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Review Article

The Pharmacogenomics Aspects of Drugs Used in COVID-19 Treatment

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Abstract

The increase in mortality and morbidity related to the novel COVID-19 virus led researchers to work on developing new therapies to destroy the virus. Numerous clinical trials have started to find drugs that will effectively treat the signs and symptoms of the virus. This review aims to summarize the pharmacogenomic aspects of drugs such as hydroxychloroquine, chloroquine, azithromycin, remdesivir, favipiravir, ribavirin, lopinavir/ritonavir, darunavir/cobicistat, interferon beta-1b, tocilizumab, ruxolitinib, baricitinib, and corticosteroids used in the treatment of this virus. The data will be collected from various websites such as PubMed, Lancet, WHO website, PharmGKB website, IDSA Guidelines on the treatment & management of COVID-19 Patients, the U.S. Food and Drug Administration (FDA) product labeling, and pharmacogenomics tables. Incomplete data exists related to the efficacy and safety of these drugs and healthcare providers are struggling to make the right treatment choices. Drug-gene variants may alter the pharmacokinetics and safety of some drugs and thus produce adverse drug reactions. Therefore, pharmacogenomics may help doctors decide the correct course of treatment by knowing the genetic makeup of an individual. This can eventually help to eliminate adverse drug reactions and reduce the mortality rate.

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Abbreviations: *The significance of different abbreviations and acronyms used in this article are summarized in the table below.*

Abbreviation	Meaning
ABCB1	ATP-binding cassette sub-family B member 1
ABCC2	ATP-binding cassette sub-family C member 2
ACE 2	Angiotensin converting enzyme 2
ARDS	Acute respiratory distress syndrome
CDC	Centers for Disease Control
CETP	Cholesteryl ester transfer protein
cN-II	Cytosolic 52 -nucleotidase II
CNT	Concentrative nucleoside transporters
CPA	Cyclophosphamide
CQ	Chloroquine
CRP	C-reactive protein
CYPs	Cytochromes P450
DCQ	Desethyl-chloroquine
DILI	Drug-induced liver damage
EM	Extensive metabolizer
ENT	Equilibrative nucleoside transporters
ET	Essential thrombocythemia
EULAR	European League Against Rheumatism
FDA	U.S. Food and Drug Administration
GWAS	Genome-wide Association Study
hAOX1	Human aldehyde oxidase
HCoV-229E	Human coronavirus 229E
HCQ	Hydroxychloroquine
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLM	Human liver microsomes
IDSA	Infectious Diseases Society of America
IFNs	Interferons
IL-6	Interleukin 6
ISG	Interferon-stimulated genes
ITPA	Inosine triphosphatase
JAK	Janus kinase
MCP 1	Monocyte Chemoattractant Protein 1
MDR1	Multidrug resistance mutation 1
MERS	Middle East respiratory syndrome
MERS CoV	Middle East respiratory syndrome coronavirus
MF	Myelofibrosis
MPNs	Myeloproliferative neoplasms
Mrp2	Multidrug resistance-associated protein 2
MS	Multiple sclerosis
NAbs	Neutralizing antibodies
NSAIDs	Non-steroidal anti-inflammatory drugs
OATPs	Organic anion transporting polypeptides
OATs	Organic anion transporters
OCTs	Organic cation transporters
PM	Poor metabolizers
P-pg	P glycoprotein
PRR	Pattern recognition receptors
PV	Polycythemia vera
PXR	Pregnane X receptor
RA	Rheumatoid arthritis
RdRp	RNA dependent RNA polymerase
RDV	Remdesivir
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SLC	Solute carrier transporters
SLE	Systemic Lupus Erythematosus
SNPs	Single-nucleotide polymorphism
TCZ	Tocilizumab
TNF	Tumor necrosis factor
WHO	World Health Organization

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Introduction

In December 2019, the first case of a novel enveloped RNA beta-coronavirus (COVID-19) which was later on known as Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was announced in Wuhan city, China.[1] From that moment on, COVID-19 has caused an unexpected global pandemic & a healthcare crisis with high morbidity and mortality. As of 22 September 2020, a total of 31, 174, 627 COVID-19 cases and a total of 962, 613 deaths have been reported in the whole world to the WHO.[2] The coronavirus belongs to a family of viruses that have a single strand RNA genome, having a length of 26 to 32 kilobases, and can cause diseases that vary from the common cold to SARS.[3] The coronavirus strains have been identified in different types of hosts e.g. cats, dogs, camels, bats, and mice. In 2012, Middle East respiratory syndrome (MERS) caused a pathological respiratory disease due to novel coronavirus termed Middle East respiratory syndrome coronavirus (MERS CoV) which was originally detected in Saudi Arabia with the death of roughly 35% of patients infected with MERS.[4]

Many non-genetic factors can influence how the person responds to a particular drug e.g. gender, age, and diet, nevertheless genetics is as well an important factor in responding to particular drug. Genetic variations are the variations seen in the genetic code of different people. These genetic variations can change the mechanism of drug absorption by the body, the delivery of this drug to the target tissue, the drug distribution in the body, and its metabolism. If any of these processes are changed, the drug might not work probably as it should be, or it might have an adverse/ side effect that can affect this drug's overall safety and effectiveness. The study of this relationship between the response of a drug and the genetic variation is known as pharmacogenomics.[5] Pharmacogenomics studies how the genetic makeup of a person alters their response to drugs. In the 1950s, the term pharmacogenomics was coined and then described as the idea that several variants across the genome can vary across populations and alter the drug response. Studying the variations of RNA and DNA characteristics in terms of drug response is to some extent different from pharmacogenetics, which is the study of variations in DNA sequence in terms of drug response.[6]

According to the CDC, people infected by COVID-19 may sometimes be asymptomatic or might show mild to severe symptoms that appear two to fourteen days after exposure to the virus. The symptom may include fever or chills diarrhea, nausea, shortness of breath vomiting, fatigue, headache, body aches, runny nose, cough, or difficulty breathing, loss of taste or smell.[7] Old individuals or individuals who suffer from chronic medical conditions e.g. diabetes, cardiovascular, chronic lung disease, or any disease that may cause suppression of the immunity system are at higher risk for developing serve complications if they got infected with coronavirus. Even though these individuals have the highest mortality rate and experience severe symptoms, young people who have no comorbidities appear to be at risk of serious illness that may involve multiorgan failure or death.[8] Th e introduction of pharmacogenomic directed-medication therapy management for individuals with chronic medical conditions before getting infected with COVID-19 could increase their chances of surviving if they got infected later.

In an urgent effort to ease this dreadful tragedy, many drugs without a well-established efficacy, safety, or data have been given to patients. Moreover, those treatments which are given individually or in combination, have very limited information on their pharmacogenomics that's why some of them are not effective and may even have fatal adverse effects. Besides, some of these medications may be the correct drug of choice for coronavirus treatment but the initial dose given is incorrect which decreases the drug exposure and absorption in the body. For example, if the drug is given at a low dose the virus strain might get a chance to increase resistance to this drug, or if the drug is given in high dose it might increase the adverse effect of the drug.[9] Evaluating the use of pharmacogenomics has been proven to cut the number of emergency department visits and re-hospitalizations.[10] The application of pharmacogenomics can improve the elimination of the adverse effects of these medications by selecting the correct first-line drugs and the correct dose of these drugs according to the person's genetic information. Furthermore, pharmacogenomics can be used to determine the specific genetic markers that may increase the efficacy of COVID-19 medications and decrease their toxicity.[9] Hence, this article aims to review the pharmacogenomic aspects of medications used in the treatment of novel coronavirus and their influence on the human body.

Methodology

A large-scale literature review of articles was conducted using Lancet, PubMed, WHO website, PharmGKB website, IDSA Guidelines of COVID-19, National Guidelines for Clinical Management and Treatment of COVID-19 in UAE, the FDA product labeling, and pharmacogenomics tables. The terms we searched for were "COVID-19", "coronavirus", "novel coronavirus", "pharmacogenetics", "cytokine storm", "pharmacogenomics", "metabolizers", "transporters", "variants", "pharmacokinetics", "SNPs", "genetic variations", "adverse side effects" alone or combined. This review included case reports, clinical trials, review articles,

and randomized controlled trials. This article aims to reviews the pharmacogenomic aspects of drugs such as hydroxychloroquine, chloroquine, azithromycin, remdesivir, favipiravir, ribavirin, lopinavir/ritonavir, darunavir/cobicistat, tocilizumab, ruxolitinib, baricitinib, corticosteroids, and interferon beta-1b used in the treatment of this virus.

Hydroxychloroquine & Chloroquine

The 4-amino-quinoline (Hydroxychloroquine) and the 9-aminoquinoline (chloroquine) are antimalarial drugs that were established in the mid-twentieth century. Hydroxychloroquine has an extra hydroxyl group than chloroquine & has a lower prevalence of adverse effects with chronic use than chloroquine.[11] Furthermore, they are used as antiviral drugs with direct effects against a number of viruses e.g. HIV type 1, herpes simplex virus type 1, hepatitis B, and HCoV-229E.[12] Besides having a direct antiviral effect, they have been broadly used to treat auto-immune diseases, for example, systemic lupus erythematosus and rheumatoid arthritis by inhibiting the production and release of interleukin 6 (IL-6) and tumor necrosis factor (TNF), which facilitate the inflammatory complications of the diseases.[13] Following the COVID-19 pandemic, the use of the anti-viral HCQ and CQ have gained a renewed interest. Even though the mechanisms of action of HCQ and CQ on COVID-19 are not fully understood, several in vitro studies demonstrated that they have an inhibitory effect on the viral replication of this new strain in Vero cells.[14]

HCQ and CQ are well known to elevate the endosomal pH which influences the early stage of viral replication through the inhibition of the virus/cell fusion.[15] The S-glycoprotein is a type I membrane protein that enables the viral attachment to the cellular receptor of COVID-19 and the beginning of the infection. When Coronavirus was analyzed using the Golgi apparatus, the S-glycoprotein was incorporated into the virion. Likewise, it was identified that the ACE 2 is the functional cellular receptor of COVID-19. HCQ and CQ were found to meddle with terminal glycosylation of the ACE 2 receptor, the site where COVID-19 targets cell entry. This adversely influences the binding of the virus receptor and revokes the infection, that in mind as well as the increase of endosomal pH, causing the inhibition of COVID-19 spread & infection.[14]

HCQ and CQ were the first antiviral drugs that were officially approved by the FDA to be clinically used to treat COVID-19 in late March 2020.[16] Regarding the approved use of these drugs, they were known to show adverse effects such as QT prolongation, hematologic toxicity, ocular toxicity, and other cardiac adverse effects. Furthermore, it was reported that there was no decrease in the mortality rate or other positive outcomes with the use of HCQ and CQ. That's why the FDA in June 2020 revoked this article based on new data indicating that the benefits of HCQ and CQ do not exceed their harmful effects.[17] Additionally, the IDSA Guideline panel advised against using either HCQ alone or in combination with azithromycin for treating COVID-19 patents.[11] In metropolitan New York, a retrospective study of 1438 COVID-19 patients showed that patients who received HCQ showed a high prevalence of prolonged QT, arrhythmia, and cardiac arrest, alongside diarrhea and hypoglycemia.[18]

While the role of HCQ and CQ in treating COVID-19 is limited, biomarkers for toxicity are potentially significant. Besides the other adverse effect of HCQ and CQ, when they are given in high dose & in long term treatment, they can cause retinal toxicity which leads to irreversible retinopathy and possibly maculopathy. A study proved that retinopathy and maculopathy predisposition is significantly reduced in those who have minor alleles of genetic variants in the ABCA4 gene.[19] HCQ and CQ are metabolized by the human cytochrome P450 (CYP) enzymes: CYP1A1, CYP2D6, CYP3A4, and CYP2C8 and the HLM together in the liver, generating one main metabolite which is N-desethyl-chloroquine (DCQ). Low affinity and high capacity were associated with CYP2C8 and CYP3A4, while higher affinity and lower capacity were associated with CYP2D6. This illustrates clearly the ability of CQ to inhibit CYP2D6 facilitated metabolism in vivo and in vitro [20]. HCQ concentrations have been reported to be high in poor or intermediate CYP2D6 metabolizers (CYP2D6*4; CYP2D6*10). HCQ reduces the CYP2D6 activity because it is a CYP2D6 inhibitor leading to the prolongation of the QT interval. When HCQ and CQ are given in combination with other drugs which prolong the QT interval e.g. haloperidol, the metabolisms of these combinations will radically be reduced which might potentiate the QT prolongation.[21] In a random double-blind study, HCQ or a placebo was given for eight days to seven individuals who are extensive metabolizer (EM) for CYP2D6, after a single dose of metoprolol was examined. Metoprolol was used in this study as test substrates for CYP2D6 because 70% of metoprolol metabolism depends on CYP2D6. Two mutant CYP2D6 alleles are carried by subjects with poor metabolizers (PM) and subjects with typical CYP2D6 are either heterozygous or homozygous for the wild-type allele CYP2D6*1. This study's results demonstrated that the administration of HCQ in the homozygous EM subjects increased the concentration of metoprolol in plasma, whereas the heterozygous individual increased the bioavailability and decreased the elimination of metoprolol compared with the other subjects.[22] An Additional study was carried out in Korea on 194 patients

with Systemic Lupus Erythematosus (SLE) who are receiving oral HCQ for less than three months. They measured the blood HCQ and N-desethyl hydroxychloroquine [DHCQ] concentrations corresponding to their association with genotypes that were studied. The study showed that the ratio of [DHCQ]: [HCQ] in patients with the G/G genotype of the CYP2D6*10 (rs1065852) was greater than patients with the A/A genotype. Correspondingly, the ratio of the [DHCQ]: [HCQ] in patients with the C/C genotype of the CYP2D6*10 (rs1135840) was greater than patients with the G/G genotype.[23]

Influx transporters such as solute carrier transporters (SLCs) are the proteins accountable for the cellular uptake of exogenous and endogenous substances. SLCs members include the organic anion/ cation transporters (OATs)/ (OCTs) encoded by SLC22A genes and the OATPs encoded by SLCO genes. They oversee the cellular transport of a variety of endogenous substances and drug access to the epithelia of the body. Medications that fight for transporters with these endogenous substances are one of the main reasons for drug toxicities. A study was conducted to explore the CQ and HCQ interaction with these SLC transporters. It was observed that CQ slightly inhibited the transporter activity of OAT2, OAT3, and OATP1B3 whereas, HCQ mildly reduced substrate uptake mediated by OAT4, OAT2, OAT1, OATP1B1, and OATP2B3. Nevertheless, the inhibitory impact of CQ and HCQ on OATP1A2 transporter activity was very potent. When transporter inhibitors compete for OATP1A2, it might result in a toxic effect such as retinal degeneration or impaired visual function that may lead to CQ or HCQ induced retinopathy.[24]

Azithromycin

Azithromycin is a widely used macrolide antibiotic that is derived from erythromycin and is used to inhibit bacteria growth by interfering with the protein synthesis of the bacteria [25]. It is used in the treatment of bacterial infections that cause pneumonia, strep throat, middle ear infections, sinusitis, typhoid, and bronchitis.[25] In addition to treating respiratory tract infections, they are used in the treatment of infections of the gastrointestinal tract, skin, and genital tract.[26] Furthermore, azithromycin demonstrates both immunomodulary and anti-inflammatory activities which suppresses hypercytokinemia.[27] The immunomodulary action of azithromycin could help the COVID-19 patient because the coronavirus causes inflammation and following tissue damage in the lungs and the drug can stop this inflammation and inhibit the cytokines causing the COVID-19 severe respiratory syndrome.[28]

A study was done on Han Chinese ethnic group, showed that the pharmacokinetics of azithromycin is influenced by specific ABCB1 gene polymorphisms such as 2677GG/ 3435CC, 2677TT/3435TT, and 2677GT/3435CT phenotypes and thus affect the pharmacodynamics of the substrate drugs.[29] Moreover, it was reported that the CYP3A4 inhibitor does not influence the pharmacokinetics of azithromycin, so it's not metabolized, induced or inhibited by CYP3A4.[29] A study was done on rats demonstrated that intestinal & biliary excretion of azithromycin is facilitated by the multidrug resistance-associated protein 2 (Mrp2) and P glycoprotein (P-gp) which are coded by ABCB1 and that azithromycin is a substrate for these transporters.[30] In another experiment, they studied the effects of the macrolides and ketolide on the human OATP family (OATP1B3 and OATP1B1) facilitated uptake were using pravastatin (an HMG-CoA reductase inhibitor) and BSP as substrates. This experiment showed that all the macrolides except "azithromycin" in high concentrations inhibited the OATP1B3 and OATP1B1 mediated uptake of pravastatin and BSP.[31] This means that azithromycin has fewer drug-drug interactions than all other macrolides which can be considered in the treatment of COVID-19.

The key clinical evidence about the advantage of using azithromycin with or without HCQ in COVID-19 patients emerged from the open-label non-randomized trial in France. Forty-two COVID-19 patients received HCQ as monotherapy or HCQ plus azithromycin. On day 6 after admission, 100% of patients who took HCQ plus azithromycin indicated no viral load when tested with the swab compared with 57.1% in patients who received HCQ alone.[32] Another case series was done on eighty-one hospitalized patients, where they received HCQ for 10 days plus azithromycin 5 days. Results showed that 1 patient died, 3 patients were required to be transferred to the ICU, 12 patients needed oxygen therapy, and 65 patients were discharged to home or assigned to other units for continuous therapy. Besides, on day seven the PCR test was negative in 83% of patients, and on day eight the test was negative in 93% of patients.[33] All the above studies recommended the combination of HCQ and azithromycin as it will have a beneficial impact on the clinical outcomes and viral load of COVID-19 patients and consequently, physicians all over the world adopted this regimen. With this massive use of this regimen, some adverse effects were observed on COVID-19 which is mild QTc prolongation.[34] Another study was done on 109 non-ICU COVID-19 patients which assessed the effect of giving HCQ plus azithromycin for five days on ECG. In the results, there were no clinically major differences between QTc intervals and no ventricular fibrillation, tachycardia, or conduction seen through follow-up.[35]

Hence, we recommend that the QTc should be monitored in patients with co-morbidities and patients with cardiovascular disease history. We also propose that azithromycin should be considered as one of the main treatments of coronavirus and further studies should be done on this drug as monotherapy and combined with HCQ.

Remdesivir, Favipiravir, and Ribavirin

For many years' nucleotide analogs, remdesivir, favipiravir, and ribavirin, have been used in the treatment of viral infections. They have low affinity to human enzymes and high affinity to viral enzymes, which is why they can inhibit viral reverse transcription, DNA replication, and virion protein biosynthesis. In addition, nucleotide analogs inhibit RNA polymerase enzyme after being metabolized into their active forms.[36] These analogs have a broad-spectrum antiviral activity in vivo and vitro against RNA viruses of the Filoviridae such as Ebola virus, Paramyxoviridae e.g. Nipah virus, and Pneumoviridae e.g. respiratory syncytial virus families.[37,38] The antiviral activity against coronaviruses included SARS-CoV and MERS-CoV, however, in vitro studies showed no inhibition in several viruses such as Lassa virus and Crimean Congo hemorrhagic fever virus. Remdesivir (RDV) is an adenosine analogue prodrug, its triphosphate form (RDV-TP) bears a resemblance to ATP and it is employed as a substrate of many viral RdRp enzymes. The RDV-TP from ability to compete with the ATP, showed more selected and delayed chain termination which eventually inhibited the mechanism of action of SARS-CoV, SARS-CoV-2 RdRp, and MERS-CoV complexes.[38]

In May 2020, RDV was authorized by the Emergency Use in the U.S. for severe COVID-19.[39] A study done by the IDSA in hospitalized patients without mechanical ventilation showed that patients treated with RDV for five days do not show a decrease in mortality than in patients who did not receive RDV. Moreover, the patient treated with RDV for five days showed increased clinical improvement, but the patient treated with RDV for 10 days showed no clinical improvement than those who did not receive RDV.[11] Another clinical study was done with severe 397 COVID-19 patients who do not demand mechanical ventilation, showed that no meaningful difference between five days and ten days treatment course of RDV.[40] At ten hospitals in China, a randomized, double-blind controlled study was conducted on 237 patients who had severe COVID-19, 158 patients were given RDV, and 79 patients were given a placebo. 66% of the patients who received RDV showed adverse drug reactions versus 64% of the patients who received the placebo.[41]

Despite the fact that no enough pharmacogenomic in vivo were found for RDV, Some in vitro studies were done and indicated that RDV is an inhibitor of the OATP1B1, OATP1B3, and CYP3A4.[42,43] In addition, RDV is a substrate for CYP3A4, CYP2C6, and CYP2D8, as well as OATP1B1 and P-gp transporters.[43] The use of steroids with RDV in severe COVID-19 patients will affects the CYP3A4 transcription, which may result in a lower therapeutic drug level of RDV, and hence higher IL-6.[44] This may be the real cause of adverse drug reaction, which was reported in the double-blind, placebo-controlled study. In a summary, RDV is a strong candidate for the treatment of the patient who requires supplemental oxygen as it showed beneficial outcomes and decreased the time of recovery in severe COVID-19.

Ribavirin is a broad-spectrum antiviral agent that has been used for the treatment of hepatitis C virus (HCV) infections. It is a guanosine analog that has two mechanisms of action which are indirect mechanisms e.g., inhibit inosine monophosphate dehydrogenase enzyme and direct mechanisms e.g., interfere with RNA capping and inhibit polymerase enzyme.[45] Ribavirin is metabolized by adenosine kinase I and Cytosolic 52 -nucleotidase II (cN-II) and it is transported by two transporters, 1st is the concentrative nucleoside transporters (CNT) 2/3 which is coded by SLC28A2/3 genes, and 2nd is the equilibrative nucleoside transporters (ENT) 1/2 which is coded by SLC29A1/2 genes. A study was done on 1/4 HCV-Italian patients with 4 weeks of ribavirin treatment, the study showed that patients of the SLC28A2 genotype had lower trough concentrations and patients of SLC28A3 and SLC29A1 genotype had greater ribavirin levels.[46] A Genome-wide association study was conducted on patients revering pegylated interferon and ribavirin (PEG-IFN/RBV) for treatment of chronic hepatitis C, which showed that the ITPA variants in rs11697186 were associated with a huge reduction in platelet count [47]. A meta-analysis was done to find the relation between the ITPA polymorphisms, and the hemolytic anemia observed in HCV patients after receiving ribavirin therapy. This analysis revealed that rs1127354 CC, rs7270101 AA, and rs6051702 AA genotypes were coupled with a decrease in hemoglobin. The rs1127354 CC genotype and absence to ITPase deficiency haplotype were also coupled with severe anemia.[48] As a result, it is recommended to screen for ITPA polymorphisms to prevent hematologic toxicity and enhance adherence ribavirin therapy.

Favipiravir is a purine analog that selectively inhibits the viral RdRp. It is used in the treatment of the Ebola virus and 53 types of influenza viruses.[49] In addition, this antiviral agent has a strong anti-influenza activity against a large variety of RNA viruses such as enteroviruses, norovirus, arenaviruses, filoviruses, rhabdoviruses, and alphaviruses.[50] There is not sufficient data published regarding the

pharmacokinetics of favipiravir however, it is mainly metabolized via aldehyde oxidase and slightly via xanthine oxidase.[51] A study proofed that the human aldehyde oxidase (hAOX1) polymorphism and other genetic elements alter hAOX1 expression and may result in diminished metabolism of some drugs.[52] at The University of Tokyo Hospital, eleven patients were admitted to the ICU for treatment of COVID-19, and they received dual therapy of nafamostat mesylate plus favipiravir for 14 days. Eight patients required invasive mechanical ventilation, and three patients required venovenous extracorporeal membrane oxygenation. After the end of the treatment, 1 patient died in ICU on day seven and 7 patients were effectively removed from mechanical ventilation and the rest were discharged from the ICU.[53] Despite the absence of evidence to support the use the favipiravir and that it is not as effective as remdesivir, it deserves to be considered for use in mild to moderate cases.

Dexamethasone

Corticosteroids have been widely used to decrease lung inflammatory responses which may progress into acute lung injury and acute respiratory distress syndrome (ARDS). ARDS is an inflammatory disease process of the lungs and is a life-threatening disease with a great mortality rate of 40% to 50% leading to hypoxemia and pulmonary edema which requires mechanical ventilation. If this disease is not treated it will exacerbate and cause a series of complications, leading to secondary systemic inflammatory reactions which cause multiorgan failure.[54] Corticosteroids play an important role as anti-inflammatory cytokines and in immune homeostasis, that's why corticosteroids are believed to be an important therapy for ARDS patients. A meta-analysis was done using 327 potential studies that recommended that long-term low-dose glucocorticoid treatment, when started at early stages, decreases the mortality rate of patients with ARDS.[55] Another meta-analysis also recommended the early use of glucocorticoids as mentioned above to decrease mortality as well, glucocorticoids improve the number of days without mechanical ventilation without raising the chance of infection.[56]

Glucocorticoids have been commonly used in diseases closely related to coronavirus such as SARS, MERS, community-acquired pneumonia and influenza.[57] At the beginning of the pandemic, many studies did not support the use of corticosteroids and indicated that it causes more harm than benefit.[58] However, a new study proved that the low-dose corticosteroids prove to be beneficial in the treatment of COVID-19 patients who are moderate to critically ill. Other studies suggested that glucocorticoids, specifically dexamethasone, can help COVID-19 with ARDS. ARDS has been identified as one of the leading causes of high mortality in COVID-19 patients, implying that corticosteroids should be used in COVID-19 care plans.[59] An additional study recommended that COVID-19 patients with moderate to severe ARDS who used dexamethasone plus standard care for 28 days showed a remarkable rise in the number of ventilator-free days compared with standard care alone [60]. Moreover, a new study suggested that the use of corticosteroids may decrease mortality in COVID-19 patients with ARDS.[61] A preliminary study was done in the UK on hospitalized COVID-19 patients, 2104 patients received dexamethasone and 4321 patient received regular treatments. After 28 days, 22.9% of the patient who received dexamethasone and 25.7% of patients who received regular treatments died. This suggests that while dexamethasone reduced mortality in patients who were getting oxygen or mechanical ventilation, it had little effect in patients with moderate COVID-19.[57] After careful consideration, the WHO on the 2nd of September published an article advising the systemic use of corticosteroids for the treatment of severe COVID-19 patients and the recommendation not to use corticosteroids in the treatment of non-severe COVID-19 patients because there are no advantages.[62]

Dexamethasone is mainly metabolized by CYP3A4 and to a lesser extent by CYP3A5 in vitro in humans by the liver.[63] This means that any genetic variation in CYP3A4 or CYP3A5 may impact the pharmacokinetics of dexamethasone as well as the drugs that inhibit or induce these CYPs. Dexamethasone has as well been shown to enhance the expression of some enzymes e.g. CYP3A4 by xenobiotics.[64] and CYP2A6 mediated by the glucocorticoid receptor[65] as well as UGT1A1 protein mediated by the PXR activator.[66] A study was conducted to see the effect of cyclophosphamide (CPA) with/ without dexamethasone on CYP3A4 and CYP2B6, indicated that dexamethasone in combination with CPA, in a concentration-dependent manner, induced the expression of CYP3A4 and CYP2B6 via the activation of PXR.[67] An additional study was conducted to assess the expression of CYP2C genes, the results indicated that dexamethasone generated the maximum induction of CYP2C9 and CYP2C8 via PXR and glucocorticoid receptor.[68] Dexamethasone is also a strong inducer of drug transporter e.g. P- glycoprotein, MDR1, and ABCB1.[69,70]

All these studies and findings imply that physicians & healthcare providers should carefully assess the treatment plan of their patients to avoid the possibility of inducing CYPs in vivo which may influence the pharmacodynamic and pharmacokinetics of dexamethasone and result in side effects. On the other hand, another study was done to determine the effects of short-term use of dexamethasone

on cardiovascular biomarkers that indicated that dexamethasone caused an increase in weight, high-density-lipoprotein-cholesterol, and blood pressure. It also showed a decrease in high-sensitivity CRP, resting heart rate and aldosterone, and there was no effect on heart rate recovery, low-density-lipoprotein-cholesterol (LDL-C), or triglycerides this indicates that further studies should be done to assess the side effects and benefits of dexamethasone to support its use.[71]

Anti-retrovirus agents (Lopinavir/ ritonavir & Darunavir/ cobicistat)

Lopinavir is a selective and potent protease inhibitor antiretroviral agent derived from ritonavir. Both drugs go through extensive and fast first pass metabolism by hepatic CYP3A4 isoenzyme.[72] Lopinavir alone has poor bioavailability due to its rapid metabolism. In addition to CYP3A4, CYP1A2 and CYP2D6 also participate in the activation of lopinavir.[73] When lopinavir is co-administrated with low-dose ritonavir, the pharmacokinetic features of lopinavir are greatly improved, and metabolic inactivation by the CYP3A4 enzyme is inhibited. Co-formulated lopinavir/ ritonavir is a novel protease inhibitor that diminishes the viral load, provides a constant improvement in CD4+ cell counts, and enhances immunological status in patients with HIV-1 infection.[72]

Co-formulated lopinavir/ritonavir has a high possibility of interacting with a large range of drugs by several mechanisms, primarily concerning the CYP enzymes. Co-administering lopinavir/ritonavir with medications that rely heavily on CYP3A or CYP2D6 for clearance is contraindicated because it may result in elevated plasma concentrations, which have been related to severe or harmful incidents. Moreover, co-administration of lopinavir/ritonavir is not advised for drugs or herbal products such as rifampicin that may significantly decrease lopinavir plasma concentrations or drugs whose plasma concentrations are increased by the co-formulation which may result in serious adverse effects such as simvastatin. To decrease the risk of drug toxicity when co-administered with lopinavir/ritonavir, we suggested to monitor the drug plasma concentration in drugs such as immunosuppressants and antiarrhythmics or use of different drugs such as atorvastatin or adjust the dose of drugs as in atorvastatin, dihydropyridine calcium-channel blockers, and ketoconazole.[72] A pharmacokinetics – pharmacogenetics analysis of lopinavir/ritonavir was done a Caucasian people, identified 1380 SNPs. People with SLCO1B1*4 had a higher clearance of lopinavir in comparison to people with 2 or more variant alleles of SLCO1B1*5, CYP3A, or ABCC2.[74] Another genetic analysis was done in 106 HIV-infected European identified 290 SNPs that had a major influence on toxicity resulted from receiving lopinavir/ritonavir treatment. Elevated bilirubin and dyslipidemia were associated with SNPs in SLCO1B3, ABCC2, CETP, ABCC2, and MCP 1 and diarrhea was associated with SNPs in IL-6.[75]

These HIV-protease inhibitors are not currently recommended for COVID-19 therapy by the Guidelines since they do not achieve sufficient drug concentrations to block COVID-19 proteases and they failed to show efficacy in a randomized controlled trial. In addition, lopinavir/ ritonavir showed several side effects including nausea, diarrhea, QTc prolongation and hepatotoxicity.[76] A clinical trial was done to measure the plasma drug concentrations of lopinavir/ ritonavir at the normal doses, the results indicated that they achieved concentrations lower than the levels that are needed to inhibit COVID-19 replication.[77] A randomized controlled open-label trial was done on hospitalized adult COVID-19 patients who received lopinavir/ ritonavir and patients who received regular care. Treatment with lopinavir/ ritonavir showed no difference from regular care in 28-days mortality rate, in the clinical recovery time, or viral load.[78] All this evidence implies that lopinavir/ ritonavir is not useful in the treatment of COVID-19.

Darunavir is another protease inhibitor that is used in HIV treatment and it has to be co-administered with ritonavir to enhance its pharmacokinetics. Darunavir is a recognized substrate for influx transporters as SLCO1A2 and SLCO1B1 and it is a substrate for efflux transporters as MRP1. A study was done to determine the pharmacokinetics and pharmacogenetics of darunavir/ ritonavir when given to HIV-infected patients, it revealed that individuals with SLCO3A1 SNPs showed a lower clearance of darunavir and affected more of its pharmacokinetics.[79] There is not enough evidence or research to back up the use of darunavir in the treatment of COVID-19 patients, and the trials we found did not back it up. For instance, a study was done on the COVID-19 patients who received darunavir and remdesivir which revealed that darunavir exhibited no antiviral activity against COVID-19 virus (EC50 > 100 ìM) in comparison with remdesivir which showed strong antiviral activity (EC50 = 0.38 ìM) [80]. Furthermore, another study was conducted on severely ill COVID-19 patients showed that darunavir/ ritonavir did not decrease the mortality rate of these patients despite the fact that it was well tolerated.[81]

Interleukin-6 (Tocilizumab)

Interleukin-6 (IL-6) acts as an anti-inflammatory myokine and a pro-inflammatory cytokine.[82] The pro-inflammatory cytokine is generated by different cell types such as monocytes, lymphocytes, and fibroblasts in the body. In a

study done on 69 COVID-19 patients, it was found that patients with SpO2 level < 90% demonstrated more comorbidities and elevated levels of IL-6, IL10, CRP, lactate dehydrogenase, and D-dimer. This data indicated that systemic inflammation and respiratory failure are associated with increased release of cytokines.[83] The cytokine storms that occur due to the high production of proinflammatory cytokines and elevated IL-6 have been associated with a huge number of severely ill COVID-19 patients.[84] As a result, a large number of inflammatory cells penetrate the lungs of COVID-19 patients which may be accountable for weakening the immunity and causing injuries lung resulting in death.[85] Thereby, it is assumed that controlling the IL-6 levels in the blood or controlling its effects may change the pattern of disease. The FDA has two classes approved to inhibit the IL-6, anti-IL-6 receptor monoclonal antibodies (tocilizumab and sarilumab) and anti-IL-6 monoclonal antibodies (siltuximab).[84]

Tocilizumab (TCZ) which is known as Atlizumab is an immunosuppressive monoclonal antibody drug that is primarily used for the treatment of cytokine-release syndrome caused by CAR-T therapy and rheumatoid arthritis.[84] Several coherent studies were conducted to investigate the influence of the genetic factors on response in patients with rheumatoid arthritis who received TCZ based on the European League Against Rheumatism "EULAR" treatment guidelines. The first study included 42 patients of whom 87 received TCZ, discovered that patients with the FCGR3A (rs396991 TT genotype) demonstrated better responses than the others.[86] The second study revealed that the SNPs of the IL-6 receptor, rs12083537 AA genotype and rs11265618 CC genotype, had a better EULAR response to TCZ, also they altered the intracellular signaling pathway of IL-6 receptor bound to TCZ.[87] On the other hand, patients with the IL-6 receptor rs4329505 CT and CC genotypes had reduced response to TCZ in comparison with patients who have the TT genotype [88]. The final study conducted on 79 patients who received TCZ as a treatment for 6 - 18 months exhibited improved EULAR response rates in patients who carried CD69 (rs11052877 AA genotype) or the GALNT18 (CC genotype) gene than those who carried CLEC2D, ENOX1, and KCNMB1 genes. In contrast, the patients who carried the CD69 rs11052877 GG and AG genotypes had a way decreased response to TCZ in comparison with patients who have the AA genotype.[89] All this information indicates that TCZ may be a potential treatment for COVID-19 according to the genetic makeup of patients.

The hepatic CYP enzymes are crucial for drug metabolism and elevated levels of cytokines e.g. IL-6 in blood have been demonstrated to downregulate the activity of the CYP enzymes which results in decreased clearance of co-administered drugs.[90] This means that drugs that inhibit IL-6 may improve CYP function. An article screened texts that report IL-6, TCZ, and their effect on CYP metabolized drugs revealed that the bioavailability of omeprazole was reduced by TCZ induced CYP2C19 activity and that the bioavailability simvastatin which is a CYP3A4 substrate was decreased by TCZ. Accordingly, the bioavailability of more drugs may be decreased by the administration of TCZ because CYP3A4 is responsible for the major proportion of drug metabolism which can cause many adverse effects.[91] Additional studies conducted have proved that monoclonal antibody therapy such as TCZ when used against IL-6, it stopped the IL-6 suppression of the activity CYP3A4 and CYP1A2 enzymes.[92]

The IDSA panel recommended the use of tocilizumab plus the standard therapy instead of standard therapy alone in hospitalized adults with progressive severe or critical ill COVID-19 patients who have higher indicators of systemic inflammation e.g. CRP.[8] Nevertheless, ADRs data were collected from a series of randomized controlled clinical studies of long-term use of tocilizumab. The most common ADRs were serious infections such as pneumonia, cellulitis, urinary tract infection, sepsis, herpes zoster and gastroenteritis. Gastrointestinal perforations were mainly a complication of diverticulitis such as lower GI perforation, abscess, and fistula. Most patients who developed GIT perforations received NSAIDs, methotrexate or corticosteroids at the same time. Therefore, healthcare providers must be aware of the risk of serious infection, thrombocytopenia, liver damage and other ADRs caused by tocilizumab.[93]

Janus kinase inhibitors (Ruxolitinib & Baricitinib)

Myelofibrosis (MF), essential thrombocythemia (ET), and polycythemia vera (PV) are mentioned as the Philadelphia chromosome (BCR-ABL1) negative myeloproliferative neoplasms (MPNs). Each one of them has different pathologic characteristics, but all three exhibit changes in the Janus kinase (JAK) signal transduction activation resulting in abnormal activation of the JAK-STAT pathway.[94] Ruxolitinib is a potent selective oral inhibitor of JAK 1 and 2, which has been approved for the treatment of MF by the FDA in 2011 and by the EMA in 2012.[95] Baricitinib is also an oral inhibitor of JAK1 and JAK2, which is used in the treatment of RA in moderate to severely ill.[96] Most of the COVID-19 patients with severe symptoms exhibit high pro-inflammatory cytokines levels in the plasma, which may give rise to cytokine storm, subsequently huge immune cell penetration into the lungs resulting in the damage and

reduced function of lungs. The inhibition of the JAK pathway will inhibit the increased cytokines signals, which will lessen the cytokine storm and lower the mortality rate associated with COVID-19.[97]

Unfortunately, no studies have been published regarding the effect of the genetic variants in any population in both drugs. Also, there is no pharmacogenetic information for both drugs in Pharma GKB. Nevertheless, they mentioned that ruxolitinib is metabolism by CYP2C9 and CYP3A4 so, it should be avoided or reduce its dose when administered with potent CYP3A4 inhibitors or dual inhibitors of CYP2C9 and CYP3A4 enzymes because it can result in hematologic adverse drug reactions.[98] Furthermore, baricitinib is mainly transported by the OAT3 transporter, so it can cause ADRs when administered with potent OAT3 inhibitors such as probenecid.[99]

A randomized clinical trial was conducted on 42 severe COVID-19 patients, patients either received ruxolitinib combined with standard therapy or placebo based on standard therapy. 90% of the patients who received ruxolitinib improved at day 14 compared with 61.9% patients in the control group and 14.3% of the patients in the control group died in comparison with no death in the patients who received ruxolitinib.[100] Despite the positive outcome of this trial, more studies and further investigation should be done on the pharmacogenomics of ruxolitinib for its use in coronavirus. A double-blind, randomized clinical trial was conducted, 1033 patients received remdesivir and either baricitinib or placebo. Patients who received baricitinib recovered in 7 days compared with 8 days with patients who received the placebo. After 28 days the mortality was 5.1% in the group who received baricitinib and 7.8% in the group who received the placebo. Serious ADRs were less in the group that received baricitinib than in the group that received the placebo. The combination of baricitinib plus remdesivir reduced the recovery time, improved the clinical condition and showed fewer serious ADRs among COVID-19 patients.[101]

The IDSA panel recommended the use of baricitinib plus remdesivir instead of remdesivir alone in hospitalized patients with severe COVID-19 who cannot take corticosteroids (Dexamethasone) because of the contraindication.[8] It is unclear whether baricitinib with remdesivir will have the same advantage/ outcome as dexamethasone and only a few clinical trials are there, so further investigation is needed.

Interferon beta-1b

Interferons (IFNs) are a type of immunomodulatory compound generated by host cells in response to pathogen-specific motifs being detected, causing IFN secretion that affects both, the stimulated cells, and the neighboring cells. IFN stimulation causes changes in the cellular transcriptional process early in infection, resulting in an antiviral state featured by the activation of a large number of host genes with poorly specified antiviral functions. IFNs have been used for the treatment of newly evolving viral infections where no specific antiviral treatments stated, depending on these doubtlessly beneficial immunomodulatory characters with the utmost benefits resulting from very early administration following infection.[102]

Type 1 IFN refers to a category of cytokines that includes the widely distributed á and â subtypes along with the å, ù and ê subtypes. When the pattern recognition receptors (PRR) recognize viral elements, they are secreted by a variety of cell types, particularly plasmacytoid dendritic cells. As a result, IFN-I is one of the first cytokines released during a viral infection. The IFNAR receptor, which is found on the plasma membrane of most cell types, recognizes them. The phosphorylation of transcriptional factors including STAT1 and their re-localization to the nucleus, where they activate interferon-stimulated genes (ISG), is induced by interferon fixation on IFNAR. The majority ISGs are engaged in signaling, inflammation, and immunomodulation. They disrupt viral replication and transmit through a variety of mechanisms, including the secretion of cytokines or slowing cell metabolism that facilitate adaptive immunity activation. Antivirals that target a certain step in the viral cycle, PRRs which makes the cell more vulnerable to viruses, and proteins that reduce membrane fluidity, preventing viral egress or membrane fusion are all examples of ISGs. As a result, IFN-I plays a critical function in antiviral immunity. IFN-I is used to treat a variety of diseases due to its immunomodulatory properties; for instance, subcutaneous IFN injections have been used to treat people with MS for over 20 years.[103]

Despite variations in pathology, epidemiology, and certain proteins, MERS-CoV and SARS-CoV are coronaviruses that are closely related to COVID-19 and have common properties. In vitro and in vivo studies with IFN-I combined with or without lopinavir/ritonavir, remdesivir, ribavirin, and corticosteroids have been studied versus MERS-CoV and SARS-CoV in many trials. IFNâ1 seems to be the most significant interferon in the treatment of coronavirus infections. This is because IFNâ1 protects the lungs by upregulating CD73 in pulmonary endothelial cells, which leads to the secretion of anti-inflammatory adenosine and the preservation of endothelial barrier activity [103]. The effectiveness and safety of combination IFNâ1, lopinavir/ ritonavir, and ribavirin for treating 127 COVID-19 patients were studied in an open-label, randomized phase 2 clinical

trial. The study revealed that in mild to moderate COVID-19 patients, the combination treatment was safe and reduced symptom severity while also shortening the time of virus shedding and hospital stay. There was no difference in the number of patients who experienced self-limited nausea and diarrhea between the two groups, and no one died during the trial.[104]

Pharmacogenomics variables for IFNâ1 are not well-defined, as they are for other biologic drugs. Reduced potency and elevated side effects as a result of immunogenicity, on the other hand, are a particular problem for biologics. Neutralizing antibodies (NAbs) form in a large number of patients with MS who undergo IFNâ1 treatment, reducing drug effectiveness. The role of HLA gene carrier in the likelihood of developing NAbs and titers of NAbs high enough to influence the biological response to IFNâ1 was studied in a cohort study. This study was conducted on Swedish patients diagnosed with MS, the results demonstrated that patients with the HLA-DRB1*04 allele had a higher chance of developing biologically NAbs, whereas those with the HLA-DRB1*15 allele had a lower risk.[105]

Up to 60% of MS patients who have been subjected to IFN develop adverse liver test findings, and one of every fifty suffers from drug-induced liver damage (DILI). Despite the fact that the number of treatment alternatives for MS is growing, IFNs remain the most commonly used disease-modifying therapy. While liver damage caused by IFNâ1 has the potential for significant consequences, there is no way to foresee this adverse reaction. Nevertheless, due to non-biologics, GWAS has identified variants with wide impact sizes correlated with DILI using comparatively limited, but rigorously phenotyped cohorts. A two-stage GWAS was conducted on MS patients from Canada (stage 1) and the U.S./Sweden (stage 2), and it demonstrated that patients with variants of IRF6, which codes for an interferon regulatory factor implicated in promotion of liver damage, had a higher risk of DILI. In at-risk patients, pharmacogenomic testing for this variant prior to IFNâ1-therapy, rather than only checking liver enzymes during treatment, can help to avoid DILI. DILI may then be prevented in rs2205986-carriers by exploring different treatments or increasing liver damage control.[106]

Molnupiravir

Molnupiravir is an antiviral prodrug of nucleoside analogue beta-D-N4-hydroxycytidine (NHC), which is hydrolyzed to NHC by esterases CES1 and CES2. After the uptake of circulating NHC into cells, host kinases and phosphatases involved in the endogenous pyrimidine nucleoside pathways then anabolise/catabolise NHC to/from NHC-TP which is an active form, this active form binds to the genome of RNA virus either to guanosine or adenosine, and then can be substituted to either (CTP) cytidine triphosphate or uridine triphosphate (UTP), by viral RNA polymerase which in turn results in accumulation of many mutations in the viral genome leading to inhibition and suppression of the virus inside the tissues.[109] Genetic variations in the genes encoding esterases CES1 and CES2 may sometimes inhibit the conversion of Molnupiravir to NHC. NHC is a substrate of the human nucleoside transporters CNT1, CNT2, CNT3, and ENT2 while molnupiravir is a weak substrate of CNT1. Genetic variations in the genes encoding human nucleoside transporters CNT1, CNT2, CNT3 and ENT2 may result in not allowing the drug Molnupiravir to work in some individuals.

A randomized- double blinded clinical trial on 709 infected patients who received Molnupiravir, suggested that only about 6.8% were hospitalized or died compared to 9.7% of patients of the 699 people who received a placebo. One individual who received Molnupiravir died during the follow up period, on the other hand about nine people died during follow up period who received placebo.

Another clinical study on (mouse / pig / hamster) models for viral infection, showed that Molnupiravir has broad-spectrum activity against many viruses including SARS-COV-2 as well as different variants B.1.1.7 (Alpha), B.1351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) of corona virus.[110] Therefore, FDA approved to use Molnupiravir in treating mild to moderate covid-19 patients above 18 years.

Paxlovid

It's a synthetic drug which inhibit viral replication in the host, it works by inhibiting the nonstructural protein, it is responsible to cleave down 1a & 1ab proteins which contain mainly the cystine residue in order to stop viral replication in the host.

Paxlovid is mainly metabolized by CYP3A4, Nirmatrelvir is co - administered with ritonavir to decrease metabolism of it and increase the plasma Nirmatrelvir concentrations in the host cell. Any genetic variation in the gene encoding CYP3A4 may not allow the drug to be metabolized resulting in side effects.

Paxlovid was approved by FDA in emergency in patients suffering from mild to moderate symptoms of COVID-19 disease.

A randomized double-blind trial was done on 1039 patients who received Paxlovid and 1046 patients who received placebo, it was seen that about 0.8% of patients who received Paxlovid were hospitalized or died during the treatment in comparison to 6% of those who took placebo were hospitalized or died during treatment.

Paxlovid is not recommended for people who have severe kidney or liver impairment, but for patient who have mild to moderate kidney or liver impairment dose can be adjusted.

Paxlovid is contraindicated with products that are potent CYP3A inducers where significantly reduced PF-07321332/ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance.[111]

Casirivimab and Imdevimab

These are recombinant IgG monoclonal antibodies which work by targeting the receptor of the spike protein. They play an important role in viral fusion. These monoclonal antibodies fuse with the non-overlapping epitopes of the spike protein which in-turn prevents the virus from interacting with human ACE receptor. Genetic variations in the ACE receptors may sometimes lead to the interaction of virus with ACE receptors. This combination is used in treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which was approved by FDA on 21st of November 2020. They are co-administered together either by intravenous infusion or subcutaneous injection.

Study showed that single infusion of 1200 mg (Casirivimab 600 mg and Imdevimab 600 mg) reduced COVID-19-related hospitalization or death from any cause compared to placebo by day 29 by 1% and 3,2% respectively (HR 0.30; NNT 44.3).

Conclusion

With the rise in COVID-19-related mortality and morbidity, many researchers are working to develop new treatments to combat the virus. The clinical importance of a pharmacogenetic instrument in preparing customized therapies is likely to become crucial in the pharmacological management of COVID-19 patients, according to the findings of a large study of genetic variants associated with the key medications used for COVID-19 therapy. Successful pharmacogenomics approaches can be effective in slowing the development of COVID-19, particularly in the later stages. This may ultimately aid in the elimination of adverse drug reactions and the lowering of mortality rates.

With more and more COVID-19 targeted therapies in the field, additional options for the treatment of the virus became available. Modern genomic technologies, along with a strategic assessment among the most probable gene-drug candidates, may allow practitioners better understand the role of pharmacogenetics in the treatment of COVID-19. Pharmacogenetics can only be effective in urgent conditions like COVID-19 if genetic test information were already obtained or could be obtained quickly. Several establishments have already adopted pre-emptive pharmacogenetics testing, and few patients may already have their results.[107] Even though the clinical point-of-care pharmacogenetics tests are obtainable, they often do not include the possible variations that are relevant to COVID-19 treatments.[108]

Recent studies suggest that HCQ and CQ would not be useful in treating COVID-19 patients and that these drugs' known, and possible benefits do not balance their known, and possible harms. Low-dose dexamethasone, on the other hand, has been demonstrated to be helpful in treating COVID-19 patients, increasing the number of ventilator-free days, and lowering the mortality rate. In the presence of the COVID-19 pandemic's overwhelming obstacles, collaboration among the medical community is more vital than ever to enhance the effectiveness of these therapies and assure their safety. Pharmacogenomics is being evaluated in certain huge national COVID-19 studies, which will help in understanding the significance of pharmacogenomics markers in future clinical applications.

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