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Review Article

Mechanism and adverse effects of COVID-19 drugs: a basic review

Nadia Mohammad Zadeh[1], Nazli Sadat Mashinchi Asl[2], Khatereh Forouharnejad[3], Keyvan Ghadimi[4], Sara Parsa[3], Sima Mohammadi[4], Ashkan Omidi[1]

[1]School of Medicine, Islamic Azad University Tehran Faculty of Medicine, Tehran, Iran; [2]Postdoc Associate, Texas Medical Center, Texas, USA; [3]School of Medicine, Islamic Azad University of Najafabad Branch, Isfahan, Iran; [4]School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

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Abstract: Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Coronavirus disease 2019 (COVID-19) is chronic, inflammatory. Although the exact mechanisms of COVID-19 have not been yet discovered some drugs are found helpful for its treatment. These drugs which are divided into some lines therapies, have demonstrated to be helpful for COVID-19 patients based on immune basic and its antiviral properties of the disease. Previous studies have been indicated that deterioration of COVID-19 condition is associated with a weaker immune system. Most of these therapies impact on the immune system and immune cells. Beside many beneficial effects of these drugs, some adverse effects (AE) have been reported in many experiments and clinical trials among patients suffering from COVID-19. In this review, we conclude some AEs of vitamin-D, zinc, remdesivir, hydroxychloroquine or chloroquine, azithromycin, dexamethasone, amantadine, aspirin reported in different papers and we continue the rest of the drugs in second part of our review article.

Keywords: Mechanism, adverse effect, COVID-19, drugs

Introduction

COVID-19 is an infectious disease caused by SARS-CoV-2, the coronavirus that was discovered in December 2019 and has caused a huge pandemic in the world. The disease is spread primarily through inhaled drops when coughing, sneezing, or talking to infected people [1-4]. In addition, infection may occur by touching an infected surface as a result of contact with the face [4-6]. SARS-CoV-2 is a positive, single-stranded RNA virus (~30 KB in length) with an nucleocapsid, which undergoes endocytosis or membrane fusion to enter infected cells and can cause respiratory and intestinal diseases, liver and nerve in different species, including humans and some animals [7]. SARS-CoV-2 contains spike (S) glycoproteins, which are composed of two functional subunits called S1 protein, which binds to the host cell receptor and S2 protein, which fuses viral and cell membranes [3]. Angiotensin II converting receptor (ACE2) is known as a functional receptor for SARS-CoV-2 entry into cells [8-10], and ACE2 expression is high in lung, heart, ileum, kidney and bladder [11]. So far, many efforts have been made to develop a vaccine, but at this time, there are some specific vaccine or treatment for COVID-19, and the elderly with underlying diseases are at higher risk for severe disease [12]. Therefore, the important information for most people is to know how they can boost their immune system to prevent SARS-CoV-2 infection or control the severity of disease progression. There is a lot of research around the world every day trying to find an effective drug that shows promising results in preventing or treating and controlling COVID-19. Some drugs are found helpful for the treatment of COVID-19. Here, we try to investigate some of them include vitamin-D, zinc, remdesivir, hydroxychloroquine and chloroquine, azithromycin, dexamethasone, amantadine, aspirin. Besides the clinical efficacy of these drugs, there have been some adverse effects (AE) reported in experimental studies and clinical trials. For the first

time, to the best of our knowledge, in this review article, we aimed to briefly describe mechanisms of actions of these drugs and then conclude the AE of them. It should also be explained that this systematic review over these drugs was done using PubMed and Google Scholar research engine and searching for different clinical trials and review articles all around the world. That would be a very long review article if we wanted to bring all these drug complications in only one article.

Vitamin D

Vitamin D is a group of fat-soluble steroids that are the most common forms of vitamin D supplementation: colecalciferol (vitamin D3) and ergocalciferol (vitamin D2), precursors 1,25 (OH) 2D3 (active form of vitamin D) [13-17]. Vitamin D plays important (classical) biological roles including bone metabolism, calcium and phosphorus homeostasis, and more recently (non-classical) roles including immune system modulation, lung and muscle function, cardiovascular health, and infection prevention Has been. There have been many recent reports of a positive effect of vitamin D on COVID-19. In fact, vitamin D reduces the risk of respiratory infections through three main mechanisms: maintaining tight connections to prevent immune cells from penetrating the lungs and other respiratory tissues, killing some viruses by stimulating antiviral mechanisms, and Reducing the synthesis of pro-inflammatory cytokines by modulating the immune system and preventing the development of pneumonia [18]. The findings show that increasing levels of vitamin D increases protection against infections, but this relationship has not yet been fully established. However, an observational study reported that 38 ng/ml was appropriate for reducing the risk of acute viral respiratory infections [19]. On the other hand, some authors suggest that serum vitamin D levels be maintained at least 30 ng/ml, or even to reduce infectious processes, between 40 and 60 ng/ml. In addition, Alipio et al. has recently provided significant information to physicians and health policymakers. In particular, it was concluded that vitamin D supplementation improves the clinical course of patients with COVID-19 based on an increased likelihood of having a mild outcome when serum vitamin D levels increase while serum vitamin D decreases with worse clinical development [20]. The same recommendation was reinforced by Grant et al., Who suggested that vitamin D supplementation could reduce the risk of COVID-19 infection [19]. Griffin et al. have recommended vitamin D supplementation, at least for those in the Northern Hemisphere who are at higher risk for severe disease and death [21]. Vitamin D is taken orally and in shots. Vitamin D may be unsafe for long periods of time in doses above 4,000 units (100 micrograms) per day and may cause very high levels of calcium in the blood and can cause side effects. Have their own. For example: includes weakness, fatigue, drowsiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting and more. Also, taking vitamin D in people with underlying diseases such as atherosclerosis in this case, taking vitamin D can make the situation worse, especially in people with renal failure. In histoplasmosis, a fungal infection, vitamin D may increase calcium levels in people with histoplasmosis. This can lead to kidney stones and other problems. In patients with the hyperparathyroidism, vitamin D may increase calcium levels in people with hyperparathyroidism. Vitamin D may also increase calcium levels in people with lymphoma. This can lead to kidney stones and other problems. Vitamin D, on the other hand, may increase calcium levels and increase the risk of “atherosclerosis” in people with severe kidney disease. This should be balanced with the need to prevent osteodystrophy of the kidneys, and calcium levels should be carefully monitored in people with kidney disease. Vitamin D may increase calcium levels in people with sarcoidosis. This can lead to kidney stones and other problems. It has also been reported that the side effects of high doses of vitamin D are greater in women than men. Recently, high resolution peripheral quantitative computed tomography (HR-pQCT) has been used to evaluate bone mineral density (BMD) changes and volume strength associated with 3 years of high-dose vitamin D supplementation [22]. In this study of healthy male and female participants who were initially deficient in vitamin D, it was found that higher doses of vitamin D supplementation (4000 IU or 10,000 IU daily) were associated with a further reduction in BMD. Although the gender difference in bone response to vitamin D supplementation was not a predetermined result of this study, it is unclear whether there is a difference in bone response to high-dose vitamin D supplementation between men and women.

Zinc

Zinc is an essential mineral that the body cannot produce on its own. Zinc has effect on some parts of the body such as immune function [23, 24], protein synthesis, wound healing, DNA synthesis, and cell division [24-26]. It appears that zinc have antiviral effects against viruses such as influenza and coronavirus due to the increasing of immune system function and also zinc can prevent coronavirus replication by inhibiting RNA synthesis [27, 28]. Therefore, we assume that due to its antiviral properties of zinc, it can protect the body against coronavirus, and it is also better to consider taking this drug in the early days of the virus or before. It is also mentioned in works such as its antiviral property against COVID-19 [29-31]. The most common side effects of zinc which is usually due to its high dose can be referred to as headache, nausea and vomiting.

Remdesivir

Remedsivir 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 coronavirus family (including coronavirus Mers and SARS) [32]. This drug has been successful in the treatment of Quid 19 in many cases and is also being studied and researched a lot [32]. Remdesivir is a precursor that is actively converted 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 [32]. 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 [33]. Reported side effects include gastrointestinal upset, increased levels of transaminases in the blood (liver enzymes), and injection site reaction [34]. 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 [34]. 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 [34].

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 [35, 36]. Various side effects of CQ/HCQ have been reported, including cardiac side effects, neurological 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 atrioventricular block, QT prolongation and subsequent cardiac torsion) and cardiomyopathy (hypertrophy and congestive heart failure). Neurological side effects include muscle weakness, 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 [37].

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, 38, 39]. 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 intracellular protein kinase (MAPK), especially extracellular signal-controlled kinases 1/2 (ERK1/2) and the NF-κB pathway downstream of ERK [40]. 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 rhino-sinusitis, sepsis and diffuse pan-bronchiolitis [40, 41]. 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 [40, 42]. There are other observations of antiviral activity as well as limited evidence for the usefulness of azithromycin in viral infections similar to 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 complex, 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 intravenous injection, and the effect may last for up to a week [48]. Recently, this drug has been widely used in the treatment of COVID-19, which is actually 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 [44]. Horby et al. Also showed that among the 2104 patients receiving dexamethasone, lower mortality was reported than when they were routinely admitted [45]. 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 [46].

Amantadine

Amantadine is an antiviral drug prescribed to treat influenza A. The mechanism of action of the drug is such that in the early stages when the virus enters the cells. It is not yet known whether this drug may work for COVID-19 [47, 48]. However, due to its antiviral properties, we assume that it can reduce the symptoms of coronavirus. In fact, amantadine blocks the COVID-19 viral purine channel and prevents the release of the viral nucleus into the cell cytoplasm [47]. There are also some papers that indicate amantadine can improve the effects of

COVID-19 and most of them talked about antiviral of it [49-51]. It is also good to prescribe this drug in the early days of infection with the virus. The most common side effects of Amantadine are also Neurological like drowsiness (especially while driving), light headedness, falls, and dizziness; Cardiovascular like orthostatic hypotension, syncope, and peripheral edema; Gastrointestinal like dry mouth and constipation; Skin problems; have been reported with Amantadine [52].

Acetylsalicylic acid (ASA) or aspirin

Aspirin, also known as acetylsalicylic acid (ASA), is a drug used to reduce pain, fever, or inflammation. Acetylsalicylic acid (ASA) inhibits prostaglandin synthesis. It is not selective for COX-1 and COX-2 enzymes. Inhibition of COX-1 leads to inhibition of platelet aggregation. Recently, some articles have suggested that aspirin is useful for patients, which can help improve patients. Because one of the leading causes of death from COVID-19 is cardiovascular problems and pulmonary embolism. Diffuse alveolar hemorrhage [53] reported as a common finding of lung pathology in COVID-19 patients raises safety concerns about the use of antiplatelet therapy in life-threatening bleeding complications among patients infected with COVID-19 has increased [54]. The association between Non-steroidal anti-inflammatory drugs (NSAIDs) and respiratory and cardiovascular side effects leads to recommendations to prevent the use of aspirin and NSAIDs [55]. In addition, Kwiatkowski et al. works showed that pregnant women during the COVID-19 pandemic should not stop taking aspirin [56, 57]. Aspirin common side effects such as cramping, nausea, bleeding, upset stomach, abdominal pain. Recently, the side effect of its use in COVID-19 patients has been controversial, as the drug irreversibly inhibits platelet cyclooxygenase, and its effect continues for life on circulating platelets (7-10 days). There has been some concern that the delay between a positive SARS-CoV-2 test and its clinical deterioration is similar to the delay between the last aspirin dose and the end of its clinical effect [58].

Conclusion

There are some drug reported that can be helpful for COVID-10, different kinds of drugs are used to improve the disease. Each of these drugs has its own efficacy and indication of usage but the important issue is that some patients confront different AEs during treatments. In this review article, we had a survey on different AEs associated with some COVID-19 drugs which can be a great helpful when choosing a drug. Taken together, along with specific characteristics of drugs, their AEs should also be noticed in order to prevent serious problems for patients.

Disclosure of conflict of interest

None.

Address correspondence to: Ashkan Omidi, School of Medicine, Islamic Azad University Tehran Faculty of Medicine, Tehran, Iran. Tel: +1 (979) 627-1020; E-mail: ash_omd@yahoo.com

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