Original Article

Safety Concerns Of Drugs And Vaccines Used In The Treatment Of COVID-19

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Abstract

The Novel Coronavirus disease 2019 pandemic which is named as COVID-19 or '2019 n CoV ' or 2019 novel coronavirus by WHO is a highly contagious viral respiratory disease caused due to SARS- CoV-2. Various drugs used to treat this pandemic are Hydroxychloroquine, Remdesivir, Favipiravir, Dexamethasone, etc. These drugs are effective, but they have also shown adverse drug reactions (ADRs) during the treatment of COVID-19 and when an ADR arises due to their use, they add an additional level of complexity in the management of COVID-19 disease. This review aims to demonstrate the mechanism of action as well as the safety issues associated with the drugs used for COVID-19. It also focuses on the safety issues related with two vaccines manufactured by Pfizer and AstraZeneca, respectively. A comprehensive search in PubMed, Science direct, Drug bank, PubChem, CDC, WHO, FDA database was accomplished for research regarding ADR case reports associated with the drugs and vaccines for COVID-19.

Keywords. Adverse drug reaction; COVID-19; Coronavirus; Case reports; Vaccines

INTRODUCTION

Coronavirus disease (COVID-19) is a viral infectious disease that mainly affects the respiratory system by the causative agent SARS-CoV-2 [1]. After MERS-CoV and SARS-CoV-1, SARS-CoV-2 belongs to the coronavirus category as the 7th member that infects people and is a group 2B beta coronavirus with a a genetic sequence with similarity of over 70% to SARS-CoV-1 [2,3]. Coronavirus (COVID-19) is mainly found in human and animals and belongs to the family of Coronaviridae [4,5].

Coronavirus is transmitted when an infected person sneezes, coughs, talks, and comes into contact with a healthy person [6]. The current diagnostic test for COVID-19 includes the RT-PCR test, negative ultrasound imaging, Chest CT scans, chest radiograph diagnosis [7]. WHO has given recommendations for the prevention of COVID-19, such as avoiding close contact with the COVID-19 infected person, wash hands regularly, avoid unprotected contact with farm or wild animals, the infected person should maintain distance from a healthy person, and people having a weak immune system should avoid public gatherings [8]. The incubation time of the new coronavirus for 2019 is right now comprehended and be between 2 to 14 days and its sign and symptoms are depicted in Fig. 1 [9,10].

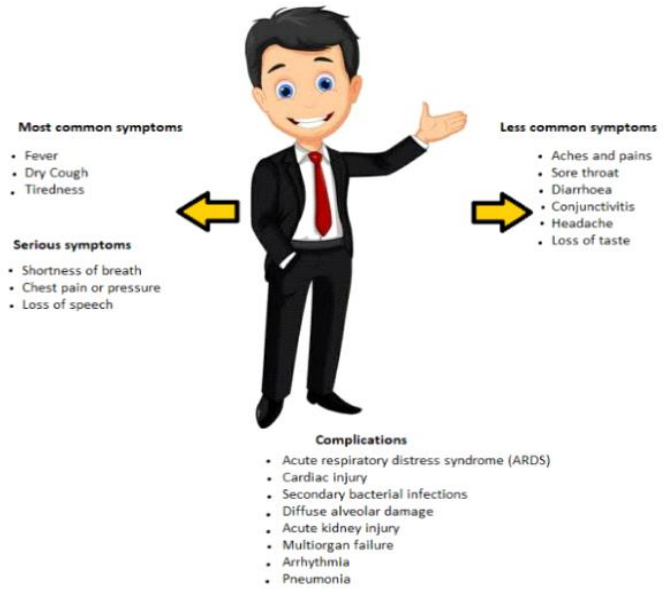

FIGURE 1. Sign and symptoms related to COVID-19

Some of the important dates related to development of COVID-19 are as follows [8,11].
31 December 2019: Chinese authorities gave information to WHO related to pneumonia cases identified in Wuhan city.
7 January 2020: The novel coronavirus was first identified.
30th January 2020: WHO Director-General announces the 2019-novel coronavirus flare-up public health emergency.
11 February 2020: WHO gives the official name COVID-19 to the new coronavirus.
11 March 2020: The WHO Director-General announced the COVID-19 outbreak as a pandemic.
Till 29 September 2021: The worldwide total cases of COVID-19 ~232 million; Total death ~4.75 million.

Although there is no specific drug for the treatment of COVID disease, certain drugs are being tried like Hydroxychloroquine, Remdesivir, Favipiravir, and Dexamethasone. In spite of offering benefits, they have also been associated with toxicity/adverse drug reactions. An Adverse Drug Reaction is any kind of undesired or unacceptable effect due to the drug that can take place at doses generally utilized in persons and it requires either reduction or discontinuation of the drugs. So, our review has compiled the ADR's detected after a detailed study of these drugs by using published data of Google Scholar, Pubmed, Science Direct, Drug Bank, and WHO. Currently, two major vaccines, one of Pfizer and the other of Astrazeneca, have also been launched on the market so we have also tried to throw an insight into their safety issues.

DRUGS FOR THE MANAGEMENT OF COVID-19

Hydroxychloroquine

Hydroxychloroquine sulphate (HCQS) is derived from 4- aminoquinoline, which shows immunosuppressive and antimalarial activities. In addition to working against malaria, this drug is also proclaimed to show anti-inflammatory, antiviral effects and also exert therapeutic effects on the prophylaxis of many chronic diseases such as rheumatoid arthritis and systemic lupus erythematosus [12,13]. Because hydroxychloroquine is highly hydrophilic, less harmful and fewer adverse effects have been reported compared to chloroquine. It is an inexpensive, readily accessible and comparatively safer drug.

In vitro studies have demonstrated that HCQS can impede the entry of virus dissemination and replication of viruses [14,15]. The mode of action involves enhancing the pH of cell endosomes to prevent virus entry into the cell [16,17]. It also obstructs the glycosylation of ACE-2 virus membrane receptors thus prevents the binding of SARS-CoV-2 to the ACE-2 receptor [18,19]. Furthermore, HCQS has also shown an immunomodulatory effect and has reduced inflammation by controlling the release thus obstructing harm to any organ [20]. Furthermore, HCQS is efficacious in later phases of COVID-19 by suppressing the hyper-active immune system and improving tissue repair mechanisms [21]. Despite its effectiveness, HCQS alone has been found to be associated with QT interval prolongation, thus causing a risk of arrhythmias. In a cohort study, it was found that HCQS if administered in conjunction with Azithromycin to COVID positive patients has a tendency to enormously prolong the QT interval [22]. In addition to arrhythmias, published data from sources in the literature have shown certain other uncommon adverse effects of this drug, which are listed in the table 1 below.

TABLE 1. Safety Concerns of Hydroxychloroquine sulphate

S. No.	Drug	ADR detected	Evidence	Case report details	Remarks
1	Hydroxychloroquine	Hemolytic anemia	Case report [23]	**Age-** 51 year **Gender-** Male **Dose-** 400 mg **COVID-19 Test Positive** **Co-morbidities:** Type-2 Diabetes, hypertension, morbid obesity **Other medications: -**levofloxacin for pneumonia	Drug was discontinued Patient status-Recovered
2	Hydroxychloroquine	Steven Johnson Syndrome	Case report [24]	**Age-** 42 years **Gender**-Female **COVID-19 Test Positive** **Dose-** 200 mg **Other Medication:** Acetaminophen for COVID-19	Drug was discontinued Patient status-Recovered
3	Hydroxychloroquine	Toxic epidermal necrolysis	Case Report [25]	**Age-** 78 years **Gender- Female** **Co-morbidities: Cardiometabolic syndrome** **COVID-19 Test Positive** **Other Medications: -** Antibiotics, dexamethasone, paracetamol, heparin for COVID-19.	Drug was discontinued Patient status-Recovered
4	Hydroxychloroquine	Hepatotoxicity	Case Report [26]	**Age-** 29 year **Gender-** Female **COVID-19 Test-** Positive **Dose-** 400 mg **Medications for co-morbidities: -** Azithromycin, Piperacillin-tazobactam for COVID-19	Drug was discontinued Patient status-Recovered

Remdesivir

Remdesivir is a monophosphoramidate precursor of an adenosine derivative [27], that exhibit antiviral properties against the viruses, by targeting and preventing the replication and growth of a wide spectrum of pathogen viruses such as Ebola virus, MERS-CoV, and SARS-CoV-2 [28] and other coronaviruses such as CoV-OC43, CoV-229E, and PDCoV [29].

On 1 May 2020, FDA declared emergency use authorization for remdesivir treatment in serious cases of coronavirus disease even when there was no approved indication and results of large clinical trials [30]. When Remdesivir enters the respiratory cell, it is rapidly converted by metabolism to monophosphate and is then transformed to an active triphosphate form [31]. The structure of this active triphosphate form of remdesivir is similar to that of adenosine triphosphate (ATP), i.e., a natural substrate important in of synthesizing the RNA. This active form competes with ATP by inhibiting the RNA-dependent RNA polymerase (RdRp) and gets incorporated into the developing RNA strand. Thus, it causes an interruption in the virus replicating process [32]. Additionally, the exoribonuclease of the virus that is normally utilized in the proofreading and correction of the replication error cannot show activity against the active triphosphate form of remdesivir [33].

As per the USFDA, remdesivir shows an interaction with chloroquine phosphate and hydroxychloroquine sulfate so, both drugs cannot be administered together because it results in reducing the antiviral activity of remdesivir [34]. On 20 November 2020, WHO suspended remdesivir from its medication list and also warned against remdesivir treatment, as it affords no benefit in prolonging the survival of COVID-19 patient [35].

Case report studies collected from the reputed journals about the ADRs of Remdesivir are depicted in the table 2 below.

TABLE 2. Safety concerns of Remdesivir used in COVID-19 positive patients

S. No.	Drug	ADR detected	Evidence	Case report details	Remarks
1.	Remdesiver	Liver toxicity	Case Report [36]	**Age-** 64 year**;** **Gender-** Male **Co-morbidities**: hypertension and hypercholesterolemia **Medications for Co-morbidities -**Enalapril, amlodipine, and simvastatin used for hypertension and hypercholesterolemia	The drug was discontinued Patient Status-Recovered
2.	Remdesiver	SDRIFE	Case report [37]	**Age**-67 year; **Gender-** Male **Other medication-**Sufentanil, propofol, norepinephrine, pantoprazole, macrogol, metoclopramide, enoxaparin	The drug was discontinued patient, treated with systemic gluco-corticoids Status-Recovered
3.	Remdesiver	Bradycardia (prolonged QT interval)	Case series [38]	**Patient: 1** **Age-**26 year **Gender-**Female **Other Medications-**Ceftriaxone, azithromycin, methylprednisolone **Patient: 2** **Age-**77 year **Gender-**Female **Other Medications-**Ceftriaxone, azithromycin, methylprednisolone	The drug was discontinued Patient Status-Recovered
4.	Remdesiver	Maculopapular rash as well as alanine transaminase Elevation	Case series [39]	**Patient: 1** **Age-**31 year **Gender-** Male **Patient: 2** **Age-**39 year **Gender-** Male **Co-morbidities-**Obese patient with obstructive sleep apnoea syndrome.	The drug was discontinued Patient Status-Recovered
5.	Remdesiver	Multiple organ failure	Case series [39]	**Patient: 1** **Age-**70 year **Gender-** Male **Co-morbidities -** Thyroid Cancer and chronic obstructive pulmonary disease **Patient: 2** **Age-** 70 year **Gender-** Male **Other Medications** - NSAID for renal lithiasis & Dexamethasone, lopinavir/ritonavir	The drug was discontinued Patient Status-Died

Favipiravir

Favipiravir is a manmade prodrug that is formed by synthetic alteration of the pyrazine moiety of T-1105 (non-fluorinated analog of favipiravir [40], having a wide range antiviral property against RNA viruses of many virus families and developed in Japan in 2002 [41]. DCGI (Drugs Controller General of India) has approved favipiravir for the management of mild and moderate cases of coronavirus diseases throughout India and is also known by the name "Avigan" [42]. Favipiravir is also used as a prophylactic for infections by hazardous microorganisms, i.e., Ebola virus, Lassa virus, and now SARS-CoV-2 virus. When Favipiravir enters inside the cell, it undergoes phosphorylation and ribosylation and is then transformed into the active metabolite Favipiravir ribofuranosyl-5′-triphosphate [43]. Favipiravir-RTP selectively and effectively inhibits the RNA dependent RNA polymerase (RdRP) by competing with the purines, then getting incorporated in place of adenine and guanine (purine bases) into the viral RNA strand [44,45]. Moreover, while the active form of Favipiravir binds to RNA polymerase, it results in deadly mutations, therefore stopping the integration of nucleotides for virus RNA replication and transcription [46,47].

Favipiravir shows interaction with pyrazinamide as it was found that when these two drugs are administered together, it can increase the level of uric acid. This is evident from the case reports of acute gouty arthritis in the COVID-19 patient suffering from hyperlipidemia and hyperuricemia. Favipiravir can inhibit the metabolism of Repaglinide by blocking the CYP2C8 pathway, thus, it can enhance the

toxicity of antidiabetic drug Repaglinide, so the combination needs to be monitored [48]. Theophylline, a bronchodilator when administered along with Favipravir can increase the latter toxicity. Case report of favipiravir from the published literature due to the use of the favipiravir as depicted in table 3.

TABLE 3. Case report of Favipiravir

S No.	Drug	ADR detected	Evidence	Case report Details	Remarks
1.	Favipiravir	Acute gouty arthritis	Case report [49]	**Age-** 42years **Gender-** Male **COVID-19 Test-**Positive **Dose-** 1,800 mg BD on 1st day and 800 mg BD thereafter **Co-morbidities**: Type-2 diabetes, hyperlipidemia, hyperuricemia, gout attack **Medications for Co-morbidities-**Alogliptin benzoate, luseogliflozin, rosuvastatin, and febuxostat	The drug was discontinued and NSAIDs were given for the treatment of gouty arthritis. Patient Status-Recovered
2.	Favipiravir	Fever	Case report [50]	**Age-** 82years **Gender-** Male **COVID-19 Test-** positive **Dose-** 1,600mg BD on 1st day and 800mg BD on 2nd day. **Comorbidities-** hypertension, colon cancer, and cerebral infarction. **Medications for Comorbidities-** Aspirin, Amlodipine, Lansoprazole, and Levetiracetam. **Other Medications:** Clarithromycin, Ampicillin - sulbactum, Azithromycin	The drug was discontinued Patient status-Recovered

Clinical trials conducted on Favipravir has shown an elevation in blood uric acid level as represented in table 4 [51].

TABLE 4. Clinical trial of Favipiravir

S. No	Drug	ADR	Evidence	Participant Details	Remarks
1.	Favipiravir	Elevation in blood uric acid level	Clinical trial [51]	Total no: 8 male/female Case detected: 7 participants Increase range: 4.4mg/dL	After discontinuation of the drug, patients got recovered.

Dexamethasone

Dexamethasone is an effective, prolonged-release extremely selective corticosteroid utilized in numerous conditions due to its anti-inflammatory and immunosuppressive activities [52]. It is a well-known synthetic lifegiving medication and broadly used for treating various disorders such as rheumatic disorders, skin infection, asthma, many kinds of allergies, mind inflammation, and bronchospasm [53]. Dexamethasone serves as a glucocorticoid antagonist. When a glucocorticoid bind with the corticoid receptor, it goes under the conformational change that allows its migration to the nucleus and initiates the transcription of specific mRNA leading to the formation of proteinaceous substances like cytokines [53,54]. Dexamethasone, being lipophilic has the potential to cross the cell membrane and block these corticoid receptors and interfere with the production of cytokines like IL-1, IL-2, IL-6, IL-8, TNF, and IFN-gamma. All these five cytokines are associated with increased severity of COVID-19 disease [54,55]. It was found that the patients with serious symptoms of COVID have undergone a severe inflammatory response, whose characteristics were identical to a rare hematological disorder called haemophagocytic lymphohistiocytosis. Dexamethasone controls the state by its immunosuppressive mechanism [56].

The common implications of Dexamethasone therapy include hyperglycaemiaa, infections, bacteremia, psychiatric effects, myocardial infections, hypertension, etc. [57,58]. Clinical trials demonstrating the use of Dexamethasone for COVID-19 patients have also shown the same results in the participants as depicted in table 5. If Dexamethasone is taken with Nicorandil and steroidal anti-inflammatory drugs, then it may enhance the risk of peptic and gastrointestinal ulceration [59].

On studying the published literature, we came across the certain adverse effect of Dexamethasone found in clinical trials, as mentioned in the table 5 below:

TABLE 5. Clinical trials of Dexamethasone

S. No.	Drug	ADR with affected patients	Evidence	Participant details
1.	Dexamethasone	1)Hyperglycemia 2) new infections 3)Bacteremia	Clinical trial in Brazil [60]	**1**.Total no:151 Case detected:47 participants **2.** Total no:151 Case detected:33 participants **3.** Total no:151 Case detected:12 participants
2.	Dexamethasone	1. Hyperglycemia 2. new infections (e.g., pneumonia or sepsis and barotrauma)	Clinical trial in Spain [61]	**1**. Total no:139 Case detected: 105 participants **2.** Total no:139 Case detected: 33 participants for pneumonia 10 participants for barotrauma

VACCINES FOR MANAGEMENT OF COVID-19

We have reviewed two coronavirus vaccines from the literature survey. The first one is AstraZeneca COVID-19 vaccine and the other one is Pfizer BioNTech COVID-19 vaccine and the other. Both these vaccines have been developed targeting the spike proteins of SARS-CoV-2. The working of a coronavirus vaccine is described in Fig.2.

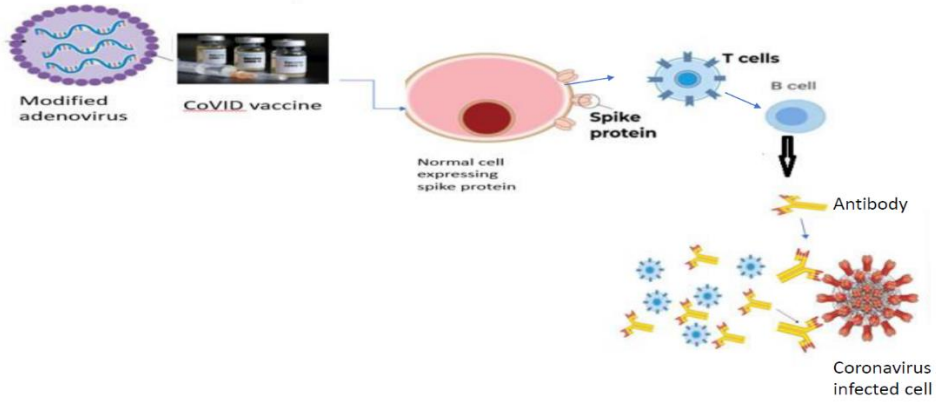

FIGURE 2. Working of Coronavirus Vaccine

In the development of Astrazeneca vaccine, scientists modified the genome of a chimpanzee's adenovirus by adding a gene of a coronavirus spike protein so that it can enter into the cells but does not allow replication. Adenovirus, being a foreign particle is able to stimulate the immune cells, mounting a strong immune response. Also, when vaccinated cell dies, the debris contains the protein fragments that is taken by antigen presenting cells that presents these fragments to the T-helper cell and help to combat the infection. These helper T cells can further activate B cells and cytotoxic T-cells. The stimulated B cells produce antibodies targeting the spike protein. They get bind onto the coronavirus spikes and mark them for destruction and also prevent infection by blocking spikes attaching to other cells. The activated cytotoxic T lymphocytes can destroy any coronavirus infected cells that displays spike proteins on their surface [62]. Safety and efficacy were tested in the blinded controlled trails held in Brazil, South Africa and United Kingdom. Two doses 28 days apart, with first dose as half of the strength of the second was able to show 90 percent efficacy [63]. UK authorized emergency use of vaccine from 3rd Jan 2021 onwards. The vaccine requires a temperature of 38 to 46°F i.e. 2-8°C to prevent its degradation [62].

BioNTech, a German company had partnered with Pfizer to develop and test Pfizer-BioNTech coronavirus vaccine and its clinical trials had shown the vaccine has efficacy rate of 95 percent in preventing CoVID-19 when given two doses of same strength 21 days apart. The vaccine uses mRNA, the genetic material that allows the cells to form proteins. This mRNA is wrapped up in oily bubbles made up of lipid nanoparticles to prevent its degradation by the natural enzymes of the human body. The cells build the spike proteins that get sticked on the tips of the cells. In response to these proteins, the immune pathways get stimulated. One of the major disadvantages with Pfizer vaccine is that it needs a temperature of -70°F [64].

Adverse events of COVID-19 Vaccine

The COVID-19 vaccine by Pfizer BioNTech was found to produced pain at the administration site. However, not showing any oedema or inflammation [65]. Rare events reports were fatigue & headache in 2-4% patients. Older adults tend to report fewer adverse events following vaccination. In people receiving AstraZeneca COVID-19 vaccine, insignificant pain was observed at the site of injection and the symptoms of fever, fatigue and headache were found to be reduced with increasing age, viz., 86% patients in the age group of 18-55 years; 77% in the age of 56-69% and 65% in the age group of 70 and above [66]. In younger persons, mild pyrexia was reported in first 2 days of vaccine administration, which can be treated by taking a dose of paracetamol [67].

Reporting anaphylaxis & other allergic reactions and their management

Any vaccine has a potential to elicit anaphylactic reaction. So, any such case should be immediately notified to MHRA through the Yellow Card Scheme for Coronavirus in UK [68]. In India, similar cases can be reported via. "Serious AEFI Case notification Form-ADR Monitoring centre" form [69]. In the present scenario, there is less evidence that can aid the usage of COVID-19 vaccines as a preventive measure or to block COVID-19 transmission. So, a supervision becomes mandatory in the community which can be achieved with the help of local health safety teams.

CONCLUSION

A detailed review was conducted to study the drugs used for managing the theCOVID-19 disease. Various case reports were researched using published data. The findings were that Hydroxychloroquine has shown ADRs such as; haemolytic anaemia, Steven Johnson syndrome, toxic epidermal necrolysis, hepatotoxicity, QT interval prolongation in some of the COVID-19 treated patients. Similarly, Remdesivir has shown adverse effects like; liver toxicity, intertriginous, and flexural exanthema related to symmetric drugs (SDRIFE), bradycardia and prolonged QT interval, maculopapular rash &elevation, multiple organ failure, etc. Favipiravir has shown undesirable effects such as acute gouty arthritis and fever, so it should be contraindicated in patients suffering from high uric acid level. The use of Dexamethasone has been associated with hyperglycemia, infections like pneumonia, barotrauma, bacteremia, etc., so it should be avoided in patients of diabetes. It can be concluded that the monitoring of SARS-CoV-2 patients receiving these drugs is essential for achieving the optimum treatment. The article also looked at the adverse events encountered while using the Pfizer BioNTech COVID-19 vaccine and the AstraZeneca COVID-19 vaccine, and it was found that its use in vulnerable patients must be discussed with local health teams.

ABBREVIATIONS

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2;
MERS-CoV: Middle East respiratory syndrome;
SDRIFE: Symmetrical drug-related intertriginous and flexural exanthema

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