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Treatment and vaccination of Covid-19

Muhammad Akram ^{1*}, Tehreem Riaz ², Isha Ishtiaq ^{3*}, Husnain Karim Riaz ⁴, Sana Shahzadi ⁵, Marriyam Talat ⁶, Saba Irfan ⁷, Wasfa Farooq ⁸, Sara Khan ⁹

^{1,2} Department of Eastern Medicine, Government College University Faisalabad Pakistan

^{3,5,6,9} Department of Biotechnology, University of Sialkot, Pakistan

^{4,7,8} Department of Microbiology, University of Central Punjab, Pakistan

Corresponding Author: **Muhammad Akram, Isha Ishtiaq**

Abstract

The outbreak of this wide-ranging pandemic has forced the world to identify and produce the therapeutics for the treatment & prevention of it. The Covid-19 is a virulent pneumonia-like disease caused by SARS-COV-2. This pandemic has caused several thousands of deaths. For a few months this pandemic has set pressure on laborites to diagnose this novel virus properly and on the pharmacists, researchers, doctors, scientists, and pharmaceutical companies to develop proper medicine and vaccination against this virus. Proper diagnosis and treatment are essential to treat patients suffering from covid-19. Despite extraordinary advancements in the medical field, presently,

there is no effective treatment for this global pandemic. However, fast and rapid research on the epidemiology of SARS-COV-2 is helping in unveiling the potential therapeutic against covid-19. clinical trials and screening for drug development are going on some drugs. Favipiravir, Remdesivir, & dexamethasone have shown promising potential against covid-19. Interferon, tocilizumab, and convalescent plasma therapy have beneficial effects on viral clearance. Trials are going also going on viral S protein targeting vaccines. This review aims to summarize all current therapeutic advancements and vaccinations in the global medicinal system against covid-19.

Keywords: Covid-19, clinical features, diagnosis, treatment of covid-19, anti-viral, steroids, antibiotics, vaccination

Introduction

Corona virus disease is severe pneumonia and virulent disease with systematic manifestations. Covid-19 has been declared as a pandemic by the world health organization. The etiological agent of this disease is novel SARS-CoV-2. This dreadful virus has set an unexpected pandemic & results in severe panic all around the world. This virus is still spreading all over the globe as a second wave of covid-19. The etiological factor SARS-CoV-2 is a beta corona virus which was 1st emerged in Wuhan the city of china in late 2019. Viruses causing covid-19 are known as coronaviruses. The coronaviruses are giant, enveloped, unsegmented single-stranded RNA viruses having the ability to infect human beings as well as animals. To date, coronaviruses are divided into 4 subfamilies, which are alpha coronavirus, beta coronavirus, gamma coronavirus, and delta coronavirus. Alpha & beta viruses are originated from bats while gamma and delta coronaviruses have their origin from birds (Hui et al., 2020).

The infection of this virus spread through respiratory droplets as an asymptomatic or symptomatic carrier. Most of the patients with this novel pathogenic disease having mild or moderate symptoms, about 15 percent progress to severe pneumonia and 5 percent develop ARDS & multiple organ failure. To date, this viral disease has affected more than 200 countries, more than 10 billion cases have been identified, and results in more than 508000 deaths all over the world. Covid-19 has become a challenge for the world to increased patient rates and fewer therapeutic measures. Coronavirus disease-19 has high transmissibility and cause common cold-like symptoms.

This novel illness has imposed major threats & challenges to humanity & has been recorded as one of the most dreadful pandemics recorded in history (CS & Madathilkovilakathu, 2020). Presently there is no anti-viral regime or anti-covid-19 drugs and vaccination for the treatment of critically ill patients. The patients are only managed by the provision of supportive treatment such as fluid management, oxygen, and ventilation. Combined treatment with anti-viral, low dose corticosteroids, and inhalation have been encouraged for the management of the affected person (Liu, Li, & Feng, 2020). It is an extreme necessity to identify & develop influential medicines and efficacious vaccines for the cure and treatment of this novel viral disease as it is a serious threat to public health.

It is condemnatory to develop medicines and vaccinations against this disease rapidly because the second wave of this pandemic has started that also results in increasing the death rate by causing respiratory problems and organ failures.

For advanced and better therapeutic measures demand has been increasing because it is an intense need to combat this situation. In this review, I have briefly discussed the treatment and vaccination strategies about covid-19. In therapeutic measures, the medicines and ways which help for the cure of this outbreak are also described in this review. Further research is needed for a better understanding of the influence of medicines and vaccinations on this novel viral problem to make anti-covid-19 medicines and vaccinations.

Clinical Features

Non-respiratory symptoms

Non-respiratory symptoms which are reported in 2-40% percent of cases are gastrointestinal symptoms and diarrhea (Alhazzani et al.; Park et al., 2018). SARS-CoV-2 indirectly involving the neurological system results in neurological involvement. Cardiovascular symptoms are also reported in patients with covid-19. Myocarditis, myopericarditis, heart failure, and arrhythmias are included in cardiovascular symptoms (Bonow, Fonarow, O'Gara, & Yancy, 2020; Khalid et al., 2020; Roden, Harrington, Poppas, & Russo, 2020; Yang et al., 2020). Hyperenemia increased secretions, and chemosis is also reported in 32 percent of infected persons.

Respiratory symptoms

Sore throat, runny nose, fever, difficulty in breathing, Mild or moderate to severe pneumonia, and ARDS are included in respiratory symptoms of covid-19.

Diagnosis

Covid-19 can be diagnosed by following tests:

- Sample or swab
- Blood profile
- Nucleic acid amplification test
- Serological testing
- Radiological diagnosis
- Viral sequencing
- Viral culture

COVID-19 TREATMENT

Presently, the patients who are suffering from the covid-19 are receiving anti-viral, anti-biotics, and steroids in their treatment. Some patients also receive oxygen therapy and convalescent plasma therapy. Several other agents including anti-viral such as lopinavir, interferon-alpha, ribavirin, and Arbidolchloroquine phosphate for the treatment of covid-19 are recommended according to the guidelines, treatment & diagnosis protocols for this novel pandemic, issued by national health commission and state administration of TCM (traditional Chinese Medicine). In severe cases when the patient suffers from extensive lungs lesion and having an increased IL-6 level, tocilizumab is recommended. No adverse effects have been reported of chloroquine used in treatment.

1. Anti-malarial drugs

Chloroquine

Recently chloroquine is reported as promising antiviral drugs that are widely used to combat and treat malaria (Wang et al., 2020). It seems effective for the SARS-CoV-2 virus by having immunomodulatory effects. The exact action of chloroquine for this disease is not well known. though, it

interferes with glycosylation of cell surface receptors of SARS-CoV and enhances the endosomal pH which is mandatory for the virus. This anti-viral drug plays its inhibitory role by diffusing to cell passively through cell membrane to endosomes, lysosomes & Golgi vesicles and increase pH of surroundings cells and tissue. Also, it possesses a resistant modulating role which can improve therapeutically anti-viral effects (Colson, Rolain, Lagier, Brouqui, & Raoult, 2020; Cortegiani, Ingoglia, Ippolito, Giarratano, & Einav, 2020; Savarino, Di Trani, Donatelli, Cauda, & Cassone, 2006). Chloroquine phosphate has a promising effect in inhibiting pneumonia & reducing disease course.

Hydroxychloroquine

Hydroxychloroquine is another anti-malarial drug that is used for the treatment of chloroquine-resistant malaria. Hydroxychloroquine is a 4-aminoquinoline. Medicinal activities of hydroxychloroquine are anti-malarial, anti-autophagy, and immunosuppression. In addition to these activities, hydroxychloroquine possesses the potential to treat autoimmune diseases & lupus erythematosus. It is reported that hydroxychloroquine has promising activity against the SARS-CoV virus (Biot et al., 2006). Hydroxychloroquine has a greater clinical safety profile and has a more substantial effect against SARS-CoV as compared to chloroquine. Against SARS-CoV, hydroxychloroquine has anti-viral activity. It can minimize the replication of the virus. It increases the pH of the endosome it prevents virus or cell diffusion.

2. Anti-viral drugs

There is no specific anti-viral treatment that has been proven against covid-19. This novel pandemic is treated by the repurposing of anti-viral drugs. Combination of more than three anti-viral drugs against COVID-19 is not recommended. It has been mentioned in the report that most of the patient suffering from COVID-19 has been taking anti-viral drugs in china and some other countries. The most commonly used antiviral drugs used for the treatment of covid-19 are.

Remdesivir

It is a far-ranging anti-viral drug having promising effects for the treatment of coronaviruses. It is a monophosphoramidate prodrug, a polymerase inhibitor, and an analog of a nucleoside. It has been suggested from animal studies that this anti-viral drug successfully decreases the load of virion in lung tissues of an infected animal. It also increases the lung's functionality & decreases disease disruption in the tissues of the lungs (Sheahan et al., 2020). It is considered a beneficial antiviral drug for the treatment of this pandemic outbreak. This drug has been used previously for the treatment of MERS and SARS.

Favipiravir

This antiviral drug & used for the treatment of all viral diseases caused by RNA viruses. It was initially screened for anti-influenza activity in vitro. It plays its antiviral activity by blocking the replication of RNA viruses (Delang, Abdelnabi, & Neyts, 2018). Thus, it can also have antiviral activity averse to SARS-CoV. By undergoing intracellular phosphorylation, it is converted into its active form which is

named Favipiravir-ribofuranosyl-5- triphosphate. Its active form then interacts with RNA polymerase and inhibits the replication of the virus. After the clinical trials, it has been suggested that favipiravir has strong antiviral activity averse to SARS-CoV as compared to lopinavir. No potential side effects have been reported of this drug.

Ribavirin

Ribavirin is a nucleoside analog. This is given in conjunction with recombinant interferon which is a broad-spectrum antiviral that has shown promising inhibitory effects on MERS-CoV replication. In some report's combination of Ribavirin with recombinant interferon in the treatment of MERS has shown low efficacy. It is recommended by the Chinese National Health Commission that administer Ribavirin through intravenous infusion in conjunction with oral Lopinavir and inhaled interferon-alpha in the treatment of this COVID-19.

Arbidol

Arbidol is an anti-viral medicine use for the treatment of influenza in Russia and China. This anti-viral drug plays its anti-viral activity by inhibiting the interaction between the host cell and virus and prevents the invasion of the virus into host cells. By activating the macrophages and by inducing the production of interferon it also plays immunomodulatory activity. It strengthens and promotes the cycle o virus clearance and shows a beneficial effect in the treatment of covid-19.

3. HIV-1 protease inhibitors

Lopinavir

It is a human immune deficiency virus drug. It is used in conjunction with other drugs for the treatment of HIV-1 because it is a highly specific HIV-1 protease inhibitor. It has been reported after clinical trials that it has anti-SARS-CoV activity. It plays is the anti-SARS-CoV activity by binding with Mpro. Mpro is a main or key protease enzyme with lead to viral replication. Lopinavir by binding with Mpro inhibits the replication of the virus (Ratia et al., 2008).

4. Antibiotics

Azithromycin

It is a semi-synthetic derivative of erythromycin & a member of macrolide antibiotics. It differs from erythromycin by a methyl-substituted nitrogen atom in the lactone ring. It has bacteriostatic activity & interrupts protein synthesis by reversing the binding of 50 S ribosomal subunit of microorganisms (Matzner et al., 2013). Beyond its antibacterial activity, it also possesses immunomodulatory and anti-inflammatory activity. By reducing the inflammation and minimizing the generation of cytokines in pulmonary viral infection, macrolides play role in viral clearance. However, the exact mechanism of action is no known. It plays its immunomodulatory activity by reducing neutrophil chemotaxis in lungs, minimizing mucus hypersecretion, decreasing the synthesis of pro-inflammatory cytokines, inhibiting the production of oxygen reactive species, disrupting the stimulation of nuclear transcription factor, and inducing apoptosis. Azithromycin reduces both acute & chronic inflammation in viral bronchiolitis due to its promising anti-inflammatory activity. Additionally, it prevents secondary bacterial infections (Gautret et al., 2020).

5. Steroids

Corticosteroids

Corticosteroids are used in severe cases when there is a high production of cytokines by MERS-CoV, SERS-CoV, and SERS-CoV-2. Usually, Corticosteroids are not recommended routinely as therapy as they are used for the treatment of severe cases. According to the guidelines approved by the National Health Commission of China and the World Health Organization, corticosteroids are used with caution when a patient is suspected of having SARS-CoV-2 infection. Corticosteroid therapy is only considered for treatment in case of excessive activation of the immune response, deterioration in oxygen index, and rapid progression of radiological findings. The use of corticosteroids in the treatment of COVID-19 varies with the severity of the disease(Commission, 2020).

6. Anti-inflammatory

Baricitinib

It is an approved drug to treat rheumatoid arthritis disease. This drug is JAK. It will be an effective treatment against SARS-CoV infection by inhibiting viral entry and reducing inflammation. Apart from the Janus kinase inhibitor, it possesses empathy for AP2-associated protein kinase-1 & binds with cyclin GAK, which is one of the most promising regulators of endocytosis. By disrupting the endocytosis, it can inhibit the entry of the virus into cells & decreases in vitro viral infection. Baricitinib is highly specific to NAKs and having anti-inflammatory activity& its potential to decrease the chronic inflammation associated with inter feronopathy accompanying its promising pharmacological activities contributing to produce it as a highly suitable contender for the treatment of SARS-CoV.

Biological agents

7. Tocilizumab

It is a recombinant monoclonal immunoglobulin antibody G1 against interleukin-6 receptors in human bodies. By binding with interleukin-6 receptor Tocilizumab inhibits signal transduction. It is used in the treatment of rheumatoid arthritis, a cytokine released syndrome, castle's man syndrome, and juvenile idiopathic arthritis. It is reported that it plays a significant role in the treatment of covid-19 by inhibiting the release of prion flammatory cytokines. Patients with MERS, SARS, and COVID-19 have high plasma levels of cytokines, increased growth factors, and proteins which is an indication of cytokine storm which is associated with the severity of the disease. Interleukin-6 is critical and responsible for the inflammatory storm so, Tocilizumab by interfering with interleukin-6 plays a significant role in the treatment of covid-19(Shen et al., 2020).

8. Interferons

Interferons are made up of groups of a helical secreted cytokine. There are different types of interferons such as interferon-alpha, interferon-beta, etc. alpha interferon is used to treat hepatitis as a broad-spectrum antiviral drug. Interferon beta is a naturally occurring protein that plays anti-viral activity in the body. Both interferon-alpha and beta have shown anti-viral activity in in vitro experimentations. In 12

in vitro studies, the anti-viral activity of interferon-beta has been tested. It was revealed from studies that interferon beta has strong anti-viral activity toward SARS-CoV as compared to interferon-alpha (Scagnolari et al., 2004). Both interferon-alpha and beta play their anti-viral activity against SARS-CoV by inhibiting the replication of this virus. Despite, several other pharmacological agents, interferon-alpha is also recommended in the treatment of covid-19 in the guidelines issued by the National Health Commission & State Administration of TCM(Commission, 2020).

9. Stem cell therapy

Stem cell therapy is a way of treatment against covid-19 in which mesenchymal stem cells are used based on the clinical & preclinical studies according to efficacy and safety. Mesenchymal cells can differentiate and possesses immunomodulatory activity. The mesenchymal cells possess immunomodulatory activity as they can directly communicate with immune cells or various forms of cytokines. It was reported after the study that patients receiving mesenchymal stem cell therapy have a fast recovery with good outcomes (Leng et al., 2020)

10. Convalescent plasma therapy

- From experimental studies, it has been revealed that plasma therapy appears as a hope for the treatment of this dreadful pandemic. Immunoglobulin or convalescent plasma therapy has been used as a last option to improve the condition suffering from SARS infection having deteriorated condition despite the treatment. It was reported the patient receiving convalescent plasma therapy showed less mortality rate and a short stay in hospital. In 2014, the use of convalescent plasma therapy was recommended by the world health organization for the treatment of Ebola virus disease (Organization, 2014). For the treatment of coronavirus diseases and respiratory problems, the use of convalescent plasma therapy was recommended in 2015. Studies showed that the convalescent plasma from those patients who have a successful recovery from viral infectious diseases can be used as a therapy without the occurrence of side effects. Convalescent plasma therapy plays a significant role in decreasing viral load.

Vaccine for covid-19

Vaccines are harmless or non-toxic preparation of pathogens used to provide immunity against infectious diseases. It produces B cells and T cells in large amounts in the body by stimulating the immune response. When the body comes in contact with that same pathogen next time, that pathogen will be destroyed by vaccines. Presently, there are some approved vaccines for covid-19 that are being given to people. However, clinical trials are going on in various countries to produce some more promising vaccine against covid-19.

Vaccine design

it comprises the selection of antigen, vaccination platform & vaccine route & regime. The selection of vaccine platform describes the relative immunogenic durability of viral antigen which are vaccine-derived, to test the requirement of adjuvant immunity & the nature of protective immunity also tested at this platform. These features also describe the appropriateness of the vaccine for a specific route of

vaccination, and whether a prime-boost vaccination regime is required to enhance vaccine-mediated protective immunity and strengthen it. additionally, selecting a route for a live viral vaccine which is named as live attenuated will also demand more safety testing.

Selection of antigen (SARS-Cov-2 antigen)

Those structural proteins which are found in infectious virion are N protein, S protein, envelop protein, and matrix protein. The N protein coats the large positive-stranded RNA genome, which is encased in a lipid envelope derived from the host cell membrane, into which the other three proteins are inserted. It has been shown that for the case of SARS-CoV, only those antibodies which are directed to S proteins can prevent the infection by neutralizing the virus. So, all the vaccines which are in development must include S protein in them(Buchholz et al., 2004).

Vaccine platform

Generally, the vaccine platform is categorized into 6 forms

- Live attenuated virus vaccine
- Recombinant viral vector vaccine
- Inactivated or killed virus
- Protein subunit vaccine
- Nucleic acid-based vaccine
- Virus-like particles

In general, vaccines consist of 2 components which are antigen and infectious signal. The antigen is obtained from the target pathogen and is provided to the vaccine recipient. The infectious signal is that which activates and alerts the immune system of the host. Live attenuated vaccine is best as it provides both antigen and infectious signals naturally. The non-viral platform of vaccine provides the antigen but usually, it requires the provision of infectious signal artificially to activate the host immune system. Live attenuated vaccines possess the potential to provide "one-shot immunity" whereas non-viral vaccines demand several vaccinations to provide protective immunity(Rauch, Jasny, Schmidt, & Petsch, 2018).

How Vaccine help:

Antibodies contain debilitated or latent pieces of a specific living being (antigen) that triggers an insusceptible reaction inside the body. Fresher antibodies contain the outline for delivering antigens as opposed to the actual antigen. Whether or not the antibody is comprised of the actual antigen or the outline with the goal that the body will create the antigen, this debilitated form won't cause the illness in the individual getting the immunization, however it will provoke their resistant framework to react much as it would have on its first response to the genuine microbe.

Routes and regimens of vaccination:

It is an integral consideration to select the route and regimen of vaccination in addition to select the platform and vaccine antigen. This selection is highly valuable for mucosal pathogens (causing covid-19) & to those pathogens who required optimal protection against them to neutralize antibodies and for innate & adaptive immunity. The time for the control and clearance of COVID-19 against SARS-CoV-2 is an asymptomatic and pre symptomatic period in which all immune elements must be present in respiratory mucosa

and the route of administration of vaccination play a crucial role in this way. Induced by parenteral vaccination, protective IgG antibodies appears at respiratory mucosa readily but this route is unable to induce IgA antibodies in lungs effectively (Belyakov & Ahlers, 2009; Xing et al., 2020; Yao et al., 2018). Nucleic acid vaccine & inactivated virus vaccines are not administered by this route due to their unsafe and repeated delivery. As compared to these vaccines, a recombinant viral vectored vaccine is considered highly effective and safe.

Discussion

Assessment of killing antibodies levels post immunization is exceptionally useful to decide level of humoral invulnerability, after immunization, albeit cell resistance can't be assessed in clinical lab. Thus, we showed for the first time that among Sputnik V inoculated bunch, before second portion organization, the SARS-CoV-2 spike antibodies levels were significantly high which demonstrates promising results for vaccination against COVID-19. In light of this investigation, it tends to be conjectured that after the second portion organization of Sputnik V, the SARS-CoV-2 spike counter acting agent levels will additionally increase significantly to inoculate against COVID-19. Likewise, speedy resistance with first portion gives Sputnik V an edge over different immunizations, which can be valuable when

infection spread is quick and numerous patients get tainted prior to second portion of different immunizations. (Saeed, U., Uppal et.al. 2021)

The approval (EUA) by the US-FDA for two mRNA-based vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna) has brought any expectation of inclining to the COVID-19 pandemic which has killed in excess of 2,000,000 individuals worldwide. Nanotechnology has assumed a huge part in the achievement of these antibodies. Nanoparticles (NPs) help in further developing security by shielding the epitomized mRNA from ribonucleases and work with conveyance of unblemished mRNA to the objective site. The mind-boggling accomplishment of these two mRNA based immunizations with ~95% viability in stage III clinical preliminaries can be ascribed to their remarkable nanocarrier, the "lipid nanoparticles" (LNPs). LNPs are remarkable contrasted and bilayered liposomes and give further developed security of the freight, have inflexible morphology, and help in better cell infiltration. This EUA is a significant achievement and features the monstrous capability of nanotechnology for immunization conveyance and for battling against future pandemics. At present, these two antibodies are supporting in the mitigation of the COVID-19 wellbeing emergency and show the possible utility of nano medicine for handling medical issues at the worldwide level. (Khurana, A., Allawadhi, et.al. 2021).

Table 1: Some approved vaccines

Name	Developer	Country	Route	Targets	Immunogenicity	Safety
mRNA-1273	Moderna	USA	IM	S-2P	Two doses of mRNA-1273 afforded an efficacy of 94.1% (95% credible interval, 89.3e96.8%) in preventing COVID-19.	Systemic adverse events were more common after the second vaccination. Serious adverse events were rare.
BNT162b2	BioNTech	Germany	IM	S-2P	The BNT162b2 vaccine with two injections showed 95% efficacy (95% credible interval, 90.3e97.6%) at preventing COVID-19.	The adverse events included mild-to-moderate pain at the injection site, fatigue, and headache. The frequency of serious adverse events was low and was similar in the vaccine and placebo groups.
Vaxzevria	University of Oxford and AstraZeneca		IM	S-2P	According to AstraZeneca’s primary analysis of phase 3 trial data, the vaccine has a 76% efficacy rate after both doses.	According to the vaccine’s safety profile within the product information, the most common side effects include mild-to-moderate symptoms of one or more of the following: headache (52.6%) fatigue (53.1%) muscle or joint pain (44% or 26.4%) fever (33.6%) chills (31.9%) nausea (21.9%)
Ad26.COV2.S	Johnson & Johnson		IM	S-2P	The Johnson & Johnson vaccine has a 66% efficacy rate. While this is lower than the efficacy rates of the Pfizer or Moderna vaccines, it should be noted that the clinical trials of the Johnson & Johnson vaccine took place in different contexts — globally in regions where variants were more prevalent, and in the U.S. during a period of significant increase in COVID-19 cases. The vaccine is around 85% effective at preventing severe disease from COVID-19, including hospitalization and death.	As with other COVID-19 vaccines, the Johnson & Johnson vaccine has a low but potential risk of causing an allergic reaction. A non-severe allergic reaction may include symptoms such as hives, swelling, rash, and respiratory problems
ARCT-021	Arcturus	USA	IM	S-2P	Neutralizing antibody levels in both single-dose and prime-boost groups were within those observed in convalescent patient sera.	ARCT-021 was well tolerated, the majority of adverse local and systemic adverse events were mild.
BIBP	Sinopharm	China	IM	S-2P	A large multi-country Phase 3 trial has shown that 2 doses, administered at an interval of 21	Safety data are limited for persons above 60 years of age (due to the

					days, have an efficacy of 79% against symptomatic SARS-CoV-2 infection 14 or more days after the second dose. Vaccine efficacy against hospitalization was 79%.	small number of participants in clinical trials).
Corona Vac	Sinovac Biotech	China	IM	S-2P	This two-dose vaccine is recommended for individuals aged 18 years and above. It has an efficacy rate of 50.4% for preventing symptomatic infection, according to data from a Brazilian trial, and an effectiveness of 67%, according to a real-world study in Chile.	According to the data, the most common side effect reported within 28 days of the second dose was injection-site pain (13–21%, depending on the dosing schedule). Injection site reactions are common with other COVID-19 vaccines

Conclusion

In this century, coronavirus diseases caused by the SARS-CoV-2 virus is a more formidable challenge to us. The emergence of this dreadful pandemic required the development of the most promising therapeutic challenges and vaccine strategies to combat this novel viral outbreak. Currently, there is no proven promising anti-covid-19 medicine but some effective vaccines are approved and jabs are given to the people. It is considerably believed that pre-pandemic normality will never return until a highly effective & safe therapeutic and vaccine strategy becomes available and a global therapeutic and vaccination program is successfully implemented. Rapid researches and clinical trials are going on regarding the safety and efficacy of effective anti-covid-19 drugs & vaccines against the SARS-CoV-2 virus.

Abbreviations

SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2).

ARDS (acute respiratory distress syndrome).

JAK (Janus kinase inhibitor)

GAK (G-associated kinase)

TCM (Traditional Chinese Medicine)

Conflicts of interest

There is no conflict of interest in this paper.

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