19 infection at low-micromolar concentrations, thus suggesting its potential use for patients suffering from the disease. Furthermore, as reported by Gao *et al*., (6) encouraging results on this topic could be obtained by different Chinese multicenter clinical trials (ChiCTR2000029939, ChiCTR2000029935, ChiCTR2000029899, ChiCTR2000029898, ChiCTR2000029868, ChiCTR2000029837, ChiCTR2000029826, ChiCTR2000029803, ChiCTR2000029762, ChiCTR2000029761, ChiCTR2000029760, ChiCTR2000029740, ChiCTR2000029609, ChiCTR2000029559, and ChiCTR2000029542) designed for demonstrating the efficacy and safety of chloroquine or hydroxychloroquine in COVID-19 treatment. Data that emerged from these studies showed that chloroquine phosphate can be helpful to treat CoV pneumonia without inducing important side effects. An interesting review by Juurlink *et al*. (24) on the use of either chloroquine or hydroxychloroquine and azithromycin for treatment or prevention of SARS-CoV-2 infection highlighted the need for careful patient selection and monitoring. Despite the ongoing use of either chloroquine or hydroxychloroquine and azithromycin for treatment or prevention of SARS-CoV-2 infection, this is largely supported by *in vitro* findings, as the studies involving humans are extremely weak. Thus, clinical trials on patients in treating or preventing COVID-19, should be engineered taking in account potential adverse effects induced by the use of these drugs. Moreover, a recent clinicaltrial was published by Zhou *et al*. (25) on the use of oral chloroquine on patients suffering of COVID-19. This study reported that oral chloroquine phosphate tablets resulted in a high incidence of adverse reactions, suggesting that a clinical trial of chloroquine phosphate for COVID-19 treatment should be used under pharmaceutical care and timely evaluation of the drug safety during treatment.It is also important to underline that Swedish chloroquine clinical trials have stopped due to toxicity and the use of this drug has stopped altogether in Sweden.

A series of arge-scale clinical studies are ongoing and the results are due to be released in May.

Remdesivir. Remdesivir is an antiviral drug used at beginning for the treatment of Ebola virus disease and Marburg virus infections and then as an antiviral agent against single-stranded RNA viruses such as the coronaviruses (including MERS and SARS viruses). Specifically, remdesivir when metabolized into its active form, the (2R,3R,4S,5R)-2-(4-aminopyrrolo(2,1-f)(1,2,4)triazin-7-yl)-3,4-dihydroxy-5-(hydroxymethyl)oxolane-2-carbonitrile (GS-441524), is an adenosine nucleotide analog which can inhibit the production of viral RNA, although the mechanism is not completely dissected. Currently, this drug has been tested in laboratory on cultured cells and in mouse and non-human primate (NHP) models, demonstrated its efficacy as a valuable antiviral drug against SARS/MERS-CoV viruses. Another study conducted by de Wit *et al*. (26), tested the efficacy of prophylactic and therapeutic remdesivir (GS-5734) treatment in a nonhuman primate model of MERS-CoV infection. Data that emerged from this study suggested that the rhesus macaque therapeutic remdesivir treatment provided a clear clinical benefit, with a reduction in clinical signs, reduced virus replication in the lungs, and decreased presence and severity of lung lesions, suggesting the efficacy of remdesivir treatment in the context of a MERS clinical trial or coronavirus 2019-nCoV. Finally, an interesting study has been conducted on a cohort of patients with severe Covid-19 who were treated with compassionate-use remdesivir. A clinical improvement was observed in 36 of 53 patients (68%), although the authors stated that measurement of efficacy will require ongoing randomized, placebo-controlled trials of remdesivir therapy (27). Thus, this compound can be considered as a therapeutic option for the treatment of 2019-SARS-Cov-2 infections. However, its efficacy and safety remains to be further verified.

Neuraminidase inhibitors. Neuraminidase inhibitors (NAIs) are drugs that act by blocking the neuraminidase enzyme. They are commonly utilized as antiviral drugs since they arrested the viral neuraminidases function of the influenza virus, thus avoiding its replication in the host cell. Studies suggest that NAIs counteract both influenza A and influenza B (28). They could be potentially utilized for the treatment of SARS-Cov-2 disease although no evidence has yet been reported.

Other drugs. *In vitro* research proved that other anti-flu drugs such as fusion peptide (EK1), abidol, RNA synthesis inhibitors (such as Tenofovir Disoproxil Fumarate, TDF; Epivir, 3TC) anti-inflammatory drugs (such as hormones and other molecules), and Chinese medicine, could be potentially used in the treatment of SARS-Cov-2 disease (29). Nevertheless, their safety and efficacy should be confirmed by clinical trials. Overall, there no specific antiviral drugs or vaccines are available for the treatment of SARS-Cov-2 disease. All the antiviral drug options should be adopted by considering the results obtained with these drugs in patients with SARS, MERS or other types of influenza.

Tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody. It belongs to the Immunoglobulin G1(IgG1 class), directed against both the soluble interleukin-6 (IL-6) receptor (sIL-6R) and the receptor bound to the

membrane (mIL-6R) (30). IL-6 is a cytokine with proinflammatory features and is involved in many biological processes (as T-cells activation, fibrosis of tissues, metabolism of lipids). Moreover, high levels of IL-6 play a role in the pathogenesis of different ant-inflammatory processes and also in the cytokine release syndrome (CRS) (31). Tocilizumab is typically recommended for the treatment of systemic juvenile idiopathic arthritis, severe rheumatoid arthritis, and the severe or life-threatening CRS induced by the chimeric antigen receptor T-cell (CAR-T) in adults and paediatric patients (32). A group of researchers successfully treated 21 patients affected by COVID-19 pneumonia with tocilizumab (400 mg/iv) obtaining positive patient outcomes and suggesting the need for randomized clinical trial (tocilizumab vs control) in the imminent future (33). Several FDA Phase III clinical trials with tocilizumab on COVID-19 patients are actually ongoing, and an interesting study has been recently reported by Xu *et al*. where tocilizumab effectively improved clinical symptoms and repressed the deterioration of severe COVID-19 patients. Therefore, tocilizumab seems to be an effective treatment in patients with severe COVID-19 (34). Besides, a multicentre study on 330 patients with COVID-19 pneumonia will be conducted under the coordination of the legal promoter- IRCCS Institute Nazionale Tumori, IRCCS, Fondazione G. Pascale of Naples, to test the efficacy and tolerability of tocilizumab in patients with critical or severe COVID-19 pneumonia (11).

Ongoing clinical research. A multicenter randomized clinical trial (RCT) proposed by the University of Seoul, Republic of Korea, for comparing the efficacy of lopinavir/ritonavir (400mg/100mg twice daily, every 12 h for 7-10 days) with hydroxychloroquine (400mg twice daily) in patients with mild COVID-19 is ongoing (NCT04307693) (35). Another RCT is testing the combination of lopinavir/ritonavir (400mg/100mg twice daily), ribavirin (400mg/100mg twice daily) and interferon beta-1b (8 million IU in 0 to 3 subcutaneous injections) compared with to lopinavir/ritonavir alone (NCT04276688). The combination lopinavir/ritonavir is also tested compared to a fixed-dose combination of ASC09 (300 mg), another HIV protease inhibitor, with ritonavir (100 mg) given twice daily (NCT04261907) (36). A phase IV, open-labeled, RCT designed by researchers from the Guangzhou Eighth People's Hospital, Guangdong, China is randomizing COVID-19 patients into 3 groups: group A receiving lopinavir/ritonavir, group B receiving arbidol (200mg three times a day) and group C receiving standard treatment (NCT04252885) (37).

Concluding Remarks and Perspectives

Different preclinical studies on other CoV-induced pathologies suggest that promising clinical outcomes for SARS-Cov-2 patients can be obtained by using alpha-interferon, chloroquine phosphate, arabinol, remdesivir, lopinavir/ritonavir and anti-inflammatory drugs. In addition, ongoing clinical trials strongly suggest that positive outcomes should be obtained by using the tocilizumab as a therapeutic strategy for severe COVID-19 pneumonia. Moreover, more clinical trials with these suitable drugs should be performed on patients affected by SARS-CoV-2 to prove their efficacy and safety.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

The present article was mainly written by SB, AC and MC. All Authors contributed toward data analysis, drafting and critically revised the paper, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

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