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Review Article

Clinical Adverse Effects Associated with Some COVID-19 Medications Used During the First Wave of COVID-19 Pandemic

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ABSTRACT

Numerous drugs have been repurposed to effectively tackle the COVID-19 pandemic as scientists and pharmaceutical firms compete to produce vaccines and antivirals without dwelling on the toxicity aspects. This paper explores the toxicity of several major medications used in the treatment of patients with COVID-19. Relevant literature from PubMed and Google scholar were reviewed. Several toxicities such as hepatic function disorder, damage to organs, Muscle problems, skin rash, seizures, lack of appetite, vision problems, low levels of blood cells, diarrhea, hyperkalemia renal damage, and other adverse reaction were found to be associated with drugs use for COVID-19 pandemic. The current race to produce therapeutics and vaccines must be advance with caution to avoid future consequences.

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INTRODUCTION

There has been an unparalleled expedited path taken by the world community to produce efficient and secure therapeutics and vaccines. The application of "Fast tract" and "short cuts" without exploring toxicity issues can lead to errors with devastating consequences [1]. As we are witnessing progress in winning the battle against the COVID-19 pandemic, many pharmacologic agents have now been used internationally to handle the pandemic, mainly repurposed [2] to combat the causative virus, the SARS-CoV-2. To treat COVID-19, clinicians need to be sensitive to the toxicity of a wide range of potentially unfamiliar compounds being studied or repurposed [3]. Drug toxicity describes the level of harm that an organism may be caused by a pharmacologically active agent, which is often dose-dependent and can affect the whole system [4]. Drug toxicity causes can be categorized in many ways which can include (on-target) mechanism-based toxicity, immune hypersensitivity, off-target toxicity, which bioactivation/covalent alteration [5]. This paper aims to discuss the toxicity of some of the current therapeutics used in the management of COVID-19.

Chloroquine and hydroxychloroquine: Mechanism of action and toxicity

Discover back in 1934, chloroquine and hydroxychloroquine (fig 1) have long been used in the prevention and treatment of malaria, chronic inflammatory diseases, and rheumatoid arthritis [6]. By inhibiting host receptor glycosylation, proteolytic processing, and endosomal acidification, chloroquine and hydroxychloroquine tend to block viral entry into cells [7]. The mechanism of action of this drug includes interacting with viral particles binding to their cellular cell surface receptor8, interacting with enveloped viruses such as Chikungunya virus or Dengue virus' pH-dependent endosome-mediated viral entry [9-11], interfering with the post-translational modification of viral proteins such as glycosylation [12] and controlling cell signaling and pro-inflammatory cytokines [13].

Although in vitro study showed that hydroxychloroquine (EC50=0.72 μM) was more potent than chloroquine (EC50=5.47 μM) against SARS-CoV-2[14], the acute toxicity of both chloroquine and hydroxychloroquine is believed to be the result

of direct cardiovascular effects resulting in dysrhythmias of electrolyte alterations, often associated with significant morbidity and mortality[15].The American Heart Association has identified chloroquine and hydroxychloroquine as agents that can cause direct myocardial toxicity. Uncommon and severe adverse effects [< 10 percent] caused by both chloroquine and hydroxychloroquine, including hypoglycemia, retinopathy, neuropsychiatric effects, and QTc prolongation [7,16]. The ability of aminoquinoline to block myocardial sodium and potassium channels is the most acutely lethal toxicity [17]. Severe side effects include damage to organs, muscle problems, skin rash, seizures, lack of appetite, vision problems, low levels of blood cells, and diarrhea [18]. Many of the above signs of toxicity caused by chloroquine and hydroxychloroquine such as serum anomalies, respiratory, cardiac, and neurological required emergency [15].

Lopinavir and ritonavir: anti-viral and metabolic adverse reactions

Lopinavir is a protease inhibitor against HIV-1 combined with ritonavir to increases its plasma half-life [19]. Molecular interactions between lopinavir and SARS-CoV-1 indicate that Lopinavir is a strong inhibitor of SARS-CoV-1 proteases.20, highly conserved in SARS-CoV-2[21]. Lopinavir has been shown to inhibit SARS-CoV-1, SARS-CoV-2, and coronavirus Middle East Respiratory Syndrome (MERS) in vitro [22-25]. Out of 416 HIV-infected patients evaluated, the study reported the 77 patients discontinued the use of Lopinavir and ritonavir following effects such as an increase of aspartate aminotransferase (AST)/alanine aminotransferase (ALT), gastrointestinal symptoms, and hyperlipidemia [26]. In around 20 to 30 percent of COVID-19 patients, elevated transaminase levels have been observed, suggesting that these adverse effects may be aggravated by combination therapy or viral infection [27]. A COVID-19 study found that approximately 50 percent of hospitalized patients treated with lopinavir/ritonavir had adverse reactions and 14% of patients stopped treatment due to gastrointestinal adverse reactions [28]. In a HIV-infected pregnant woman, lopinavir toxicity has also been documented with non-linear pharmacokinetics, increased activity of CYP3A, and genetic polymorphism in the CYP3A4 gene encoding a non-functional protein [29]. A patient was said to have developed an adverse skin reaction due to the toxicity of carbamazepine caused by lopinavir/ritonavir through inhibition of CYP3A4, the enzyme that metabolizes carbamazepine.30 Proteases inhibitors must be used with caution as It is well-known that protease inhibitors induce metabolic dysfunction, which can in turn increase the complications of HIV, including neurocognitive disorders associated with HIV [31].

Nafamostat and camostat: Clinical Adverse effects

Both Nafamostat and camostat are synthetic protease inhibitors. Nafamostat mesylate is a short-acting anticoagulant, authorized in Japan for the treatment of acute pancreatitis, intravascular circulated coagulation, and extracorporeal circulation anticoagulation [32,33]. In vitro, Nafamostat was found to block MERS-CoV infection, and this trend is likely to be extrapolated to other viruses that depend on TMPRSS2 activity [34]. Camostat mesylate is a synthetic proteolytic enzyme inhibitor for kallikrein, thrombin, plasmin, trypsin, and tissue kallikrein [33]. Recent evidence indicates that camostat mesylate is active against TMPRSS2, a transmembrane enzyme activating S protein [35]. Nafamostat mesylate blocked human lung cell SARS-CoV-2 infection with markedly greater efficacy than camostat mesylate, although both compounds were not active against infection with vesicular stomatitis virus [36]. There have been documented incidences of nafamostat adverse reactions such as hyperkalemia, agranulocytosis, anaphylaxis, and cardiac arrest in dialysis patients [37]. Clinically significant adverse reactions associated with camostat include Shock or anaphylactoid symptoms, Thrombocytopenia, hepatic function disorder (an increase of AST, ALT, ALP, or jaundice), Hyperkalaemia, Renal (Increased BUN, increased creatinine)[38]. As elderly people are part of the COVID-19 risk community and can face the challenge of decreased renal function, the dosage of such medicines should be adjusted accordingly to prevent toxicity [39].

Remdesivir

Remdesivir is a broad-spectrum antiviral medication developed by the Gilead Sciences40 that requires metabolism by the host cell to the pharmacologically active triphosphate to inhibit virus replication [41,42]. As a nucleotide analog, remdesivir inhibits RNA-dependent RNA polymerase (RdRp), proteins that are necessary for viral replication [40]. Remdesivir exhibits effective antiviral activity against zoonotic and human coronavirus in mouse models and cell cultures including SARS-CoV, MERS-CoV, and SARS-CoV-2 [43]. Although remdesivir is the first treatment for COVID-19 to be endorsed by the US Food and Drug Administration (FDA) for emergency use, the COVID-19 trial traces adverse effects such as thrombocytopenia, constipation, anemia, hypoalbuminemia, increased total bilirubin, and hypokalemia

surrounding the drug and significant patients in the remdesivir group than the placebo group discontinued the trial due to either adverse events or serious adverse events [44]. Other adverse effects associated with the use of remdesivir include elevation in transaminases, infusion site reactions, and gastrointestinal disturbances [45].

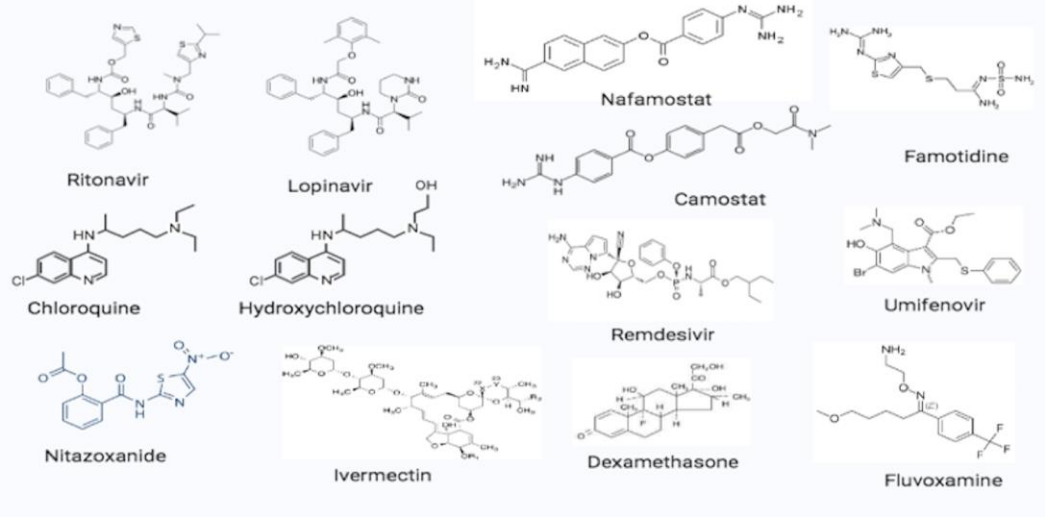

Figure 1. Common pharmaceutics used for treating COVID-19

Famotidine

Famotidine is a blocker of histamine-2, which acts by reducing the amount of acid that the stomach releases. Famotidine was reported to have suppressed human immunodeficiency virus [HIV] replication [46]. A computational study conducted by Wu et al. recently predict protein structures encoded by the genome of SARS-CoV-2 and identified famotidine as one of the drugs most likely to inhibit 3-chymotrypsin-like protease from SARS-COV-2 [47]. A retrospective study showed the use of famotidine was associated with a decreased risk of clinical decline leading to intubation or death in patients hospitalized with COVID-19 [48,49]. In patients with moderate to severe renal impairment, QT interval prolongation has been recorded.50 Adverse effects reported for Famotidine include rare cases of seizures, thrombocytopenia, leukopenia, agranulocytosis, intrahepatic cholestasis of pancytopenia, jaundice, and increased abnormalities of liver enzymes have also been reported. Moreover, psychological symptoms, such as depression, anxiety, and hallucinations, can only rarely be induced [50].

Umifenovir

Umifenovir (fig1), marketed under the brand name Arbidol, is an antiviral drug used in Russia and China in the treatment of influenza infections [51]. Umifenovir inhibits viral envelope membrane fusion by targeting the interaction of viral S-proteins with ACE2 receptors52 and has been reported to possess broad-spectrum antiviral activity against poliovirus, Ebola virus, human herpesvirus, hepatitis B virus, hepatitis C virus, and Lassa virus [32,52]. Several reports indicate the efficacy of Umifenovir against COVID-19 [53], and accordingly treatment of COVID-19 with umifenovir alone was considered to be more effective than treatment with lopinavir/ritonavir [54]. By enhancing the levels of CD4 and CD8 lymphocytes, B-lymphocytes, in serum immunoglobulins, umifenovir modulate the immune system [55]. Umifenovir is rapidly absorbed and distributed to organs and tissues with a maximum blood plasma concentration of approximately 415 ng / mL / mL after a single 200 mg dose is administered [56,57]. Umifenovir may cause side effects of dizziness and psychological symptoms, but it is usually considered safe and can be well tolerated [58,59].

Nitazoxanide

Nitazoxanide is a broad-spectrum antiparasitic and antiviral medicinal agent, which is used to treat various protozoal, helminthic, and viral infections in medicine [60,61]. Nitazoxanide shows in vitro activity against MERS-CoV, SARS-CoV-1, and SARS-CoV-2 inhibiting viral N protein expression. This pharmacological agent also suppresses pro-inflammatory cytokine production in peripheral blood mononuclear cells and suppressing the production of interleukin 6 in mice [62]. Through amplifying body defense mechanisms, nitazoxanide interferes with a viral infection, imposing the

bypass of the virus [63]. The inherent antiviral mechanisms are also unregulated by the large amplification of cytoplasmic RNA sensing and type I IFN pathways [64]. This drug's mechanism of action involves interfering with enzyme-dependent electron transfer of pyruvate ferredoxin oxidoreductase, thus keeping protozoan at the bay of the anaerobic energy sufficient for metabolism [65]. A double blind, placebo-controlled study involving 260 participants found that nitazoxanide treatment [age ≥12 years, 600 mg twice daily; age 4-11 years and 1-3 years, 200 or 100 mg twice daily] did not shorten the length of hospital stay in serious influenza-like patients, and 7 out 130 participants reported severe adverse effects [66]. Gastrointestinal, headache, nausea, and stomach pain are the most common adverse effects of nitazoxanide. Other adverse effects include skin rash, urine and eye discoloration, dizziness, diarrhea, and gastroesophageal reflux disease [65].

Ivermectin

Ivermectin has been used for many years to treat several mammalian infectious diseases and therefore is believed to have anti-microbial, viral, anticancer activity [67]. The mechanism of action of Ivermectin involves inhibition of nuclear transporter importin α/β thereby preventing SARS-CoV-2 entry [68]. Ivermectin was found to inhibits SARS-CoV-2 after single addition to Vero-hSLAM cells 2 h post-SARS-CoV-2 infection, and approximately 5000-fold reduction in viral RNA was observed at 48 h.69 Although ivermectin is considered to be one of the drugs with the potential to target SARS-CoV-2[69], large-scale community-based ivermectin treatment campaigns against Onchocerciasis volvulus in Africa, reported severe neurological adverse effects [70]. Ivermectin also interferes with the metabolism of vitamin K by altering vitamin K-dependent coagulation factors II, V, VII, and X [71]. Adverse affects such as joint pain, headache, fever, itching, and dizziness have been documented in Nigeria following annual treatment with ivermectin for onchocerciasis [72]. A key safety concern predicted is neurotoxicity, which can manifest as depression of the central nervous system and consequent ataxia in most mammalian species, as may be predicted from the potentiation of inhibitory GABA-ergic synapses.

Adverse effects associated with Corticosteroid use

Corticosteroids and their synthetic analogs belong to the class of steroid hormones formed in the adrenal cortex of vertebrates. Two major classes of corticosteroids, glucocorticoids, and mineralocorticoids possess a wide range of physiological processes, including immune response, stress response, inflammation control, protein catabolism, carbohydrate metabolism, behavioral and blood electrolyte levels [73]. Corticosteroids are important for the treatment of various diseases and illnesses. Therapeutic doses, as well as the adverse effects, differ greatly and common corticosteroids consist of the following hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, fludrocortisone, dexamethasone, and betamethasone [74]. An early, short-term analysis of methylprednisolone 0.5 to 1 mg/kg/day divided into 2 intravenous doses over 3 days resulted in a substantial decrease in the median hospital length of stay in the early corticosteroid group, reflecting the fact that the early short-term course of methylprednisolone in patients with moderate to extreme COVID-19 reduced escalation and enhanced clinical outcome [75]. An observational analysis of 309 MERS-infected patients found that approximately half of those receiving corticosteroids [mean equivalent dose of 300 mg/day of hydrocortisone [i.e., methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4] were far more likely to need mechanical ventilation, vasopressors, and renal replacement therapy [76]. The preliminary RECOVERY research reveals that the use of dexamethasone resulted in a lower 28-day mortality rate for those receiving either invasive mechanical ventilation or randomized oxygen alone but not for those receiving no respiratory support [77]. Adverse effects associated with Corticosteroid use include fulminant forms of amebic colitis [78], hyperglycemia [79], fear and anxiety [80], mood change [81], steroid-induced osteoporosis [82], peptic ulceration [83], candidiasis [84], diabetes mellitus [85]. Others are vomiting, behavioral changes, and sleep disturbance, which were reported to occur in children following short-term usage [86].

Tocilizumab

Tocilizumab is a humanized monoclonal antibody and immunosuppressive agent commonly used to treat rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis, a serious type of childhood arthritis [87]. It is used against the IL-6R receptor (interleukin-6R) to block binding to Interleukin 6 (IL-6), a cytokine playing an important role in the immune response and is involved in several diseases, including prostate cancer, multiple myeloma, and autoimmune diseases, and the pathogenesis of several diseases [88]. The use of tocilizumab was included by China's National Health Commission in the 2019 recommendations for the treatment of coronavirus disease (COVID-19) patients [89]. Retrospective analysis of

tocilizumab in severe COVID-19 patients revealed tocilizumab was an effective treatment to reduce mortality [90]. The research shows that fever symptoms returned to normal on the first day while oxygen intake was lower in 15 out of 20 patients with 1 patient needing no oxygen within the 5 days after tocilizumab. The percentage of peripheral blood lymphocytes also returned to normal in 52.6% of patients (10/19) on the fifth day after therapy. However, a recent clinical trial concluded that Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19[91]. Upper respiratory tract infections, common cold, headache, and elevated blood pressure were the most frequent adverse effects observed in clinical trials [92]. Elevated total levels of cholesterol [92], abnormal liver function tests, and decreases in the neutrophil count were common [93].

Sarilumab

Sarilumab [Kevzara ®], an interleukin-6 (IL-6) receptor monoclonal antibody, is approved for moderately to seriously active rheumatoid arthritis (RA) in adults who have reacted inadequately to or are intolerant to one or more DMARDs in several countries, including the USA, the EU, and Japan [94]. In an open-label cohort study using 400 mg of Sarilumab in 88 patients and 28 contemporary patients receiving standard of care alone as controls, 61% of sarilumab-treated patients reported clinical improvement at day 28 of follow-up, although the results were not significantly different from the comparison group [95]. The adverse effects reported from this open-label cohort study include infections, neutropenia, an increase in liver enzymes, and thromboembolism [95].

Bevacizumab in COVID-19 treatments and possible side effects

Bevacizumab is a humanized anti-VEGF monoclonal IgG1 antibody [96]. Bevacizumab competes with VEGF receptors for VEGF binding on endothelial cell surfaces, thus inhibiting the effects of VEGF binding on its receptors, such as proliferation and neovascularization of endothelial cells [97]. Bevacizumab has been used to treat a variety of tumors and a particular form of eye disease [98]. Side effects for use as anticancer include nose bleeding, fever, and high blood pressure [98]. Other serious side effects include gastrointestinal perforation, bleeding, allergic reactions, blood clots, and an increased risk of infections [98]. In a COVID-19 Trial, Bevacizumab has demonstrated clinical effectiveness by improving oxygenation and reducing the length of oxygen support [99].

Fluvoxamine

Fluvoxamine, marketed, among others, under the brand name Luvox, is a selective serotonin reuptake inhibitor (SSRI) type antidepressant mainly used for the treatment of the obsessive-compulsive disorder (OCD). Depression and anxiety disorders, such as panic disorder, social anxiety disorder, and post-traumatic stress disorder, are also used to treat it [100-102]. Researchers from the United States are still exploring the early use of this drug for COVID-19 in a trial termed as ‘’A Double-blind, Placebo-controlled Clinical Trial of fluvoxamine for Symptomatic Individuals With COVID-19 Infection [STOP COVID]’’[103]. Fluvoxamine tends to exhibit low overdose toxicity. Sometimes, the symptoms are minimal: nausea, vomiting, dizziness, and sleepiness.104 There is one confirmed case after the ingestion of 5.5 g of prolonged cerebral depression. Minimal symptoms were reported by overdoses of up to 9 g and total recovery was achieved [104].

CONCLUSION

Several pieces of evidence show most drugs used for the treatment of COVID-19 have adverse effects and must be used with caution most especially in elderly people with underlying diseases. The current race to produce therapeutics and vaccines must also be advance with caution to avoid future consequences.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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