Review Article:

A Review on Current Side Effects of Used Drugs During Treatment of Patients With COVID- 19

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Article info:
Received: 16 Oct 2020
Accepted: 11 Sep 2021

Keywords:
COVID-19, Medicines, Toxicity, Convalescent plasma, Nanotherapeutics, Clinical observations, Side effects

ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). To increase the success in treating patients with COVID-19, many drug suggestions and some clinical studies are shared in the literature. However, the combination of several drugs with other clinical care has improved patients' conditions. And this review discusses some side effects of Covid-19 drugs' adverse effects.

Objectives: Here, we have shortly reported the recent updates on the most common and plausible drugs for treating COVID-19 patients. We also compare these treatment options based on their impact on symptom management, inpatient length of stay, and overall morbidity and mortality.

Methods: An extensive literature search was performed through PubMed, Scopus, Web of Science, and Google Scholar. Most of the keywords used were: "COVID-19", "Side effects of used drugs," "Treatment of COVID-19", "Risk factors," "Organ damage," and "Methods of diagnosis and treatment."

Results: Anti-inflammatory, antimicrobial, and vitamin supplements do not have obvious benefits, but there is limited information to consider. Other factors and drugs such as improved plasma, eculizumab, immunoglobulins, IgG1-neutralizing monoclonal antibodies, remidseiver, steroids, and tosilizumab have shown potential effects on patient's length of hospital stay and mortality. Currently, there is no evidence that any other vaccines, apart from those specifically designed for the SARS-Cov-2 virus, will protect against COVID-19.

Conclusion: Since the prevention of the COVID-19 virus is a new issue in the medical world, there is no known effective treatment option in this area, and the prevention of its adverse side effects has not been conclusively proven. Of course, the occurrence of side effects in patients undergoing treatment such as hepatotoxicity, retinal damage, nephrotoxicity, and cardiotoxicity proves that the necessary caution should be used in drug combination methods.

Citation Saberi Hasanabadi P, Ataee R. A Review on Current Side Effects of Used Drugs During Treatment of Patients With COVID- 19. Pharmaceutical and Biomedical Research. 2021; 7(4):251-260. http://dx.doi.org/10.18502/pbr.v7i4.9371

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Introduction

Patients with confirmed COVID-19 infection have reportedly had mild to severe respiratory illness with symptoms of cough and shortness of breath, along with other symptoms, appearing anywhere from 2 to 14 days after exposure. Older adults and people with severe underlying medical conditions like heart or lung disease or diabetes seem to be at higher risk for developing serious complications of COVID-19 illness [1].

At present, special drug treatment for this disease has not been recommended by the World Health Organization (WHO). However, several clinical trials have been conducted to examine the efficacy of the already registered medicines used to treat other mostly virus-related diseases and conditions [2]. Because the health status of patients with COVID-19 is often complex with their underlying diseases and conditions, understanding the toxicity and side effects of drugs, especially their combinations, are essential in building successful medical strategies. Previous studies have shown that chronic fatigue, post-infection thrombotic events, irreversible lung disease, and altered mental and physical disability are among the leading complications of this disease [1, 2]. However, it is still impossible to determine these cases completely and accurately in all patients. Drug repurposing has been considered a rapid strategy for COVID-19 drug discovery, and therefore many drugs have been tested. In this study, we want to control the results of some of the most critical factors in terms of their side effects.

In the current review, we summarize the existing state of knowledge about available medications and treatment options for COVID-19 disease, along with their side effects. We hope that this review will provide valid and most updated therapeutic drugs to prevent, control, and treat COVID-19 patients until acceptable results are provided in vaccine injections and the use of effective medicines.

Treatment Mechanisms

In general, to increase the success in COVID-19 treatment, many drugs have been suggested, and some clinical studies shared in the literature (Table 1):

Medicines that directly target the COVID-19 virus and prevent it from entering, multiplying, and spreading to body tissues (chloroquine and ribavirin).

Therapies that may boost the immune system to suppress and clear the coronavirus, such as interferon or plasma injections containing coronavirus immunoglobulin (antibody)

Immunosuppressive and inflammatory regulatory methods, such as the use of corticosteroids and specific immune-lowering drugs such as tocilizumab, which block the action of interleukin-6, an essential molecule in inflammation [3].

The Side Effects of the Selected Drugs

Ritonavir

Ritonavir has gastrointestinal side effects, but it is generally well tolerated. The combined use of two lopinavir/ritonavir drugs improved 41 patients compared with controls in clinical experiments [14].

Ritonavir increases drug adsorption orally via inhibition of P-glycoprotein, a membrane transport protein of the digestive tract, whose expression and functionality can be modulated by factors, such as inflammatory state, genetic polymorphism, or age with significant consequences on drug exposition and interaction [18]. Medical staff should be aware of this adverse effect during the treatment of patients with COVID-19 and closely monitor ritonavir plasma levels, notably in elderly patients. One of the problems of using this drug is the reduction of bone mineral density. In this regard, ritonavir in low dosage does not cause hepatotoxicity, and reported cases are usually few and self-limiting. However, because this drug is an enzyme inhibitor, it can increase the plasma level of drugs that are used simultaneously and lead to hepatotoxicity [1, 14]. Only one study in China reported diarrhea associated with ritonavir use in patients with COVID-19. This study showed that after treating lopinavir/ritonavir in 33 patients with COVID-19, 15 patients developed diarrhea and rash [18].

Lopinavir

Lopinavir is associated with lipid abnormality. Since this drug is taken with other medicines, especially ritonavir, it is difficult to find side effects alone during the treatment process. In addition, lopinavir/ritonavir did not show efficacy in two large randomized controlled experiments in treated patients with COVID-19 [19].

Arbidol (umifenovir)

Arbidol is effective for COVID-19 disease treatment in some in vitro studies [20, 21]. However, no conclusive evidence of its efficacy in patients with COVID-19 was

Table 1. Overview for medicinal compounds used in patients treatment with COVID-19 along with some of their most common negative effects

Row	Drugs: Side Effects	Reference
1	Malaria drugs (hydroxychloroquine and chloroquine): They are known to cause heart rhythm problems potentially. Also, skin manifestations, such as erythematous rash, petechia, urticaria, and vesicles, have been reported in patients with COVID-19.	[4]
2	Antiviral drugs (HIV drugs, remdesivir, Arbidol): Their most common adverse effects are skin rashes and gastrointestinal problems.	[5]
3	Anti-inflammatory drugs (ibuprofen, aspirin, and dexamethasone): The results in different studies are contradictory. Researchers investigated many anti-inflammatory drugs to treat or prevent dysfunction of several organs and lung injury from infection-associated inflammation.	[6, 7]
4	Immune-based drugs (interferon-alpha, tocilizumab, and convalescent plasma): The most common side effect is a mild allergic reaction. Rare but serious side effects include problems with the heart or lungs or infection. Other symptoms were skin infection, pruritus, skin hypersensitivity reactions, and psoriasiform dermatitis.	[8]
5	Lopinavir/Ritonavir: The adverse effects include nausea, vomiting, diarrhea (common), QT* prolongation, and hepatotoxicity.	[9]
6	Lopinavir/Ritonavir + Umifenovir: Nausea/vomiting	[10]
7	Lopinavir/Ritonavir + Interferon-beta: Adverse events included self-limited nausea and diarrhea with no difference between the two groups.	[11]
8	Interferon-alpha + Umifenovir: Not specified.	[12]
9	Lopinavir/Ritonavir + Ribavirin + Interferon-beta-1b: Adverse events included self-limited nausea and diarrhea with no difference between the two groups.	[1]
10	Lopinavir/Ritonavir + Novaferon: No severe adverse events were reported associated with the tested antiviral drugs.	[1]
11	Favipiravir + Interferon-alpha: The most adverse event was raised serum uric acid. Combined side effects are not mentioned.	[13]
12	ASC09F + Ritonavir + Oseltamivir Not specified.	[14]
13	Favipiravir + Tocilizumab Not specified.	[15]
14	Darunavir + Cobicistat + Thymosin: No serious adverse effects were reported.	[1, 16]
15	COVID-19 Vaccines: Urticaria, scleroderma, maculopapular rashes injection site reactions	[17]

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*The QT interval is a measurement made on an electrocardiogram used to assess some of the electrical properties of the heart.

reported. The use of Arbidol in patients with COVID-19 can be associated with mild gastrointestinal adverse events in some patients, including nausea, diarrhea, and stomachache, as well as mild to moderate elevation in alanine transaminase and one case reported bradycardia [20]. One review stated that umifenovir could not improve the prognosis or accelerate SARS-CoV-2 clearance in non-ICU patients. A randomized control clinical trial is needed to assess the efficacy of umifenovir [22].

Remdesivir

The appropriate dose to use this drug is an initial one-time dose of 200 mg followed by 100 mg per day for 10 days. Researchers documented increases in liver enzymes in three US COVID-19 patients [23].

In line with this goal, Grein et al. evaluated the use of remdesivir according to scheduled programs for patients with COVID-19 (200 mg on the first day, plus 100 mg for the remaining 9 days) [24]. Observed side effects include the elevation of hepatic enzymes, hypotension, renal impairment, rash, and diarrhea. These side effects were reported in about 60% of patients, while in others (about 12%), symptoms such as acute kidney injury, hypotension, septic shock, and multiple organ dysfunction syndromes were seen during treatment [24]. Other medicines could make remdesivir less effective. Other reported side effects include gastrointestinal distress, elevated transaminase levels in the blood (liver enzymes), and infusion site reactions. According to international experts from the British Medical Journal, the drug probably has no important effect on the need for mechanical ventilation and may have little or no impact on the length of hospital stay [1].

A summary of the adverse effects of remdesivir is listed in Table 2. Information is taken from the research results obtained by Grein et al. [24]. In this study, a final report was obtained from 32 patients who had side effects

Table 2. Side effects of remdesivir consumption in COVID-19 patients [24]

Side Effect	No. (%)		
	Invasive Ventilation (n=34)	Noninvasive Oxygen Support (n=19)	Total (n=53)
Hepatic enzyme increased	8(24)	4(21)	12(23)
Diarrhea	1(3)	4(21)	5(9)
Rash	3(9)	1(5)	4(8)
Renal impairment	4(12)	0	4(8)
Hypotension	3(9)	1(5)	4(8)
Acute kidney injury	2(6)	1(5)	3(6)
Atrial fibrillation	2(6)	1(5)	3(6)
Multiple organ dysfunction syndrome	3(9)	0	3(6)
Hypernatremia	3(9)	0	3(6)
Deep vein thrombosis	3(9)	0	3(6)
Acute respiratory distress syndrome	1(3)	1(5)	2(4)
Pneumothorax	2(6)	0	2(4)
Hematuria	2(6)	0	2(4)
Delirium	1(3)	1(5)	2(4)
Septic shock	2(6)	0	2(4)
Pyrexia	1(3)	1(5)	2(4)

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from this drug. The most common adverse effects were elevated hepatic enzymes, diarrhea, rash, renal impairment, and hypotension. In general, adverse effects were more common in patients receiving invasive ventilation. About 12 patients (23%) had severe side effects from this drug. Four patients (about 8%) showed signs of recovery earlier than usual than the control group.

Chloroquine and hydroxychloroquine

These two drugs have mild side effects compared to other medications. Although chloroquine and hydroxychloroquine have shown promising benefits against SARS-CoV-2, several observational studies in COVID-19 have reported that chloroquine and hydroxychloroquine are associated with an increased risk of heart problems, a well-known side effect of such treatments, including cardiac arrhythmias and cardiac arrest [1, 4]. Given the lack of benefits seen in the randomized clinical trials and the potential toxicity, the toxicology researchers recommend against using hydroxychloroquine or chloroquine with or without azithromycin to treat COVID-19 hospitalized patients. When prescribing these drugs, healthcare professionals should consider pre-existing heart conditions, uncorrected potassium or magnesium imbalance, and concomitant use with medicines that prolong the QT interval as these factors may make patients more prone to heart rhythm disorders [25].

The critical dose for consumption of these drugs is usually more than 5 mg/kg. Current evidence suggests the highest risk of retinopathy is seen in patients taking more than 5 mg/kg of daily consumption of hydroxychloroquine. In addition to their effects on the heart, these drugs may cause neuropsychiatric disorders, including agitation, insomnia, confusion, psychosis, and suicidal ideation. These drugs are also known to have an adverse effect on the liver that can lead to seizures (fits) and lower blood sugar [26].

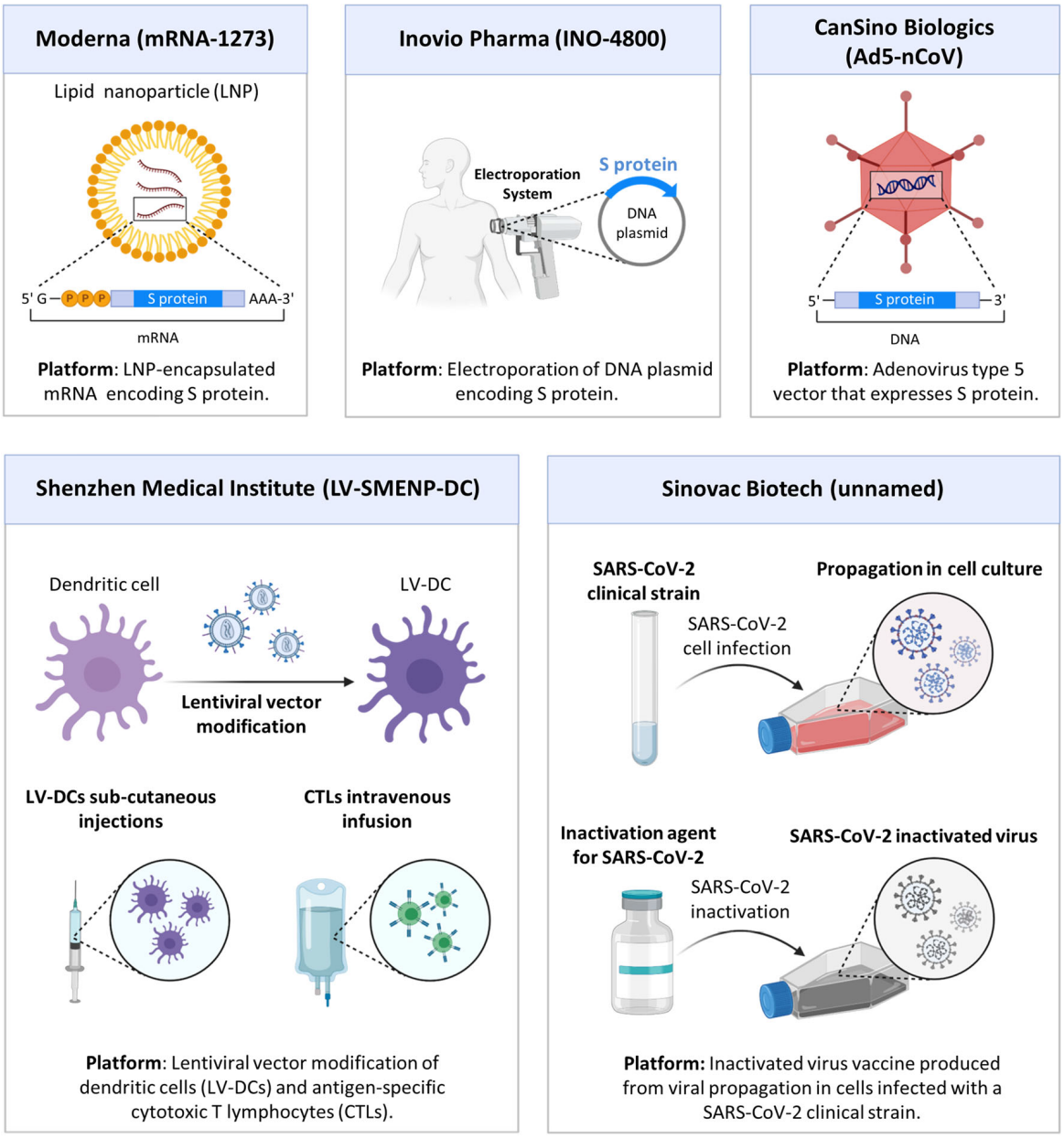

Figure 1. Types of clinical phase-related vaccines for use in the prevention of COVID-19 (as of April 2020)
The image was adapted from reference 46 with permission.

Favipiravir (avigan)

The major and commonly known contraindication of favipiravir is its effect on pregnant and locating women, which has been associated with embryonic deaths and teratogenicity. In severely ill patients, the toxic proteins known as the cytokine storm produced by the overreaction of the body's immune system inhibit the activity of the favipiravir-RTP. (Inside the cells, favipiravir is converted to favipiravir ribofuranosyl-5′-triphosphate [favipiravir-RTP] by host cells] The drug is also ineffective in stopping this cytokine storm that damages the organs. Favipiravir has been a subject of several studies. Still, researchers have claimed time and again that the research is suggestive and needs to be followed up with confirmatory trials [1, 27].

A Spanish study reported favipiravir as a well-tolerated substance, without severe adverse effects even when used in high doses (50 mg/kg). Other studies demonstrated a lower proportion of grade 1-4 the adverse drug events, gastrointestinal the adverse drug events, serious the adverse drug events, and a better overall safety profile of favipiravir than placebo [28].

Oseltamivir (Tamiflu)

Tamiflu is being used in conjunction with other drugs in several clinical trials for patients with COVID-19. The trials are testing whether short-term treatment with Tamiflu will reduce the length of illness, complications, and mortality in patients with COVID-19 [29].

In Ghafour and Elyasi study, the neuropsychiatric side effects of oseltamivir were reviewed during treatment of COVID-19. They stated that most side effects of medication are reported voluntarily by the patients, and it is difficult to estimate the true extent of psychiatric side effects with oseltamivir, but overall it seems uncommon. However, the patients treated with this drug should be closely monitored for evidence of abnormal behavior. If neuropsychiatric side effects occur, the decision to continue or discontinue the drug should be made based on the risks and benefits to each patient [30].

Interferon (IFN)-α and IFN-β

There are insufficient data to recommend either for or against the use of interferon-beta IFN-β for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19. The most frequent adverse effects of IFN-α include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities, elevated transaminases, and psychiatric problems (depression and suicidal ideation) [31]. IFN-β is better tolerated than IFN-α. Data from several large pregnancy registries did not demonstrate an association between exposure to IFN-β-1b preconception or during pregnancy and an increased risk of adverse birth outcomes (e.g., spontaneous abortion, congenital anomaly). Also, the exposure did not influence birth weight, height, or head circumference. There are limited data on the use of interferon to treat respiratory viral infections in children. There are several reports of hepatic encephalopathy, jaundice, and acute liver failure in patients receiving IFN to treat the hepatitis C virus [32].

Supporting agents

Azithromycin

In line with the mentioned drugs, azithromycin antiviral activity has been shown in vitro and or in vivo studies on a large panel of viruses: Ebola, Zika, respiratory syncytial virus, influenza H1N1 virus, enterovirus, and rhinovirus. The greatest effect of this drug on patients with COVID-19 is obtained in combination with other drug treatments. The most frequent adverse drug reactions are related to the gastrointestinal tract (e.g., nausea, vomiting, diarrhea, or abdominal pain). The risk of combination and interaction with other drugs used is low. A recent observational study reported data on azithromycin used alone in patients with COVID-19 [33].

Vitamin C (Ascorbic acid)

There are insufficient data for the COVID-19 treatment to recommend either for or against the use of vitamin C to treat COVID-19 in non-critically ill patients. Because serious COVID-19 may cause sepsis and acute respiratory distress syndrome (ARDS), the potential role of high doses of vitamin C in ameliorating inflammation and vascular injury in patients with COVID-19 is being studied. Because patients who are not critically ill with COVID-19 are less likely to experience oxidative stress or severe inflammation, the role of vitamin C in this setting is unknown [34].

Nitric Oxide and Epoprostenol

Nitric oxide can result in short-term improvement in oxygenation in patients with acute respiratory distress syndrome. Still, there is no evidence of a significant effect on mortality, and its use has been linked to renal injury. Nitric oxide can be safely used at a dose of 20-80 ppm to replace inhaled treprostinil, which needs nebulization in patients with COVID-19 [35].

Sirolimus (rapamycin)

Based on clinical observations, a strong case can be made for immediate large-scale clinical trials to assess whether rapamycin and other mTOR inhibitors can enhance resilience towards communicable and non-communicable diseases, prevent the spread of the virus in high-risk individuals, and improve the incidence with COVID-19 [36].

Checkpoints inhibitors

Immune checkpoint inhibitors are a type of immunotherapy that blocks immune checkpoint proteins from binding with partner proteins. A controversy has increased over whether the severity of COVID-19 in cancer patients who previously received immune checkpoint inhibition is different from other patients with cancer. Studies have shown that immune checkpoint inhibitors may be considered immunotherapy against COVID-19 in non-cancer patients, as it enhances T-cell activation along with proliferation. The potential of immune checkpoint inhibitors as both an anticancer treatment and a COVID-19 antiviral therapy for non-cancer

patients should be further explored [37]. More randomized clinical trials are required to evaluate the challenges and benefits of an immunomodulatory procedure such as immune checkpoint inhibitors.

Possible Future Therapeutic Targets

There is growing interest in using specific anti-inflammatory molecules such as tocilizumab, a monoclonal antibody against interleukin-6 receptor (IL-6R). Tocilizumab was used to treat 272 COVID-19 patients in China and is being investigated in an ongoing national multicenter clinical trial in Italy [1, 39]. Of course, access to the results is limited. Other potential anti-inflammatory therapies might include anti-IL-17 medications and treatment with mesenchymal stromal cells, which reduce inflammation and stimulate regeneration of tissues affected by acute respiratory distress syndrome. Another feasible option may be the amplification of anti-2019nCoV specific T lymphocytes. A human monoclonal antibody targeting IL-1b or a selective, long-acting inhibitor of the enzyme phosphodiesterase-4 that is already used to control neutrophilic inflammation in patients with chronic obstructive pulmonary disease may be another effective way to fight COVID-19 disease [38, 40, 41].

Treatments with multiple monoclonal antibodies and immunostimulants are being considered to neutralize variant strains that include the COVID-19 virus. Broad-spectrum antiviral agents, such as dsRNA-activated caspase oligomerizer, are useful to induce selective apoptosis of virus-host cells. This action may be an effective method, but it can only prevent the virus from entering the cell or disrupting viral nucleic acid if combined with other therapeutic strategies and protocols, including antiviral drugs. With the ongoing development of monoclonal antibodies as novel therapeutic strategies for a wide variety of diseases, efforts should be paid to improve our understanding of monoclonal antibodies-induced immunotoxic effects and design dedicated strategies to assess their immunological safety both non-clinically and clinically. It has long been recognized that treatments with potent immunosuppressive agents may be associated with more frequent and often more severe and relapsing infections. One of these side effects can be the occurrence of virus-induced neoplasia. In this regard, convalescent plasma therapy may be a safe treatment option for patients with severe COVID-19 disease. A transfusion can cause reactions such as allergic reactions, fluid overload, or lung damage with breathing difficulty, cardiac (heart) rhythm irregularities, and blood clotting. But, based on the available information, it is difficult to draw a tangible conclusion about whether plasma therapy improves patient mortality. This method may improve patients with COVID-19 unless we have clear evidence to the contrary [1, 42].

Vaccines

While trials have shown several COVID-19 vaccines to have high levels of efficacy, like all other vaccines, COVID-19 vaccines will not be 100% effective. At least seven different vaccines (3 platforms) have been administered. WHO is working to help ensure that approved vaccines are as effective as possible to have the greatest impact on the pandemic. Because COVID vaccines have only been developed in the last few months, it is too early to know the duration of protection of COVID-19 vaccines. In large clinical trials, most side effects were minor. For persons who were vaccinated for COVID-19 while they were undergoing chemotherapy or treatment with other immunosuppressive drugs and who have since regained their immune competence, re-vaccination is not recommended at this time. Recommendations on re-vaccination or additional doses of mRNA COVID-19 vaccines may be updated as additional information is available [43].

COVID-19 vaccines are the first to be produced using the mRNA platform (Figure 1). These vaccines are highly effective, but they are also "reactogenic," meaning they likely cause a noticeable immune response. Side effects may vary with the type of COVID-19 vaccine. In the cases of Pfizer and Moderna messenger RNA- or mRNA- vaccines, the most common side effect was soreness at the injection site. Other side effects include fatigue, headache, muscle aches, chills, joint pain, and possibly some fever, usually 24 to 48 hours, and no more than a few days. Side effects were more frequent after the second dose in the vaccine trials. Side effects are similar after the Pfizer and Moderna mRNA vaccines but could differ from other types of vaccines [44].

Nano-medicine on COVID-19 therapeutics

Various latest therapeutic approaches, such as soft nanomaterials obtained from polymers (polymeric nanoparticles), lipids (lipid-solid nanoparticles, nanostructured lipid carriers, and liposomes), surfactants (microemulsion, nanoemulsions, and liquid crystals), and proteins (protein nanoparticles) along with broad-spectrum antiviral therapeutics instead of single target antiviral drug, combination therapy of antiviral drugs with antibiotics, and nano-encapsulated antiviral drugs and vaccines have displayed promising results for the treatment of COVID-19. The versatility of nanoparticles

adjusts them to missiles that specifically target viruses. Nano-encapsulation of the medicines mentioned in this review may contribute to the development of safer treatments for COVID-19 and other viral diseases [1, 45].

Conclusion

In this review, we briefly discussed the side effects of drugs that are currently recognized as potentially effective therapeutic options for treating COVID-19 disease. In addition, some of these drugs are used together in COVID-19 treatment. The side effects caused by using combined drugs are shared. With the experimental results obtained from clinical studies, we aimed to facilitate the selection of the drugs and increase the success of COVID-19 treatment according to the targeted patients in different regions. However, we recommend caution in using these medications for selected severe critical cases of COVID-19 until the results of other much-needed large clinical trials fill some important gaps regarding their COVID-19 efficacy/inefficacy. Of course, the occurrence of side effects, such as hepatotoxicity, retinal damage, nephrotoxicity, and cardiotoxicity in patients undergoing treatments, proves that the necessary caution should be taken in drug combination methods.

Ethical Considerations

Compliance with ethical guidelines

This article is a review manuscript with no human or animal sample. There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

Both authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

Acknowledgments

We thank the Department of Pharmacy, Mazandaran University of Medical Sciences, for their input during the preparation of this manuscript.

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