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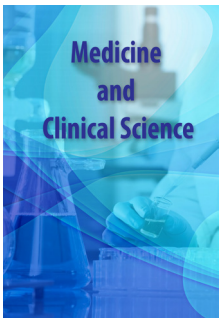
Review Article



Recent Studies on the Mechanisms and Adverse Effects of Medications Used in COVID-19 Patients

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Abstract

To increase the success in Covid-19 treatment, many drug suggestions are presented, and some clinical studies are shared in the literature. There have been some attempts to use some of these drugs in combination. However, using more than one drug together may cause serious side effects on patients. Therefore, detecting drug-drug interactions of the drugs used will be of great importance in the treatment of Covid-19. In this study, some vital drugs and supplements used for Covid-19 treatment with their mechanism of actions and possible adverse/side effects shed a light about their safety and efficacy level. Moreover, some of these drugs are used together in Covid-19 treatment for better outcome of treatment, thus the side effects caused by using these drugs together are shared. In this review, it is aimed to facilitate the selection of proper drugs by the physicians and increase the success rate of Covid-19 treatment according to the targeted patient.

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Keywords

COVID-19, SARS-CoV-2, mechanism, adverse effects, side effects.

Introduction

The well-known severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which is responsible for coronavirus disease 2019 (COVID-19), has spread across the world. Our universe has first saw the novel coronavirus disease (COVID-19) in human in Wuhan, China which was solely caused by the SARS-CoV-2 virus. Despite vaccination efforts and all necessary restrictions, SARS-CoV-2 has infected more than 1.2 million people in the United States alone, with a new wave of increasing cases partially due to novel variants, such as the Delta variant of the virus, which are more easily transmissible to human body [1–3]. Although the highest mortality rates had been seen primarily in the elderly population, as more of the vulnerable population became vaccinated, the spread of the virus shifted toward an unvaccinated, younger subjects [4]. The most common clinical characteristics represented by human in their acute stage of this disease are fever, musculoskeletal symptoms (such as: fatigue, myalgia, and joint pain), dry cough, dyspnea, gastrointestinal symptoms, and anosmia with or without ageusia [5]. Most importantly, after viral infection different types of damage occur in multiple body organs, especially the brain [6]. In addition, peripheral and central inflammatory responses (neuroinflammation) may be also triggered by the infection, and can lead to long-lasting musculoskeletal problems, cognitive impairment, and psychological disorders such as: increased depression, anxiety, post-traumatic stress disorder (PTSD), and sleep problems [7–9]. Moreover, several potential life-threatening late complications also possible such as: lung fibrosis, venous thromboembolism (VTE), arterial thromboses, cardiac thrombosis and inflammation, stroke, "brain fog", and dermatological complications [10]. More noticeably, an overall decline in quality of life has been observed even 01 year after major coronavirus attack [11]. Although, specifically in human the scope of presentations and studies of long-term complications is wide, but specific attributes of patients have been shown to be predictive of which symptoms they develop and for how long they sustain [12].

Pathophysiology

Although SARS-CoV-2 primarily affects the lungs, it has been found to damage the vascular endothelium of several other vital organs of human. The explainable exact mechanisms responsible for long-term complications of deadly COVID-19 infection

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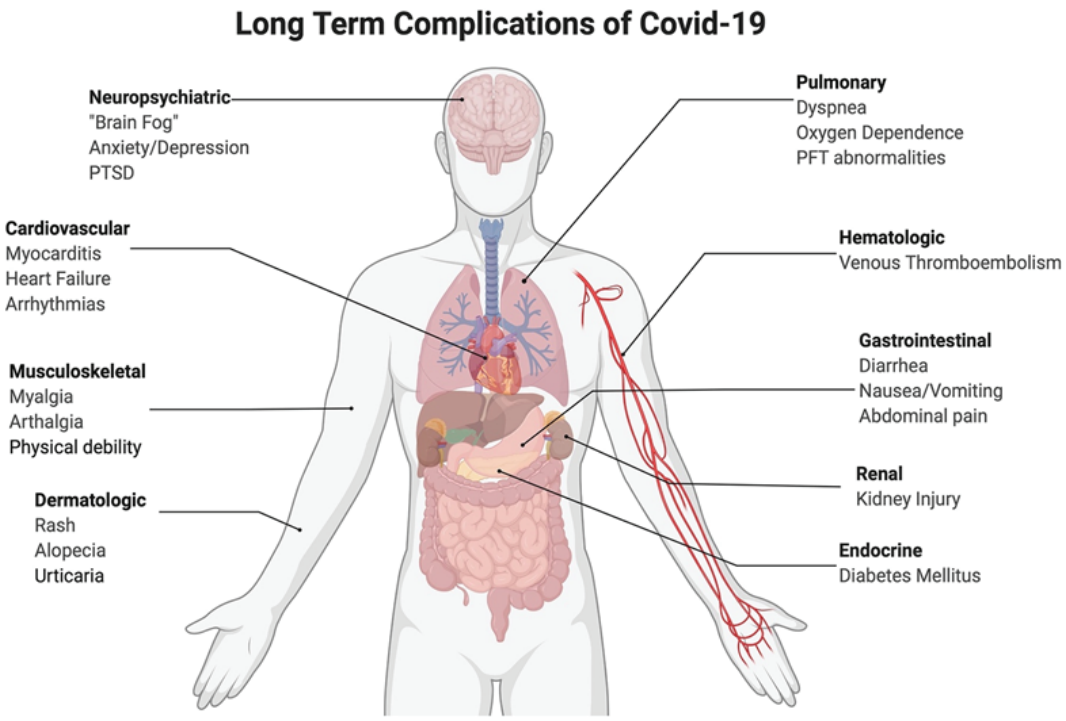

Figure 1. *Schematic representation of long term adverse effects observed following COVID-19 infection.*

remain still unknown, but there are several strong proposed pathophysiological mechanisms of the virus that can be reasonable for these longer-term complications in human. So far, possible pathophysiological mechanisms may include direct viral tissue damage of host. Mainly, the entry receptor for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2), is expressed in a variety of locations in the body allowing the virus to enter target cells through activation of its spike protein by transmembrane serine protease 2 [13,14]. These receptors are expressed in epithelial cells, nasal goblet cells, gastrointestinal epithelial cells, pancreatic beta cells, and renal podocytes suggesting that direct tissue damage may be a primary mechanism of the presentation of SARS-CoV-2 infection, which may also contribute to its longer-term complications [15–17]. Early studies revealed that, endothelial cells exhibited high expression level of "ACE2" and that ultimately led to substantial alteration to the integrity of the vessel barrier and promotion of a pro-coagulative state [18]. The long-term complications of these changes have been observed in follow-up studies of survivors of COVID-19, revealing pulmonary radiological abnormalities in 71% of patients and functional abnormalities in 25% of patients after 03 months period of COVID-19 infection [19]. Scientists also proposed several other clinical pathways leading to long-term COVID-19 infection complications. These include endothelial injury, immune system disruption, and hypercoagulability that often leading to fatal thrombosis. Immune system dysregulation has been suggested due to the finding of autoreactive T cells in autopsies of deceased individuals infected with COVID-19, likely due to mechanisms akin to those in autoimmune disease [20].

Methodology

The respected authors of this review paper have searched articles carefully from various popular search engines like: SciFinder, Sci-Hub, PubMed, Web of Science, and Scopus databases. The selected articles on novel coronavirus have been collected in between from January 2020 to July 2022, by using the key words "coronavirus", "SARS-CoV-2", "novel coronavirus", "COVID-19", or "COVID-19" in combination with "Mechanisms", "Actions", "Side effects", "Adverse effects" and "Complexities" which were frequently modified as per the requirements for the search tool of each database. Articles were incorporated based on significance, priority, and originality with regards to the topics covered in this review.

Outcomes and Discussion

In this review we will discuss and focus mostly on the mechanisms and the adverse actions of main drugs and various supplements which are frequently prescribed for COVID-19 patients.

Remdesivir

Remdesivir is an antiviral drug from the family of nucleoside analogues developed by the Gilead Pharmaceutical Company to treat Ebola virus and Marburg virus infections. Due to its antiviral properties, it has also been used against other single-stranded RNA viruses such as respiratory syncytial virus, blood virus, lasagna virus, NIPA virus, Hendra virus and corona- virus family (including coronavirus MERS and SARS) [21]. This drug has been successful in the treatment of Quid 19 in many cases and is also being studied and researched a lot [21]. Remdesivir is a precursor that is actively con- verted to GS-441524 in the body. It is an adenosine analogue that interferes with the function of the RNA-dependent RNA polymerase enzyme and prevents the virus from being sampled and genetically modified by the enzyme exoribonuclease (ExoN), thus reducing virus production and replication. It is not known whether this drug terminates the RNA chain or causes a mutation in it [21]. But like any other drug that AE has, it has been reported for Remdesivir AEs, and some AEs are associated with its use. The

most common side effects in Remdesivir studies for COVID-19 include respiratory failure and organ dysfunction, including low albumin, low potassium, low red blood cell count, low platelet count, which helps clots, and yellow skin discoloration [22]. Reported side effects include gastrointestinal upset, increased levels of transaminases in the blood (liver enzymes), and injection site reaction [23]. Other possible side effects have been reported with remdesivir due to its injection reactions; During or around the time of remdesivir injection, it has been observed that the signs and symptoms of injection-related reactions may include low blood pressure, nausea, vomiting, sweating and chills [23]. Elevated levels of liver enzymes, seen in abnormal liver blood tests. Elevated levels of liver enzymes have been observed in people receiving remdesivir, which may be a sign of inflammation or damage to liver cells [23].

Hydroxychloroquine and chloroquine

Hydroxychloroquine (HCQ) and chloroquine (CQ) are two antimalarial drugs with immunomodulatory effects, commonly used to treat rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). These drugs have been mentioned in the treatment of COVID-19 and are still being studied. But so far there is no clinical study that can prove the clinical effect of these drugs as a preventer. Chloroquine and hydroxychloroquine increase endosomal and late lysosomal pH, resulting in the release of the virus from the endosome or lysosome in antigen-presenting cells. Virus secretion requires a low pH. Therefore, the virus is unable to release and replicate its genetic material in the cell [24,25]. Various side effects of CQ/HCQ have been reported, including cardiac side effects, neuro- logical side effects, and psychiatric side effects. Among the side effects related to the heart were disorders such as conduction disorders (branch block, incomplete or complete atrio- ventricular block, QT prolongation and subsequent cardiac torsion) and cardiomyopathy (hypertrophy and congestive heart failure). Neurological side effects include muscle weak- ness, diplopia, dyskinesia, seizures, myasthenia gravis, and (long-term use) neuromyopathy. Psychiatric side effects such as insomnia, irritability, psychosis, depression, anxiety, aggression and confusion have also been reported [26].

Azithromycin

Azithromycin is an antibacterial drug and an acid-stable antibiotic that inhibits bacterial growth by interfering with their protein synthesis. Azithromycin is actively transported to the site of infection due to its high concentration in phagocytes. During active phagocytosis, large concentrations are released. Concentrations of azithromycin in tissues can be more than 50-fold higher in plasma due to ion trapping and high lipid solubility. Although the direct effect of the azithromycin on the COVID-19 has not been proved, but some clinical reports have shown significant improvements. Here, we brought some evidence of effect azithromycin on COVID-19 as follows. Use as an antibacterial effect: Although COVID-19 is an acute respiratory viral disease, reports such as bacterial infection have been reported in several patients with COVID-19 pneumonia [12,27,28]. The United Kingdom's National Institute for Health and Care Excellence (NICE) has also developed guidelines on whether to use azithromycin in patients with COVID-19 who are limited to bacterial infections because it is ineffective due to its viral etiology. Immunomodulation effect: because one of the leading causes of death in COVID-19 patients is cytokine-induced cytokine release syndrome (CRS). It seems that one of the most important effects of azithromycin is the modulation of the immune system. In fact, azithromycin affects mitogen-activated intra- cellular protein kinase (MAPK), especially extra- cellular signal-controlled kinases 1/2 (ERK1/2) and the NF-κB pathway downstream of ERK [29]. Azithromycin has also been shown to be effective in the management of several chronic lung diseases such as cystic fibrosis (CF), non- CF bronchiectasis, chronic obstructive pulmonary disease, chronic rhinosinusitis, sepsis and diffuse pan-bronchiolitis [29,30]. Although azithromycin appears to be effective in modulating the immune system of acute respiratory patients, there is no evidence that the use of azithromycin in COVID-19 reduces cytokine storms. Antiviral effect: Although azithromycin has not yet been shown to have antiviral effects against COVID-19, it appears to be controversial regarding the use of azithromycin in patients with respiratory virus-induced pneumonia. For example, in a clinical trial in patients with influenza A, azithromycin in combination with osteltamivir was associated with an improvement in some influenza-related symptoms [29,31]. There are other observations of antiviral activity as well as limited evidence for the usefulness of azithromycin in viral infections like COVID-19 infection. Azithromycin commonly used in first day of the disease and the most common side effects of azithromycin are diarrhea, nausea, abdominal pain, and vomiting. Allergic reactions such as anaphylaxis, QT prolongation, or Clostridium difficile infection have been reported with azithromycin.

Dexamethasone

Dexamethasone is a type of corticosteroid. The mechanism of dexamethasone is mainly due to its anti-inflammatory and immunosuppressive effects. The anti-inflammatory effects are com- plex, but primarily through inhibition of inflammatory cells and suppression of expression of inflammatory mediators. It is intended for use in the treatment of inflammatory and immune diseases. Dexamethasone is usually given orally, as an intramuscular injection, or as an intra- venous injection, and the effect may last for up to a week [32]. Recently, this drug has been widely used in the treatment of COVID-19, which is recommended for patients who are in critical condition and need oxygen. Numerous articles have also cited evidence of dexamethasone performance in patients with COVID-19 who are in critical condition [33]. Horby et al. Also showed that among the 2104 patients receiving dexamethasone, lower mortality was reported than when they were routinely admitted [34]. The National Institutes of Health (NIH) in UK and the National Institutes of Health (NIH) in the US, the Infectious Diseases Society of America (IDSA), the European Medicines Agency (EMA) and World Health Organization (WHO) also recommend guidelines for severe cases. The most common side effects of dexamethasone are also gastritis, vomiting, headache, dizziness, insomnia, restlessness, depression, acne, irregular or absent menstrual periods [35].

Vitamin D

Vitamin D is a fat-soluble compound which exert plays great biological roles in human like: bone and teeth formation, calcium and phosphorus homeostasis, and more recent activity is the immune system modulation. This immune system effect of vitamin D on COVID-19 is very outstanding and supportive for the patients. In fact, vitamin D decreases the risk of respiratory infections and reduces the synthesis of inflammatory cytokines by modulating the immune system and preventing

the development of pneumonia [36]. The findings show that increasing levels of vitamin D increases protection against infections. An observational study reported that 38 ng/ml was appropriate for reducing the risk of acute viral respiratory infections [32]. It was explained that vitamin D supplementation improves the clinical conditions of patients with COVID-19 based on an increased serum vitamin D level, while serum vitamin D decreases with worse clinical development [37].

Zinc

Zinc is an essential trace mineral, and human body cannot make it by itself. But we get this mineral from various foods which can make our immune function stronger [38]. It shows that zinc has antiviral activity against viruses such as influenza and coronavirus also zinc can prevent coronavirus replication by inhibiting RNA synthesis [39,40]. Hence, now a days physicians prescribe zinc supplements to the COVID-19 positive patients, and it is also better to take zinc with other drugs during the early infection of the COVID-19 virus.

Limitations

Limitations of this review article include that many drugs are emerging quickly in market and pharmaceutical industry demanding them having antiviral actions for COVID-19 patients. So, if we consider all drugs in this single review then the article would be a very long one and complicated to compile in one article. Moreover, we believe that the side effects are unique, and they differ from patients to patients during treatment. Hence, there may be a good chance of having other unmentioned adverse effects in COVID-19 patients. We must keep in mind that, side effects of any drug totally depend on various factors like age of patients, disease status, dose and duration of the drugs used, and even mode of administration of drugs.

Conclusion

Characteristics of human body is totally mysterious and at the same time the adverse reactions of drugs used for COVID-19 treatment are also unique. In our review article, we had shown different prominent adverse effects associated with some COVID-19 drugs which can be a great helpful for physicians to prescribe an effective and safe drug for the specific patients depending on his/her status. Taken together, along with specific characteristics of drugs, their adverse effects should also be noticed to prevent serious problems for patients which leads to establish a better treatment plan and thereby savings of a patient life.

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Conflict of interest

There is no conflict of interest to declare.

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