Review Article

Review of Therapeutic Agents for Treatment of COVID-19

Shadi Ziaie[1, 2], Mehran Koucheck[3], MirMohammad Miri[3], Sara Salarian[3], Seyedpouzhia Shojaei[3], Mehrdad Haghighi[4], Mohammad Sistanizad[1, 3*]

1. Department of Clinical Pharmacy, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Department of Nephrology and Kidney Transplantation, Shahid Labbafnejad Medical Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Critical Care Medicine Ward, Anesthesiology Department, Imam Hossein (A.S.) Medical and Educational Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
4. Department of Infectious Disease, Imam Hossein (A.S.) Medical and Educational Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*** Corresponding Author:**
Mohammad Sistanizad, PhD, Associate Professor of Clinical Pharmacy, Department of Clinical Pharmacy, School of Pharmacy, Pharmaceutical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran; **email**: sistanizadm@sbmu.ac.ir

Abstract

In late December 2019, a cluster of unexplained pneumonia cases has been reported in Wuhan, China, named coronavirus disease 2019 (COVID -19) which has been spreading in 204 countries. To date no pharmaceutical products have been approved for the treatment of this viral pneumonia. Based on rapid spread of the disease and high disease burden, several agents have been proposed for treatment of this viral pneumonia, mainly antivirals and immunomodulator agents and underwent in-vitro, animal and clinical trials. Some of these agents have been revealed promising preclinical results but, non of them approved yet. This review aims to summarize the current knowledge about the mechanism and considerations of widely used investigational agents that are used in the treatment of COVID-19 as off-label.

Keywords: COVID-19, Pneumonia, Antiviral, Immunomodulator, Interferon, IVIG, Tocilizumab, Remdesivir

Please cite this article as: Ziaie S, Koucheck M, Miri MM, Salarian S, Shojaei S, Haghighi M, Sistanizad M. Review of Therapeutic Agents for Treatment of COVID-19. J Cell Mol Anesth. 2020;5(1):32-6.

Introduction

In late December 2019, a cluster of unexplained pneumonia cases has been reported in Wuhan, China, named coronavirus disease 2019 (COVID -19) which has been spreading in 204 countries, areas or territories around the world with around 700,000 confirmed cases and 33,000 mortality (as time of March 31, 2020) (1). This rapid spread raised an urgent necessity for effective therapeutic strategies against COVID-19. But, as there was no approved regimen, treatment was mainly based on possible pharmacological mechanisms, non-well-designed trials and the experience of clinicians.

To date no pharmaceutical products have been approved for the treatment of COVID-19, several medicines, generally with the mechanisms of antiviral or immunomodulatory, including (list not complete) ribavirin, fabiravir, favipiravir, oseltamivir, darunavir/cobicistat, interferon, mycophenolate, tocilizumab, teicoplanin, convalescent plasma, etc. have been suggested as potential investigational therapies, many of which are now being studied in clinical trials (2). Recently, the food and drug administration (FDA) issued an emergency use authorization (EUA) for emergency use of oral formulations of chloroquine phosphate and

hydroxychloroquine sulfate for the treatment of COVID-19 at March 28, 2020 (3).

The newest guideline published by Belgium which also included recommendations from 4 other European countries, including Italy, France, Netherlands and Switzerland recommends lopinavir/ritonavir, chloroquine or hydroxychloroquine, remdesivir and tocilizumab beside supportive care, including oxygen and mechanical ventilation (4). Another antiviral agent, favipiravir (Avigan) is approved in Japan and China for influenza and is investigational for use in COVID-19 (5). This review aims to summarize the current knowledge about the mechanism and considerations of widely used investigational agents that are used in the treatment of COVID-19 as off-label.

Antivirals

Chloroquine and Hydroxychloroquine

Hydroxychloroquine is a safer analog of chloroquine that has fewer concerns about drug-drug interactions (6). Hydroxychloroquine and chloroquine are widely used antimalarial drugs that elicit immunomodulatory effects and are therefore used to treat autoimmune conditions (systemic lupus erythematosus, rheumatoid arthritis). These agents also have antiviral activities based on previous reports (7-9).

The molecular mechanism of action of chloroquine (CQ) and hydroxychloroquine (HCQ) has not been fully explained. A study in 1993, suggested that chloroquine and hydroxychloroquine may inhibit the coronavirus through a series of steps. Firstly, the drugs can change the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. It can also inhibit nucleic acid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, virus release and other processes to achieve its antiviral effects (10). Chloroquine, through the inhibition of pH-dependent steps of viral replication, restricts human immunodeficiency virus (HIV) (11), influenza virus (9), dengue virus (DENV) (12), Japanese encephalitis virus (JEV) (13), and West Nile virus (WNV) infection (14). Furthermore, Savarino et al (15) hypothesize that CQ might block the production of pro-inflammatory cytokines (such as interleukin-6), thereby blocking the pathway that subsequently leads to acute respiratory distress syndrome (ARDS).

Oseltamivir

Oseltamivir belongs to the family of neuraminidase inhibitors which inhibits viral neuraminidases; stops the release of virus from cells and prevents the virus from crossing mucous lining of the respiratory tract (16). This agent was frequently prescribed because of the concern of influenza, which is clinically similar to COVID-19. But to date, no data support its use in the treatment of COVID-19 (17-19).

In a retrospective case series of 99 patients with COVID-19 at a single center in Wuhan from 1/1/20 to 1/20/20, 76% of patients received antiviral treatment, including oseltamivir (75 mg orally every 12 hours). At the time of evaluation, 58% of patients remained hospitalized, 31% had been discharged, and 11% had died (20).

Lopinavir/Ritonavir

Lopinavir belongs to the family of protease inhibitors which inhibits cleavage of Gag-Pol polyprotein precursors, which in turn causes the formation of immature, noninfectious viral particles. The main antiretroviral effect of this combination is due to lopinavir; ritonavir inhibits metabolism of lopinavir by inhibiting CYP450, 3A4 and prolongs action/increase serum concentration of lopinavir (21).

In a recent study Bin Cao et al., randomized a total of 199 patients with laboratory-confirmed SARS-CoV-2 infection; 99 were assigned to the lopinavir-ritonavir group, and 100 to the standard-care group. Treatment with lopinavir-ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality at 28 days was similar in the lopinavir-ritonavir group and the standard care group. They concluded that in hospitalized adult patients with severe COVID-19, no benefit was observed with lopinavir-ritonavir treatment beyond standard care (22). Also in the surviving sepsis campaign guideline, the authors recommended against the routine use of lopinavir/ritonavir in critically ill adults (23).

Ribavirin

Ribavirin often proposed along with an interferon product to treat RNA viruses, in clinical trials. This agent may inhibit the initiation and elongation of RNA fragments by inhibiting

polymerase activity, which in turn results in the inhibition of viral protein synthesis (24). Typically used in combination with an interferon, ribavirin has been studied for patients with other coronaviruses, with mixed results. Additionally, its adverse effect profile can be significant (anemia), particularly at the dosages for which it has been tested for MERS (~800-3600mg/day) (25). To date, there is insufficient evidence to issue a recommendation on the use of recombinant rIFNs, alone or in combination with antivirals, in critically ill adults with COVID-19 (23).

Remdesivir (GS-5734)

Remdesivir is not FDA approved. It is currently being investigated as a treatment option for COVID-19 as an investigational IV antiviral with broad activity. Remdesivir is a phosphoramidate prodrug of a 1*0*-cyano-substituted adenosine analog. The triphosphate form of remdesivir (remdesivir-TP) was shown to inhibit the RNA-dependent RNA polymerase (RdRp), which is necessary for virus replication. No significant inhibition was seen with human RNA Pol-II and human mitochondrial RNA polymerase (h-mtRNAP) (26, 27).

Two phase 3 randomized, open-label trials, NCT04292899 and NCT04292730, initiated by the manufacturer (Gilead) to evaluate the safety and antiviral activity of 5- and 10-day regimens of Remdesivir in conjunction with standard of care in patients with severe and moderate COVID-19, respectively (28, 29) which are estimated to finalize patient recruitment by May 2020.

Favipiravir (T-705)

Favipiravir (T-705) is a nucleoside precursor that has been approved for the treatment of pandemic influenza in Japan (30, 31). Intracellular phosphoribosylation yields a triphosphate form (T-705-RTP) that is accommodated by the viral RNA-dependent RNA polymerase (RdRp) (32). This agent has been approved for the treatment of some other viruses. However, its antiviral effect in patients with COVID -19 needs demanding data to support. Several clinical trials are evaluating this oral broad-spectrum antiviral agent in different combination regimens (33-35).

Immunomodulators

When the virus enters the human body, its antigen will be presented to the antigen-presenting cells (APC) and the body's humoral and cellular immunity, B cells and T cells, will be stimulated (36). Also, there is a big amount release of pro-inflammatory cytokines and chemokines and an uncontrolled inflammatory response. Then the immune system attacks the body and causes ARDS and multi-organ failure. Therefore, it is needed to use different strategies to cut these immune responses (36). Based on this theory several immunomodulatory agents have been evaluated in the treatment of COVID-19.

Interferon beta

Interferon-beta, as a type I interferon, is the first and main drug to be approved for the treatment of patients with relapsing-remitting MS (RRMS) and there are two classes of it: interferon beta-1a and interferon beta-1b (37). This type of interferon has many effects on body immune system, decreases APCs, decreases the capacity of B cells to present antigens, decreases T-cell stimulation, decrease the production of pro-inflammatory cytokine and increase regulatory T-cell and B-cell activity (37). IFN- beta could improve pulmonary function (38). It inhibits the SARS- CoV and MERS–CoV replication in vitro and inhibit the virus cytopathic effect in culture (39).

These results suggest that in refractory or progressive patients (40), in critical patients in ICU (40) without ARDS (41), combined with an antiviral (Lopinavir/Ritonavir) or hydroxychloroquine (42), interferon beta could be as one of the treatment options. Although there is some concern about side effects such as flu-like syndrome, depression, liver enzyme elevation and cytopenia (42).

Tocilizumab

Tocilizumab, as an immunotherapy, is a humanized anti-interleukin 6 monoclonal antibody for the treatment of rheumatoid arthritis. It blocks both classic and trans-IL-6 signaling on immune cells and compete with IL-6 for binding to both membrane-bound and soluble receptors and decreases IL-6 signaling, activation of the immune system and inflammation (43, 44).

In patients with severe inflammatory response, activation of endothelial cells, complement pathway, and coagulation cascades, induce macrophage activation and leading to secretion of host cytokines such as IL-6, TNF-α, and IL-10 which could aggravate cytokine release syndrome (43, 45).

Evidence for use of this medication in patients with COVID-19 infection is limited. Some guidelines and also the IDSA blog stated that in patients with severe inflammatory response such as critically ventilated patients, ARDS or patients with cytokine release syndrome after sending serum IL-6, if the level of serum IL-6 is high, tocilizumab could be used (40, 42, 46). But neither the best time of tocilizumab injection during the disease course nor the exact IL-6 threshold for progression to severe disease is not defined yet (47).

At this time there is no published peer-reviewed case series about positive and negative effects of this medication and several clinical trials are proceeding. So, routine use of tocilizumab is not recommended.

Intravenous Immunoglobulin (IVIG)

Intravenous Immunoglobulin (IVIG), a polyclonal immunoglobulin G, is a blood product derived from healthy donors and is a safe immune-modulating agent for all age groups (39, 48).

There are many different mechanisms for IVIG action in the human body. It can inactive auto-reactive T-cells by stopping interaction with APCs. It has many antibodies to pro-inflammatory cytokines. It decreases B cell antibody production, reduces macrophage activity and modulate innate immunity (49). All of the IVIG effects are not completely understood yet (48).

According to its mechanisms, it was used extensively in 2003 in the SARS outbreak although some critically ill cases developed VTE due to IVIG-induced increase of viscosity in hypercoagulable states (39).

At this time some guidelines stated that IVIG could be used in solid organ and BMT recipients if IgG level is less than 400 (42), COVID-19 infection characterized by heart damage (50) and because theoretically, it might suppress viremia, it's better to start at the early stage of infection (40).

If it started at the right time with high dose (25 g/ day for 5 days), it shows no side effect and could effectively block the progression of disease cascade, and improve the outcome of covid19 infected patients (48). Therefore, it seems that high dose IVIG could be a choice of immunomodulatory treatment for patients with autoimmune or inflammatory disease, and for prophylaxis and treatment of severely infected immunocompromised patients (48).

Conclusion

Understanding of the treatment of patients with COVID-19 is rapidly evolving. Almost all pharmacological agents in treatment of COVID-19, are used as off label. Understanding basic pharmacological mechanisms and current evidence in using these agents, could help physicians in selecting most appropriate regimen for treatment of the infected patients.

Acknowledgment

None.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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