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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Considerations into pharmacogenomics of COVID-19 pharmacotherapy: Hope, hype and reality

Anmar AL-Taie a,∗, Ayşe Şeyma Büyük b, Semra Sardas b

a Clinical Pharmacy Department, Faculty of Pharmacy, İstinye University, Istanbul, Turkey
b Department of Pharmaceutical Toxicology, Faculty of Pharmacy, İstinye University, Istanbul, Turkey

ARTICLE INFO

Keywords: COVID-19, Pharmacogenomics, Personalized medicine, Clinical trials, Molnupiravir

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 in the future. COVID-19 medicines are of broad interest for raising the possibility of the pandemic evolving into an endemic recurring in the future. COVID-19 medicines are of broad interest for public health and clinical practice. 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.

Pharmacogenomics 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-
require supplemental oxygen. Although the WHO reported that the 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 \[6,7\].

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 rs2006283 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 (3CPro) 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
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, extensive and rapid first-pass metabolism by hepatic cytochrome P450 3A4 isoenzyme.

Hence, allelic variants of aldehyde oxidase and xanthine oxidase genes are associated with the metabolism of favipiravir. In East Asian populations, who are metabolizing lopinavir and ritonavir with SLCO1B1. The increased CYP3A4 activity is related to CYP3A4 polymorphism L292P (rs28371759, CYP*1B8) 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 (rs2982564) and S400 N (rs2229109), which can increase drug concentrations and produce more drug response via reducing the efflux of ABCB1. Asian 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.

### 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 invasitgation and clinical trials 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 metabolism and pharmacogenetic 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 8–12 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 [29].

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 oxygénated 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 homozgyosis 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 (1311 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 (MPRO). MPRO 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 3CLpro of SARS-CoV-2 and potentially other members of the coronavirus family. 3CLpro, also known as the main protease or non-structural protein 5. It is responsible for cleaving polypeptides 1a and 1b. These polypeptides contain the 3CLpro itself, a papain-like (PL) cysteine protease, and 14 other non-structural proteins. Without the activity of the 3CLpro, 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 antithrombotic 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 rs4329505 CC and CT genotypes may have a decreased response to tocilizumab as compared with patients with the TT genotype. Furthermore, the rs12083537 AA genotype was associated with a decreased response to tocilizumab as compared with the AG genotype. On the other hand, the rs11265618 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 immuno-globulin 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

| 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] |
| 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 [60] |

P-gp: P-glycoprotein.

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.

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 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].

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 or metabolized by CYP450 enzymes or be excreted renally or heptatically 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, therefore, 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-κ 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 individual [62].

The pharmacokinetics of tixagevimab and cilgavimab are comparable, linear and dose-proportional after a single intravenous (IV) or intramuscular (IM) injection 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 concentration (Cmax) of tixagevimab and cilgavimab (16.5 and 15.3 μg/mL) were reached at a median Tmax of 14 days and reaching a bioavailability 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 investigation 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/m², 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 investigation 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-κ 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-imerdevimab, 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 IgG1κ 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, therefore, 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 likely 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 hyper-inflammation 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-1 receptor 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 isoenzym and, to a lesser extent, CYP3A5. Dexamethasone is hydroxylated to 6α- and 6β-hydroxydexamethasone and is converted to 11-dehydroxymethasone 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 rs16190 (ER22/23 EK), rs56149945 (N363S), rs41423247 (Bcll) 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 Bcll 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 alleles. 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 macroclide erythromycin that was initially approved by the FDA in 1991 to treat respiratory infections like bronchitis and pneumonia, enteric bacterial infections, and gentiourinary 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 C1226T, 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 pharmacogenetic 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.

Funding

Not applicable.
References

[1] Y.C. Yao, Q.X. Deng, S.X. Dai, Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: an evaluation of the evidence, Trav. Med. Infect. Dis. 35 (2020), 101647, https://doi.org/10.1016/j.tmrid.2020.101647.

[2] J.H. Beigel, K.M. Tomashek, L.E. Dodd, et al., Remdesivir for the treatment of covid-19 final report, N. Engl. J. Med. 383 (19) (2020) 1813–1826, https://doi.org/10.1056/NEJMoA2007764.

[3] World Health Organization, WHO Recommends Two New Drugs to Treat COVID-19, 2022. Available from: https://www.who.int/news/item/14-01-2022-who-recommends-two-new-drugs-to-treat-covid-19 (Accessed 28 March 2022).

[4] WHO Solidarity Trial Consortium, Repurposed antiviral drugs for COVID-19: interim WHO Solidarity trial results, N. Engl. J. Med. 384 (6) (2021) 497–511, https://doi.org/10.1056/NEJMa2023194.

[5] European Medicines Agency, Update on Remdesivir - EMA Will Evaluate New Data from Solidarity Trial, 2020. Available from: https://www.ema.europa.eu/en/news/update-remdesivir-ema-will-evaluate-new-data-solidarity-trial (Accessed 6 July 2021).

[6] P. Zubiaur, D. Koller, M. Seraiz-Rodriguez, et al., Important pharmacogenetic information for drugs prescribed during the SARS-CoV-2 infection (COVID-19), Clin Transl Sci 13 (6) (2020) 1023–1028, https://doi.org/10.1111/cts.12692.

[7] T. Hartmann, M. Teras, G. Garattini, et al., The impact of single nucleotide polymorphisms on human aldehyde dehydrogenase, Drug Metab. Dispos. 40 (5) (2012) 856–864, https://doi.org/10.1124/dmd.111.043828.

[8] X. Ai, H. Huang, Z. Miao, et al., Relationship between sars-cov-2 genotype and antiviral efficacy, Infect. Genet. Evol. 93 (2021), 104991, https://doi.org/10.1016/j.ijigoe.2021.104991.

[9] G.P. Painter, M.G. Natchus, O. Cohen, et al., Developing a direct acting, orally available antiviral agent in a pandemic: the evolution of molnupiravir as a potential treatment for COVID-19, Curr. Opin. Virol. 50 (2021) 17–22, https://doi.org/10.1016/j.covirol.2021.06.003.

[10] S. Shah, P.R. Denkdemir, Z. Sharief, et al., The long view on COVID-19 theranostics and oral antivirals: living with emerging disease and lessons from molnupiravir, OMICS A J. Integr. Biol. 26 (6) (2022) 324–328, https://doi.org/10.1089/omi.2022.0045.

[11] F. Pourkarim, S. Pourtaghi-Anvarian, H. Rezaee, Molnupiravir a new candidate drug in treatment of COVID 19, Pharmacol. Res. Perspect. 10 (1) (2022), e00909, https://doi.org/10.1002/prp2.e00909.

[12] European Medicines Agency, Use of Molnupiravir for the Treatment of COVID-19, 2020. Available from: https://www.ema.europa.eu/en/documents/referral/lagevrio_–also-known-molnupiravir-mk-4482-covid-19-article-53-procedure-assessment-report_en.pdf (Accessed 20 February 2022).

[13] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, JAMA 323 (18) (2020) 1824–1836, https://doi.org/10.1001/jama.2020.619.

[14] C. Mizzi, E. Dalabéra, J. Kunthutti, et al., A European spectrum of pharmacogenomic biomarkers: implications for clinical pharmacogenomics, PLoS One 11 (9) (2016), e0162866, https://doi.org/10.1371/journal.pone.0162866.

[15] H. Uggglen, G. Alvan, M. Jerling, On the question of interindividual variations in chloroquine concentrations, Eur. J. Clin. Pharmacol. 25 (5) (1983) 534–553, https://doi.org/10.1007/BF00619556.

[16] E. Hørsted, M. Eklund, L. Backman, et al., Crystal structure of SARS-CoV-2 main protease in complex with the non-covalent inhibitor ML188, Viruses 13 (2) (2021) 864, https://doi.org/10.3390/v13020864.

[17] G.J. Lockbaum, A.C. Reyes, J.M. Lee, et al., Crystal structure of SARS-CoV-2 main protease in complex with the non-covalent inhibitor ML188, Viruses 13 (2) (2021) 864, https://doi.org/10.3390/v13020864.

[18] K. McClellan, C.M. Perry, Oseitamivir. Drugs 61 (2001) 263–283, https://doi.org/10.2165/00003495-200161020-00011.

[19] T. Ou, H. Mou, L. Zhang, et al., Hydroxychloroquine-mediated inhibition of SARS-CoV-2 entry is attenuated by TMPRSS2, PLoS Pathog. 17 (1) (2021), e1009212, https://doi.org/10.1371/journal.ppat.1009212.

[20] H.Z. Zhu, J.S. Markowitz, Activation of the antiviral prodrug oseitamivir is impaired by two newly identified carboxylesterase 1 variants, Drug Metabol. Dispos. 37 (2009) 264–267, https://doi.org/10.1124/dmd.108.009493.

[21] R.L. Murphy, B. Bezirits, C. Zala, et al., SABAR Study Team, Change to atazanavir/ritonavir treatment improves lipids but not endothelial function in patients on stable antiretroviral therapy, AIDS 24 (6) (2010) 885–890, https://doi.org/10.1097/QAD.0b013e3283352ed5.

[22] S. Walker, A. Bachtiar, J. Wang, et al., An update on ABCB1 pharmacogenetics: insights from a 3D model into the location and evolutionary conservation of residues corresponding to SNPs associated with drug pharmacokinetics, Pharmacogenomics J. 11 (5) (2011) 315–325, https://doi.org/10.1007/s13292-011-0016-6.

[23] C. Balram, A. Sharma, C. Srivathasan, et al., Frequency of C4345T single nucleotide MDR1 genetic polymorphism in an Asian population: phenotype-genotypic correlates, Br. J. Clin. Pharmacol. 56 (1) (2003) 78–83, https://doi.org/10.1046/j.1365-2125.2003.01820.x.

[24] J. Ryan, R.D. Mittal, R. Mittal, The effect of ABCB1 polymorphisms on the outcome of breast cancer treatment, Pharmacogenomics Personalized Med. 9 (2016) 47–58, https://doi.org/10.2147/PPM.S66672.

[25] K. Shiraki, T. Daikoku, Fivapiravir, an anti-influenza drug for life-threatening RNA virus infections, Pharmacol. Ther. 209 (2020), 107512, https://doi.org/10.1016/j.pharmthera.2020.107512.

[26] M. Ghassanejad-Berenji, S. Pashapoor, Fivapiravir and covid-19: a simplified summary, Drug Res. 71 (3) (2021) 166–170, https://doi.org/10.1055/a-1296-7925.

[27] T. Hartmann, M. Teras, E. Garattini, et al., The impact of single nucleotide polymorphisms on human aldehyde dehydrogenase, Drug Metab. Dispos. 40 (5) (2012) 856–864, https://doi.org/10.1124/dmd.111.043828.

[28] R.S. Gammal, M.H. Court, C.E. Haidar, et al., Clinical pharmacogenetics implementation consortium and Dutch pharmacogenetics network, Pharmacogenet. Genomics 19 (2009) 553, https://doi.org/10.1097/FPC.0b013e32832180c7.

[29] M. Costanzo, M.A. De Giglio, G.N. Roviello, SARS-CoV-2: recent reports on antiviral therapies based on licopid, ritonavir, darunavir/umefenovic, hydroxychloroquine, remdesivir, favipiravir and one drug for the treatment of the new coronavirus, Curr. Med. Chem. 27 (27) (2020) 4536–4541, https://doi.org/10.2174/0929877327662004161117.

[30] R.S. Cvetkovic, K.L. Goa, Ritonavir/Ritavir. Drugs 63 (2003) 769–802, https://doi.org/10.2165/00003495-200306090-00004.
