Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Considerations into pharmacogenomics of COVID-19 pharmacotherapy: Hope, hype and reality

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ABSTRACT

COVID-19 medicines, such as molnupiravir are beginning to emerge for public health and clinical practice. On the other hand, drugs display marked variability in their efficacy and safety. Hence, COVID-19 medicines, as with all drugs, will be subject to the age-old maxim "one size prescription does not fit all". In this context, pharmacogenomics is the study of genome-by-drug interactions and offers insights on mechanisms of patient-to-patient and between-population variations in drug efficacy and safety. Pharmacogenomics information is crucial to tailoring the patients' prescriptions to achieve COVID-19 preventive and therapeutic interventions that take into account the host biology, patients' genome, and variable environmental exposures that collectively influence drug efficacy and safety. This expert review critically evaluates and summarizes the pharmacogenomics and personalized medicine aspects of the emerging COVID-19 drugs, and other selected drug interventions deployed to date. Here, we aim to sort out the hope, hype, and reality and suggest that there are veritable prospects to advance COVID-19 medicines for public health benefits, provided that pharmacogenomics is considered and implemented adequately. Pharmacogenomics is an integral part of rational and evidence-based medical practice. Scientists, health care professionals, pharmacists, pharmacovigilance practitioners, and importantly, patients stand to benefit by expanding the current pandemic response toolbox by the science of pharmacogenomics, and its applications in COVID-19 medicines and clinical trials.

1. Introduction

The COVID-19 pandemic is continuing to wreak havoc with new virus variants continuing to emerge. To the extent the COVID-19 vaccines are not broadly and equitably accessible around the world, the pandemic will, unfortunately, likely continue. Meanwhile, efforts are also underway for the COVID-19 drugs, in addition to the vaccines, thus raising the possibility of the pandemic evolving into an endemic recurring infection in the future. COVID-19 medicines are of broad interest for the prevention and treatment of COVID-19.

Pharmacogenomics is a specialty that examines genome-by-drug interactions and has roots in the early 20th century in the field of biochemical genetics. "Drugs don't work in everyone" is the maxim that scholars in the field of pharmacogenetics and personalized medicine know all too well. As COVID-19 drugs are beginning to emerge in clinical practice, it is time to recall this principle and deploy the science of pharmacogenomics. Understanding the mechanisms of person-to-person and between-population variations in drug safety and efficacy is fundamental to rational drug development. Pharmacogenomics is an integral part of rational and evidence-based medical practice.

Pharmacogenetics and personalized medicine are not in conflict with public health measures against COVID-19 because they make the expeditious development of new medicines possible by helping forecast their pharmacokinetic and pharmacodynamic properties early in the discovery and clinical trials phase. The aim of the present expert review is to highlight and examine the prospects for pharmacogenomics and personalized medicine for the emerging COVID-19 drugs and some of the drug interventions deployed to date. We sort out the hope, hype, and reality and suggest that there are veritable prospects to advance COVID-19 medicines for public health benefits, provided that pharmacogenomics is considered and implemented adequately.

For this narrative review study, the search strategy and information sources was explored in databases of PubMed, ISI, Scopus, Embase, Web of Science and search engines, including Google Scholar between the years 2000–2022 using the terms of medical subject headings (MeSH) and combinations of the keywords according to the following: "COVID-

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19", "coronavirus disease 2019", "coronavirus disease 2019", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2", "pharmacogenomics", "pharmacogenetics", "pharmacogenetic testing", "drug related genetics'', "antivirals", COVID-19 treatment''. The abstracted data was screened and extracted by two researchers from the included studies to remove any duplicates, and the selection criteria were strictly adhered to. The accuracy and quality of the included data were checked by a third researcher. The inclusion criteria included screening of the titles and abstracts of eligible studies in English language identified through the keywords found from the search sources and databases. Potentially relevant articles were retrieved for an evaluation of the full text. The research process excluded studies and articles with the following criteria: (1) publications language other than English; (2) articles not discussing SARS-CoV-2 or COVID-19, COVID-19 treatment, drug related genetics or drug pharmacogenomics related to COVID-19 treatment.

2. Antiviral agents

2.1. Remdesivir

Remdesivir is a monophosphoramidate nucleoside analogue primarily developed for the treatment of RNA-viruses that have pandemic potential, such as the Ebola virus and members of the Coronaviridae family like SARS, MERS, and human coronaviruses (Eastman et al., 2020). Being an RNA-dependent RNA polymerase (RdRp) inhibitor, remdesivir inhibits the replication of multiple coronaviruses in respiratory epithelial cells [1]. The proposed mechanism of RNA-dependent RNA polymerase (RdRp) inhibitors during COVID-19 is illustrated by Fig. 1.

Remdesivir is approved by the US Food and Drug Administration (FDA) in 2020 for the treatment of COVID-19 in adult and pediatric patients requiring hospitalization. Furthermore, the National Institutes of Health (NIH) recommended remdesivir for hospitalized patients who require supplemental oxygen. Although the WHO reported that the clinical trial data shows no significant decrease in mortality, the European Medical Agency (EMA) and the FDA issued regular approval [2–5].

The plasma half-life is 20 min. Remdesivir is a *prodrug* metabolized to the pharmacologically active nucleoside triphosphate by carboxylesterase 1 (CES1), cathepsin A, and *CYP3A4* (Deb et al., 2021). In addition to *CYP3A4, CYP2C8* and *CYP2D6* are also responsible for the metabolism of remdesivir. In vivo, remdesivir is predominantly metabolized by hydrolase. Moreover, it is also a substrate for the organic anion-transporting polypeptide 1B1 *(OATP1B1)* transporter and the P-glycoprotein (P-gp) transporter [6,7].

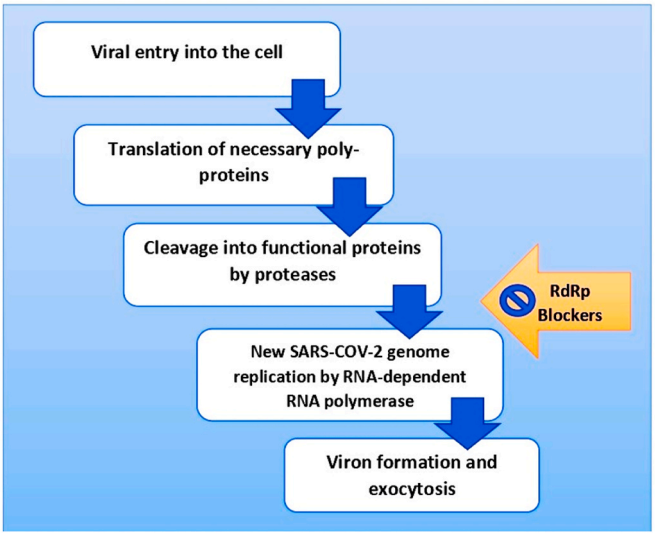

Fig. 1. Mechanism of action of RNA-dependent RNA polymerase (RdRp) inhibitors.

The OATP1B1 is encoded by the solute carrier organic anion transporter family member *1B1 (SLCO1B1)* gene with several variants that can impact drug disposition. For example, Africans, Asians, and Caucasians have been identified with the *rs2306283 c.388A > G* which are associated with a decreased transporter function. Other variants exhibit a low frequency and associate with a decreased function of the transporters *SLCO1B1 rs56101265, rs56061388, rs72559745, rs4149056, rs72559746, rs55901008, rs59502379*, and *rs56199088* [8]. P-gp, an efflux pump encoded by the *ABCB1* gene, plays a role in viral resistance and trafficking cytokines and enveloped viruses. Despite the identification of several *ABCB1* variants, only the *rs1128503 c.1236C > T, the rs2032582 c.2677G > T/A*, and the *rs1045642 c.3435C > T* are relevant in pharmacogenetics studies [9,10].

CYP3A4 is the most abundant hepatic enzyme system expressed in most populations, with the expression of more than 34 allelic variants. During the inflammatory response of COVID-19, *CYP3A4* presents a cytokine-mediated down-regulation via the JAK/STAT pathway, specifically through interleukin-6 (IL-6) [7,11]. In severe COVID-19 patients, the use of steroid therapy with remdesivir could affect the *CYP3A4* transcription, which may result in a lower therapeutic drug level of remdesivir and hence higher IL-6 [12].

CYP2C8 displays low genetic variation, while *CYP2D6* is characterized by extensive genetic variability impacting on the enzyme activity. Those with the duplication or multiplication of active alleles are associated with increased enzyme activity [13]. There is a significant interethnic variability for the *CYP2D6* variants which might cause differences in response to *CYP2D6* substrates in some populations. This is observed with a higher frequency among Caucasians, East Asian populations, and duplication/multiplication of active alleles in Middle Eastern populations, and in Black African populations [14].

The combination of *CYP2D6* alleles could also anticipate the metabolic phenotype of the patients. For example, populations carrying two null alleles are considered poor metabolizers; those with one functional allele and one null allele considered intermediate metabolizers; those with two functional alleles are considered extensive metabolizers, while those with duplicated or multiplied functional alleles are considered ultra-rapid metabolizers [15]. Generally, remdesivir has a low risk of significant genetic pharmacokinetic (PK) interactions, and theoretically, polymorphisms and variants of these genes could affect the PK of remdesivir. Therefore, no evidence recommends pharmacogenetic testing before the administration of remdesivir.

2.2. Lopinavir

Lopinavir is an antiretroviral protease inhibitor and is exclusively administered in combination with ritonavir. Coadministration with low-dose ritonavir significantly improves the pharmacokinetic properties and hence the activity of lopinavir against HIV-1 protease. This is mainly related to ritonavir which is considered a potent inhibitor of the CYP3A4 enzymes responsible for the extensive metabolism of lopinavir. In addition to reducing biotransformation of lopinavir, this combination also improves absorption and oral bioavailability of lopinavir by inhibiting OATP1B1 and OATP1B3 along with P-gp in the gut wall [16]. *CYP3A4* is primarily involved in lopinavir metabolism and is transported by *ABCB1* and *ABCB2*. On the other hand, ritonavir is metabolized by *CYP2J2, CYP3A4, CYP3A5*, and *CYP2D6*. Therefore, the simultaneous administration of lopinavir and ritonavir should be avoided with other drugs that are highly potent *CYP3A* inducers [16,17].

The antiviral activity of lopinavir is produced via the inhibition of the enzyme 3-chemotrypsin-like protease (3CLpro) that has an important role in viral RNA processing and release from the host cell [18]. In addition, lopinavir blocks a post-entry step in the replication cycle of SARS-CoV-2, making lopinavir a promising potential drug for COVID-19

treatment [19]. However, WHO recommends against its use because of the lack of sufficient evidence and potential serious side effects from this combination, such as vomiting, diarrhoea, hypertriglyceridemia, and lipodystrophy [4].

Bioavailability of this antiviral combination can be increased substantially with concurrent ingestion of fatty food. Both agents undergo extensive and rapid first-pass metabolism by hepatic cytochrome P450 (3A4 isoenzyme). With lopinavir/ritonavir 400/100 mg twice daily administration, the elimination half-life and average oral clearance of lopinavir is nearly 4–6 h and nearly 6–7 L/h, respectively. Less than 3% and 20% of the lopinavir dose is excreted unchanged in the urine and faeces, respectively. This antiviral combination has the potential to interact with wide variety of drugs or herbal products via several mechanisms, mostly involving the CYP enzymes and is contraindicated with certain drugs, such as flecainide, propafenone, astemizole, terfenadine, ergot derivatives, cisapride, pimozide, midazolam, triazolam and St. John's wort [20].

Genetic screening of Apo lipoprotein E (APOE) and APOC3 can be initiated to reduce the risk of these complications of hypertriglyceridemia and lipodystrophy associated with ritonavir [21]. Variations of lopinavir concentrations among populations are associated with SLCO1B1. The increased *CYP3A4* activity is related to *CYP3A4* polymorphism *L292P (rs28371759, CYP*18B)* causing an increased lopinavir metabolism. *CYP3A4* polymorphism *L292P* is observed more in East Asian populations who are metabolizing lopinavir and ritonavir more rapidly.

There are many coding single nucleotide polymorphisms (SNPs) in the *ABCB1* gene [22]. The Asian population has a significantly different variant allele frequency of *3435C > T* than the African and Caucasian populations [23]. Many non-synonymous polymorphisms in *ABCB1* are available, such as *S893T, S893A* (rs2032582), *N21D (rs9282564)* and *S400 N (rs2229109)*, which can increase drug concentrations and produce more drug response via reducing the efflux of *ABCB1*. African populations carry the highest frequency of *S893A*, reaching up to 90%. East Asians carry *S893T* and Europeans carry *N21D*. These patient populations may have more responsiveness to the drugs transported by *ABCB1* [24], as shown in Table 1.

Table 1
Points to consider for repurposed medications for COVID-19.

Drug	Transporters	Examples of polymorphic pathways of interest	COVID-19 Treatment Indications
Remdesivir	P-gp OATPB1	*CYP2C8* *CYP2D6* *CYP3A4* *CYP3A4*	Conditional recommendation in hospitalized patients [2–5]
Oseltamivir	P-gp and PepT1	*ABCB1, CES1, NEU2, ABCB1*	Not recommended [33–35]
Atazanavir	P-gp OATPB1	*SLCO1B1* *ABCB1* *UGT1A1* *CYP3A5*	Not recommended [94]
Lopinavir/ ritonavir	P-gp OATPB1	*CYP3A4* *CYP3A4*	Not recommended [94]
Favipiravir	OAT1 and OAT3	Aldehyde oxidase Xanthine oxidase	Not recommended [26]
Tocilizumab	P-gp	*IL6R*	Strong recommended for severe COVID-19 [56]
Interferons	(OATP) 2B1, OATP1B1, OATP1B3	*IFITM3*	Not recommended for severe cases of COVID-19 [79]
Anakinra	P-gp	*IL1α*	Recommended for adult COVID-19 patients with pneumonia at risk of severe respiratory failure [74]
Dexamethasone	P-gp	*CYP3A4* *CYP3A4* *CYP3A4* *CYP3A4*	Strongly recommended for patients with severe and critical COVID-19 [81]
Azithromycin	P-gp MRP2	*ABCB1*	Not recommended [4]

IFITM: Interferon-induced transmembrane protein.
MRP2: Multidrug resistance-associated protein 2.
OATP: Organic anion-transporting polypeptide.
P-gp: P-glycoprotein.
SNP: Single nucleotide polymorphism.

2.3. Favipiravir

Favipiravir is a *prodrug* purine nucleic acid analogue and potent RdRp inhibitor (Fig. 1), that has been licensed as an antiviral medication used to treat influenza since 2014 [25]. Favipiravir selectively inhibits the viral RNA dependent RNA polymerase or causes lethal mutagenesis upon incorporation into the viral RNA. Favipiravir inhibits SARS-CoV-2 replication in Vero E6 cells. Emergency approval of favipiravir in adult patients with COVID-19 was announced by the National Medical Product Administration (NMDA) in China (Du and Chen, 2020), and is still in use in various countries as a potential treatment for COVID-19 due to its efficacy against different viral infections. However, this antiviral agent is neither approved by the FDA nor recommended by the WHO [26].

Favipiravir is available in oral form with excellent bioavailability. It is metabolized in the liver by aldehyde oxidase and partially by xanthine oxidase. The efficacy of substrates of aldehyde oxidase, such as azathioprine or allopurinol, is associated with variants of aldehyde oxidase. Hence, allelic variants of aldehyde oxidase and xanthine oxidase genes should be considered in therapy. Overall safety profile is good with some concerns of gastrointestinal side effects and hyperuricemia [17,27,28].

2.4. Molnupiravir

Molnupiravir is the 5′-isobutyrate *prodrug* of the antiviral ribonucleoside analogue β-D-N4-hydroxycytidine (NHC). Molnupiravir was the first oral antiviral drug approved by the United Kingdom Medicines and Healthcare Products Regulatory Agency and by the FDA for the emergency treatment of COVID-19 in adults. However, molnupiravir's safety profile is still under invisatigation and clinical trilas to detect clinically important side effects regardless its safe use in patients with hepatic and renal impairment. Moreover, benefit of treatment has not been observed when treatment started after COVID-19 hospitalization. Therefore, it is neither indicated for use in younger patients than 18 years of age because of its effect on bone and cartilage growth nor for the pre- or post-exposure prevention of COVID-19 [29,30].

Molnupiravir is an inhibitor of RNA-dependent RNA polymerase (RdRp) that plays an important role in the replication of SARS-COV-2 (Fig. 1). The cellular uptake of circulating NHC is involved in the endogenous phosphorylation of pyrimidine nucleoside pathways to form an active ribonucleoside triphosphate (NHC-TP), which binds to the genome of viral RNA (guanosine or adenosine), and then can be substituted to either cytidine or uridine triphosphate, by viral RNA polymerase. This in turn results in the accumulation of many mutations in the viral genome, leading to both viral suppression and inhibition inside the tissues.

Molnupiravir is hydrolyzed to NHC by esterases *CES1* and *CES2*. The conversion of molnupiravir to NHC could be inhibited by genetic variations in the genes encoding esterases *CES1* and *CES2*. Molnupiravir is a weak substrate of the human nucleoside transporter (CNT1), while NHC is a substrate of the human nucleoside transporters CNT1, CNT2, CNT3, and ENT2. Some patients had no pharmacological response to molnupiravir due to genetic variations in the genes encoding *CNT1, CNT2, CNT3 and ENT2* [31].

Being a *prodrug*, molnupiravir is a 5′-isobutyrate ester is cleaved by

esterases present in the gastrointestinal tissues of the intestine and liver during absorption and hepatic first pass, delivering the ribonucleoside metabolite NHC into systemic circulation. This results in only very low levels of molnupiravir detected in the plasma.

Distribution of molnupiravir, NHC, and NHC-TP is quantified in lung, spleen, kidney, liver, heart and brain. No data is reported for distribution to other tissues, such as bone and cartilage, the GI tract or reproductive tissues. Since molnupiravir is not stable in plasma, the plasma protein binding of molnupiravir was not assessed. Regarding the metabolisim and pharmacogenomic situation, sufficient and reliable data is not published yet of the phase studies and more information is needed to comment on this part [32].

2.5. Oseltamivir

Oseltamivir is an inactive pro-drug antiviral drug indicated for the treatment of influenza A and B infections via peptide transporter 1 (PepT1) after being converted to the active metabolite oseltamivir carboxylate through the hepatic enzyme carboxylesterase 1 (CES1). This active metabolite inhibits viral neuraminidase (NEU2), thereby blocking progeny viral release from infected cells and viral entry into uninfected cells. However, this antiviral drug can be eliminated before being activated as it is a substrate of P-gp. Oseltamivir effectiveness in the treatment of COVID-19 is still under evaluation by several clinical trials [33–35]. A liquid formulation of oseltamivir (2 mg/kg twice daily for 5 days) is effective in the treatment of children with influenza, and may be used in high-risk populations, such as the elderly or those with chronic cardiac or respiratory disease. Furthermore, short term administration oral oseltamivir at a dose of 75 mg once or twice daily for 6 weeks significantly prevented the development of naturally acquired influenza by >70% in unvaccinated healthy adults when administered within 48 h of symptom onset in the infected person. The drug also effective when used adjunctively in previously vaccinated high-risk elderly patients. Oseltamivir is generally well tolerated [36].

After oral administration, oseltamivir is rapidly absorbed from the gastrointestinal tract and its absorption is not significantly affected by the presence of food. It has a high oral bioavailability reaching up to 79% and the plasma concentrations are detected within 30 min of an oral oseltamivir dose. It is then extensively metabolized, mainly by hepatic esterases, to its only active metabolite oseltamivir carboxylate [36]. This metabolite is rapidly distributed to the primary site of influenza virus replication (surface epithelial cells of the respiratory tract) after oral oseltamivir administration. Oseltamivir carboxylate is renally eliminated by a first-order process, primarily by glomerular filtration and renal tubular secretion and has a terminal elimination half-life of 6–10 h. Its clearance is reduced in patients with severe renal dysfunction. Furthermore, the clearance is slower in the elderly (≥65 years) and faster in children (≤12 years) than in adults. There are no clinically significant drug interactions detected with oseltamivir [36].

Clinical and pharmacogenetic studies significantly reported inter-individual variability in the pharmacokinetics and the occurrence of adverse drug reactions (ADRs) to oseltamivir related to the *CES1* genetic variants [37]. *G143E* variants were reported to be 3.7% in Whites, 4.3% in Blacks and 2.0% in Hispanic populations [38]. Variations in plasma concentration-time curve of oseltamivir was also found associated with the *rs71647871 p. Gly143Glu* (Lim et al., 2009). The *rs200707504 c.662A > G* in CES1 was associated with a decreased antiviral drug bioactivation [39].

Oseltamivir ADRs were found associated with variants in *ABCB1, CES1, NEU2*, and *SLC15A1*, the gene encoding the transporter PepT1. In this regard, the *T* allele was predominantly related to the occurrence of ADRs, in contrast to the *C* allele, which was not associated with the reporting of ADRs [40]. Both *CES1* and *ABCB1* genetic variants are considered valid biomarkers for the prediction and optimization of oseltamivir pharmacotherapy [41].

2.6. Atazanavir

Atazanavir is a potent protease inhibitor (PI), approved as a component of antiretroviral therapy (ART) regimens administered once daily for the treatment of patients with HIV-1 infection. It inhibits SARS-CoV2 replication in both Vero cells and human epithelial pulmonary cells. Atazanavir is rapidly absorbed with 60–80% oral bioavailability and reaching peak plasma concentrations (Cmax) after 2–3 h and is metabolized by CYP3A. Atazanavir is ≥ 86% protein bound being 86% bind to albumin and 89% bind to α1-acid glycoprotein [42]. It is extensively metabolized in the liver by CYP3A4 to oxygenated metabolites. After a single 400 mg dose, 79% of atazanavir is mainly eliminated via the biliary route, with only minor elimination via the kidneys (13%). Unchanged drug accounted for 20% and 7% of these quantities [43].

Atazanavir is an inhibitor of *CYP3A* and UDP glucuronosyl transferase 1A (UGT1A). The drug carries several polymorphisms in *UGT1A1*, including a variable dinucleotide (TA) repeat within the gene promoter region [41]. High risk hyperbilirubinemia has been associated with the homozygotes, while intermediate risk hyperbilirubinemia has been associated with the heterozygotes [44]. Therefore, pharmacogenomic counselling before initiating atazanavir therapy is recommended to avoid the development of hyperbilirubinemia [45].

A partial metabolism of atazanavir is mediated by the P-gp efflux pump encoded by the multidrug resistance 1 (MDR1) gene. This increases plasma concentrations of atazanavir in the presence of 3435 variable genetic homozygosis C/C, predisposing the patients to hyperbilirubinemia and severe jaundice. On the other hand, the risk of early onset lipodystrophy is related to polymorphism *238 G > A* [46], while the risk of dyslipidaemia is associated with APOA5 gene polymorphisms *(1131 T > C and 64 G > C), APOC3 (482 C > T, 455 C > T, 3238 C > G)*, and *ABCA1 (2962 A > G)* and *APOE (2 and 3 haplotypes)* [47].

2.7. Nirmatrelvir

Nirmatrelvir is an oral antiviral medication that inhibits SARS-CoV-2 main protease (M^{pro}). M^{pro} is the focus of extensive structure-based drug design efforts, which are mostly covalent inhibitors targeting the catalytic cysteine, thereby impairing the virus's ability to reproduce itself [48,49]. This cysteine is responsible for the activity of the $3CL^{PRO}$ of SARS-CoV-2 and potentially other members of the coronavirus family. $3CL^{PRO}$, also known as the main protease or non-structural protein 5. It is responsible for cleaving polyproteins 1a and 1 ab. These polyproteins contain the $3CL^{PRO}$ itself, a papain-like (PL) cysteine protease, and 14 other non-structural proteins. Without the activity of the $3CL^{PRO}$, non-structural proteins (including proteases) cannot be released to perform their functions, inhibiting viral replication. Nirmatrelvir is co-administered orally with a low dose of ritonavir (PAXLOVID™) for the prevention of COVID-19. It reduces the risk of hospitalization or death by 89% compared to placebo in non-hospitalized high-risk adults with COVID-19 [50].

PAXLOVID treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. The drug is administered orally with or without food at dosage 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days [51].

In vitro, studies suggest that *CYP3A4* has a significant role in the metabolism of nirmatrelvir, which gives the chance to improve the efficacy by co-dosing with a potent CYP3A4 inhibitor like ritonavir [52]. However, the use of ritonavir poses a significant risk of drug interaction due to its potent inhibition profile; patients and clinicians should consult the prescribing information for nirmatrelvir and ritonavir to evaluate any potential for drug interaction with existing medications prior to the initiation of nirmatrelvir.

Ritonavir inhibits not only *CYP* isoenzyme family members like *CYP3A4, CYP2D6, CYP2C19, CYP2C8,* and *CYP2C9*, but also ABCB5 P-

glycoprotein and cellular transport mechanisms via the efflux pump, breast cancer resistance protein ABCG2, organic anion transporting polypeptides (hOCT1) in the liver, and multidrug and toxin extrusion protein in renal drug handling (MATE1). On the other hand, it induces *CYP1A2, CYP2B6, CYP2C9, CYP2C19*, and the *UGT* family.

Because of the potential for the deadly adverse reactions upon its inhibitions and inductions, Nirmatrelvir is contraindicated with drugs that are highly dependent on CYP3A for clearance. The concomitant use of ritonavir with statins, steroids, sedative hypnotics, anticoagulants, and antiarrhythmic therapies is contraindicated [53]. Dosage adjustment is needed in patients with moderate renal impairment, while the drug is not recommended in patients with severe renal impairment. No dosage adjustment is needed in patients with mild or moderate) hepatic impairment. No pharmacokinetic or safety data are available regarding the use of nirmatrelvir or ritonavir in subjects with severe hepatic impairment; therefore, nirmatrelvir is not recommended for use in patients with severe hepatic impairment [51].

3. Biological agents

3.1. Tocilizumab

Tocilizumab was approved by the FDA in 2010 as a novel humanized monoclonal antibody that acts as an interleukin (IL)-6 receptor antagonist and prevents IL-6 signal transduction to inflammatory mediators of the B and T cells for the treatment of cytokine release syndrome, systemic juvenile idiopathic arthritis, giant cell arteritis, and rheumatoid arthritis [54]. Intravenous tocilizumab 8 mg/kg is effective and generally most treatment-emergent adverse events were mild to moderate in intensity and well tolerated. Tocilizumab has a long and concentration dependent half-life, allowing monthly administration. Tocilizumab undergoes biphasic elimination; total clearance is concentration dependent and is the sum of linear and non-linear clearance. Age, sex and ethnicity did not affect the pharmacokinetics of tocilizumab [55].

COVID-19 patients experience severe inflammatory responses, particularly in the lungs, because T-lymphocytes and mononuclear macrophages are activated, inducing the release of inflammatory cytokines, such as IL-6, which bind to the IL-6 receptor on the target cells, causing the cytokine storm [6]. Therefore, the use of tocilizumab has resulted in better outcomes by blocking the IL-6 receptor in patients with severe COVID-19 pneumonia. Accordingly, the WHO recommends the use of tocilizumab for severe or critical patients with COVID-19 [56].

Tocilizumab blocks the downregulation of CYP3A4 caused by IL6. The *FCGR3A* genotype I the only genetic variant potentially affecting the pharmacokinetics of tocilizumab and showed a higher response to drug treatment. On the other hand, genetic polymorphisms in the IL6R gene may affect the intracellular signaling pathway of the IL-6 receptor bound to tocilizumab. Patients with *IL6R rs4*329505 CC and *CT* genotypes may have a decreased response to tocilizumab as compared with patients with the TT genotype. Furthermore, the *rs1*2083537 AA genotype was associated with a decreased response to tocilizumab as compared with the AG genotype. On the other hand, the *rs1*1265618 CC genotype was associated with an increased response to tocilizumab as compared with the CT and TT genotypes [6]. Such genetic variation may predict and affect the therapeutic response of tocilizumab in COVID-19 patients, as shown in Table 1.

3.2. Casirivimab and imdevimab

Casirivimab and imdevimab are a combined neutralizing immunoglobulin gamma 1 (IgG1) human monoclonal antibodies targeting the receptor binding domain of the spike protein of SARS-COV-2 and blocking its binding to human ACE2 receptors [57]. The WHO recommends a combined administration of casirivimab and imdevimab for non-severe patients at the highest risk of hospitalization or severe patients who have seronegative status, as shown in Table 2. In addition, the FDA issued a EUA for casirivimab and imdevimab for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years of age and older, weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

Table 2
Polymorphic enzymes, prevalence and recommendations for medications used in COVID-19 treatment.

Drug	Transporters	Examples of polymorphic pathways of interest	COVID-19 Treatment
Molnupiravir	Unspecified	CNT1, CNT2, CNT3, ENT2	Recommend for emergent severe COVID-19 [29,30]
Nirmatrelvir	P-glycoprotein	CYP3A4*1B	Recommends for the prevention of COVID-19 [50]
	VeroE6 P-gp knock out (KO) cells	CYP3A4*20	
Casirivimab and imdevimab	Unspecified	Unspecified	WHO authorized conditional recommendation for COVID-19 [57]
Tixagevimab and Cilgavimab	Unspecified	Unspecified	Recommends for severe COVID-19 [62]
Bamlanivimab-etesevimab	Unspecified	Unspecified	Recommends for mild-moderate COVID-19 [67]
Sotrovimab	Unspecified	Unspecified	Recommends for mild-moderate COVID-19 [69]

P-gp: P-glycoprotein.

The pharmacokinetics of casirivimab/imdevimab are linear and dose-proportional after a single intravenous (IV) administration of 300–8000 mg. A single 1200 mg intravenous dose of casirivimab/imdevimab has mean maximum serum concentrations (Cmax) of 182.7 and 181.7 mg/L and mean concentrations 28 days after administration of 37.9 and 31.0 mg/L. A single 1200 mg dose subcutaneous administration of casirivimab/imdevimab achieves mean Cmax values of 52.2 and 49.2 mg/L and the mean C28 values of 30.5 and 25.9 mg/L. The intravenous and subcutaneous repeat-dose regimens of this combination achieve serum trough concentrations similar to the mean C28 values seen after a single 1200 mg subcutaneous dose [58].

A single intravenous dose of casirivimab/imdevimab 1200 mg have mean half-lives of 31.2 and 27.3 days, while a single dose of subcutaneous casirivimab/imdevimab 1200 mg, casirivimab had mean half-lives of 30.2 and 32.4 days and imdevimab of 26.5 and 27.0 days. The estimated total volume of distribution of casirivimab is 7.16 L and that of imdevimab is 7.43 L. Both antibodies are degraded into small peptides and amino acids and not metabolized by CYP450 enzymes or be excreted renally or hepatically to any significant extent [58–60].

Patient characteristics, including age, sex, bodyweight, race, hepatic or renal impairment, do not appear to impact casirivimab or imdevimab exposure to any clinically relevant extent. It is not metabolized by CYP450 enzymes or renally excreted, therefoe, no drug-drug interactions between sotrovimab and drugs that are substrates, inducers or inhibitors of CYP450 enzymes or that are renally excreted [58]. Casirivimab/imdevimab, administered via intravenous infusion or subcutaneous injection, was generally well tolerated in clinical studies. There are no risks associated with genetic polymorphisms [61].

3.3. Tixagevimab and cilgavimab

The recently FDA approved monoclonal antibodies (mAbs) are a combination of tixagevimab and cilgavimab can reduce the risk of

COVID-19 hospitalization or death in high-risk patients, as shown in Table 2. As this combination worked to neutralise all previous SARS-CoV-2 variants, these are long-acting human immunoglobulin G1 (IgG1κ) mAbs that are specifically bind to different, non-overlapping sites on the spike protein of the virus and block the SARS-CoV-2 virus' attachment and entry into human cells. The combination is only authorized for adult patients who are not currently infected with the novel coronavirus and have not recently been exposed to an infected individuals [62].

The recommended dose is 300 mg, consisting of 150 mg of tixagevimab and 150 mg of cilgavimab administered as separate sequential intramuscular (IM) injections at different injection sites in two different muscles, preferably in the gluteal muscles. A higher 600 mg dose, consisting of 300 mg of tixagevimab and 300 mg of cilgavimab, may be more appropriate for some SARS-CoV-2 variants [63].

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional after a single intravenous (IV) administration. After a single IM administration of this combination in a phase 1 trial, the mean maximum concentrations (Cmax) of tixagevimab and cilgavimab (16.5 and 15.3 μg/mL) were reached at a median Tmax of 14 days and reaching a bioavialability more than 65% for both mAbs. The central volume of distribution for tixagevimab and cilgavimab was 2.72 and 2.48 L, respectively, and the peripheral volume of distribution was 2.64 L and 2.57 L. The estimated time to reach the minimum protective serum concentration of 2.2 μg/mL in the gluteal region is 6 h [64,65]. The combination is associated with hypersensitivity reactions with some reports of serious cardiac events. Tixagevimab and cilgavimab are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies, while not likely to undergo renal excretion [66]. The pharmacogenomics properties are still under invesatigation to detect risk associated with genetic polymorphisms.

3.4. Bamlanivimab-etesevimab

Bamlanivimab and etesevimab are another mAbs combination approved by the FDA as emergency treatment for mild to moderate COVID-19 including patients with a body mass index (BMI) of ≥35 kg/m^2, chronic kidney disease, diabetes mellitus, immunosuppressive disease, elders age ≥65, and those with other high-risk comorbidities, as shown in Table 2. Both of bamlanivimab and etesevimab are recombinant neutralizing human IgG1κ mAbs to the spike protein of SARS-CoV-2 and are unmodified in the Fc region and block spike protein attachment to the human ACE2 receptor. The combination bind to different overlapping epitopes in the receptor binding domain (RBD) of the S-protein [67].

Pharmacokinetic profiles of these mAbs are linear and dose proportional following iv infusion with no change in their pharmacokinetics whether administered alone or together, suggesting no interaction between these two drugs. There is limited data about their distribution patterns into human or animal milk. They are not metabolized by CYP isoenzymes, but they are expected to be degraded into small peptides and component amino acids via catabolic pathways in the same manner as endogenous IgG antibodies. In addition, they are not eliminated by renal excretion with mean apparent terminal elimination half-life is 17.6 days for bamlanivimab and 25.1 days for etesevimab. The pharmacogenomic properties are still under invesatigation to detect risk associated with genetic polymorphisms [68].

3.5. Sotrovimab

Sotrovimab is a recombinant human monoclonal immunoglobulin G1 antibody targeted against the SARS-CoV-2 and engineered to enhance distribution in the lungs and to extend antibody half-life. It is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2. Sotrovimab is considered an alternative to casirivimab-imdevimab, a mAb approved by the FDA, EU and WHO as emergency treatment for mild to moderate COVID-19 in adolescents (aged ≥12 years and weighing ≥40 kg) who do not require oxygen supplementation and who are at high risk of progressing to severe COVID-19 [69], as shown in Table 2.

The geometric mean Cmax following a 1 h iv infusion is 117.6 μg/mL. The mean steady-state volume of distribution of sotrovimab was 8.1 L. The metabolism of sotrovimab is an engineered human IgG1 mAb degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue. Regarding the elimination, the mean systemic clearance is 125 mL/day with a median terminal half-life of approximately 49 days.

Patient characteristics, including age, hepatic and kidney impairments, do not appear to have any clinically significant impact on the pharmacokinetics or elimination of sotrovimab. It is not metabolized by CYP450 enzymes or renally excreted, therefoe, no drug-drug interactions between sotrovimab and drugs that are substrates, inducers or inhibitors of CYP450 enzymes or that are renally excreted [70]. The pharmacogenomic properties are still under investigation to detect risk associated with genetic polymorphisms [71].

3.6. Anakinra

Anakinra is a recombinant nonglycosylated form of human IL-1 receptor antagonist (IL-1ra) which designed specifically to modify the biological immune response of IL-1 and approved by the FDA in 2001 for the treatment of rheumatoid arthritis [17]. It is manufactured using recombinant DNA technology, that competitively inhibits IL-1α and IL-1β from binding to the IL-1 type I receptor. The clearance of anakinra is like that of creatinine and is directly related to renal function and is reduced in patients with renal impairment. Therefore, dosage modification should be considered only for individuals with moderate to severe renal impairment. However, no dosage adjustment is required in patients with hepatic impairment. To date, no pharmacokinetic interactions have been reported between anakinra and drugs likely to be co-administered [72].

The anti-inflammatory effect during the COVID-19-induced cytokine storm is the primary reason for its repurposing. In some studies, anakinra was found effective in reducing clinical signs of hyperinflammation in critically ill COVID-19 patients. However, more clinical trial studies need to be done to reach conclusive evidence that supports its efficacy [73]. Anakinra is only recommended by EMA for adult COVID-19 patients with pneumonia requiring supplemental oxygen and who are at risk of developing severe respiratory failure [74].

Although anakinra is not metabolized by Phase I or Phase II enzymes, IL-1 genes are responsible for the response to anakinra treatment. *The G4845T (rs17651) T allele* was found to alter IL-1α production, shifting the responsiveness to anakinra [6]. The response rate of patients carrying a rare allele of the gene is significantly higher than those who do not [75].

3.7. Interferons

Interferons (IFNs) are a group of signaling glycoproteins known as cytokines that are capable of interfering with viral replication, expressed rapidly during the process of a viral infection. Therefore, they form an important part of a very early and virus-unspecific host defense mechanism against multiple viruses. They are divided into type I interferons (several interferon alpha subtypes, interferon beta, interferon epsilon, interferon kappa, interferon omega), type II interferons (interferon gamma) and type III interferons (several interferon lambda subtypes). Interferons are licensed for their potential role against both DNA/RNA viruses. High doses of interferons should be administered to achieve high serum levels which are probably essential for antiviral treatment. Moreover, interferons are formulated in pegylated forms to prolong the

elimination half-life and thus to decrease the necessary administration frequency [76,77].

Pharmacogenomics variables for interferons are not well-defined. However, studies suggest that polymorphism on the interferon-induced transmembrane protein-3 (IFITM3) gene, particularly *SNP rs12252*, is associated with more severe COVID-19 prognosis in an age-dependent way, which is more prevalent in the Asian population, as shown in Table 1. The IFITM3 gene encodes an immune effector protein critical to viral restriction and acts to restrict membrane fusion [78]. IFNs have been suggested as a potential treatment for COVID-19 because of their antiviral properties [6]. Nevertheless, since most of the studies conducted on interferon efficacy in managing COVID-19 were of low quality and did not reach a conclusive result, the recommendation currently is against using IFNs for severe cases of COVID-19 [79].

4. Anti-inflammatory agents

4.1. Dexamethasone

Dexamethasone is a glucocorticosteroid used in the treatment of a wide variety of clinical disease conditions for its potent anti-inflammatory and immunosuppressive effects by suppressing cytokine release and inhibiting lung infiltration by neutrophils and other leukocytes. Dexamethasone decreases vasodilation, permeability of capillaries and leukocyte migration to sites of tissue inflammation by binding to the specific glucocorticoid receptors, such as *NR3C1* and *NR3C2*, which start a series of changes in gene expression [80]. Systemic dexamethasone blunted COVID-19-induced systemic inflammatory and cytokine responses that can lead to lung injury and multisystem organ dysfunction. Currently, the WHO strongly recommends the use of dexamethasone orally or intravenously only for hospitalized patients with severe and critical COVID-19 who need either mechanical ventilation or supplemental oxygen. This is also recommended by the NIH and EMA for paediatric patients [81].

P-gp is the main substrate for dexamethasone, while it has a relatively low hepatic extraction, it is majorly metabolized by the cytochrome P450 enzymatic system, primarily the *CYP3A4* isoform and, to a lesser extent, *CYP3A5*. Dexamethasone is hydroxylated to 6α- and 6β-hydroxydexamethasone and is converted to 11-dehydrodexamethasone by the action of corticosteroid 11-beta-dehydrogenase isozyme 2, which can be reconverted by corticosteroid 11-beta-dehydrogenase isozyme 1 [82]. Thus, *CYP3A4* is highly polymorphic, and the genetic variations and co-treatment with *CYP3A4* inhibitors can modulate gene function and may affect the pharmacokinetics of dexamethasone and increase its risk of systemic side effects [83].

Approximately 108 polymorphisms have been identified in the glucocorticoid receptors-*NR3C1* gene. The minor allele frequency of nine nonsynonymous SNPs and four synonymous SNPs was more than 5% among these polymorphisms [84]. On the other hand, thirteen SNPs have been identified across different populations and were clinically associated with a dexamethasone response. Among these variations, *rs2032582* and *rs1045642* in the *ABCB1* gene show the highest frequency of risk alleles in different populations of the genome aggregation database [85].

The *rs6190 (ER22/*23 EK*), rs56149945 (N363S), rs41423247 (BclI)* and *rs6198 (9beta)* are the most common four polymorphisms in the NR3C1 gene that have been linked to dexamethasone response. Two alleles were associated with increased dexamethasone response, which were the *BclI G* and *363S* alleles, whereas the *22/*23 EK allele was associated with decreased drug response [86]. Dexamethasone treatment also shows sex-specific modulation in the *NR3C2* gene via the *rs5522* and *rs2070951* allels. The *rs5522* showed a weak response in males with a homozygous AA genotype, whereas *rs2070951* showed an enhanced response in females and a weak response in male G-allele carriers [87].

5. Other agents

5.1. Azithromycin

Azithromycin is an azalide antimicrobial agent and structurally related to the macrolide erythromycin that was initially approved by the FDA in 1991 to treat respiratory infections like bronchitis and pneumonia, enteric bacterial infections, and genitourinary infections [16]. It interferes with bacterial protein synthesis by binding to the 50S component of the 70S ribosomal subunit [88]. Due to its structural properties, azithromycin does not interact with cytochrome P450 enzymes, but it is a substrate of the transporters P-gp and MRP2 [89]. The interaction of azithromycin with P-gp suggests being the reason for its efficacy in the COVID-19 treatment and its synergistic effect when combined with hydroxychloroquine [90,91].

Influence gene polymorphisms of azithromycin were found to be single nucleotide polymorphisms of *C1236T, G2677* T/A, and *C3435T* in the *ABCB1* gene, which may have a considerable impact on the pharmacokinetics of azithromycin, particularly among the Chinese Han ethnic group. The prevalence of the *3435C* allele is higher in African ancestry than in European populations [[92]. [93]].

Azithromycin was used with a well-known safety profile in combination with chloroquine and hydroxychloroquine to treat COVID-19 when the pandemic first broke out. Azithromycin showed in vitro antiviral activity against COVID-19 through different parts of the viral cycle. In addition, it has immunomodulatory properties via the ability to down-regulate cytokine production, maintain epithelial cell integrity, and prevent lung fibrosis. However, the evidence of its usefulness was questioned and of low quality and is currently not recommended for the treatment of COVID-19 [4].

6. Conclusions

Although the genetic determinants, mechanisms, and pharmacogenetic biomarkers are established and deployed to date for many of the current repurposed drugs, no evidence-based guidelines for genetic testing and pharmacogenomic data are currently available in patients with COVID-19 to minimize possible adverse events and pharmacogenomic burden. Incorporating adequate knowledge of a pharmacogenomic approach; evaluation of further pharmacogenetic biomarkers and personalized medicine aspects should be prioritized in the prospective clinical studies. Repurposed drugs and interventions of emerging therapies of COVID-19 are hoped and hyped to achieve personalized therapeutic outcomes and veritable prospects to advance COVID-19 medicines for public health benefits.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Sardas S, conceived of the study. AL-TAIE A and Büyük AS reviewed the literature, conducted the quality assessment, and extracted the data. Sardas S and AL-TAIE A reviewed the data, and drafted the manuscript. Sardas S and AL-TAIE A were the project manager and advisor on the project. All authors read and approved the final manuscript.

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