

Pharmacogenomics and Pharmacogenetics: In Silico Prediction of Drug Effects in Treatments for Novel Coronavirus SARS-CoV2 Disease

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Abstract: The latest developments in precision medicine allow the modulation of therapeutic approaches in different pathologies on the basis of the specific molecular characterization of the patient. This review of the literature coupled with in silico analysis was to provide a selected screening of interactions between single-nucleotide polymorphisms (SNPs) and drugs (repurposed, investigational, and biological agents) showing efficacy and toxicity in counteracting Covid-19 infection. In silico analysis of genetic variants related to each drug was performed on such databases as PharmGKB, Ensembl Genome Browser, www.drugs.com, and SNPedia, with an extensive literature review of papers (to May 10, 2020) on Covid-19 treatments using Medline, Embase, International Pharmaceutical Abstracts, PharmGKB, and Google Scholar. The clinical relevance of SNPs, known as both drug targets and markers, considering genetic variations with known drug responses, and the therapeutic consequences are discussed. In the context of clinical treatment of Covid-19, including infection prevention, control measures, and supportive care, this review highlights the importance of a personalized approach in the final selection of therapy, which is probably essential in the management of the Covid-19 pandemic.

Keywords: Covid-19, SARS-CoV2, drug effects, pharmacogenomics, pharmacogenetics, in silico, ADR

Introduction

Covid-19, an emergency all over the world, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a positive-sense RNA virus with higher mutation rates than DNA viruses.^{1,2} Laboratory tests on respiratory tract specimens (swab/saliva/tears PCR and serological tests) and computed tomography (CT; for chest or other tissue) should stage as soon as possible the presence of disease and its evolution/progression.^{3,4} SARS-CoV2 binds principally to the cell-membrane ACE2 receptor through the viral structural spike (S) protein, although other “virus doors” have been suggested (integrins and Toll-like receptors)⁵ (Figure 1). At the intracellular level, the virus activates cellular processes to produce viral proteins that replicate the virus’s genetic material, providing potential targets for drug therapy.^{1,5,6}

SARS-CoV2 Infection and Main Clinical Aspects

Covid-19 features, diagnostic route, and early, mild, and severe Covid-19 symptoms are summarized in Figure 1. Virus entry and multiple signaling pathways (Ca²⁺

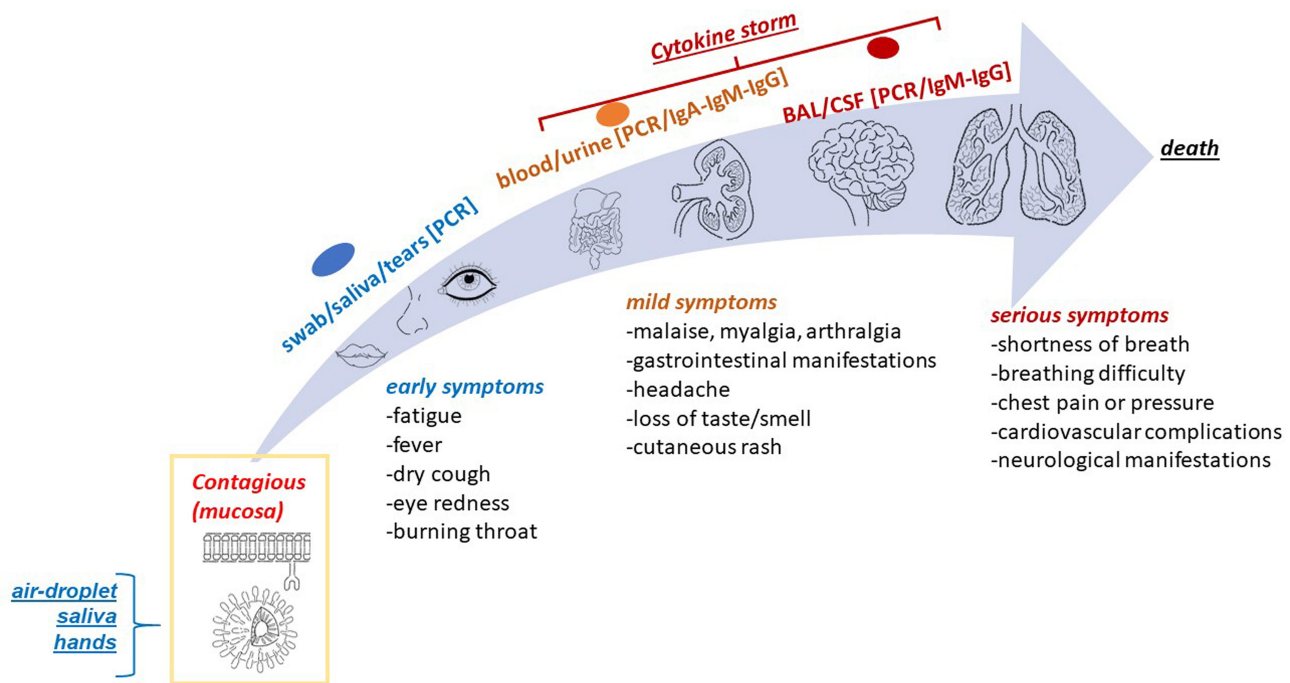


Figure 1 Overview of Covid-19 infection: SARS-CoV2–host interaction and tissue manifestation. Schematic representation of SARS-CoV2 virus interacting with mucosa epithelia (framed) and gradual sprouting to gut, kidney, brain, and lung tissue. “Virus doors” reported were ACE2, integrin, TLR3, or TMPRSS2. Overall symptoms are listed. Briefly, most common Covid-19 symptoms occur at the upper respiratory tract, together with asthenia and general malaise. Early, less common clinical features include gastrointestinal symptoms (nausea, anorexia, diarrhea), anosmia and dysgeusia. Severe cases encompass pneumonia or bronchopneumonia, severe acute respiratory syndrome, renal failure, up to death. The lower respiratory tract participation and complications are more frequent in people aged over 50 with pre-existing chronic diseases of cardiovascular and/or respiratory system, as well as some autoimmune diseases (diabetes). Cardiac involvement represents another potentially life-threatening complication, caused by direct viral damage, hypoxic injury, microvascular dysfunction and disclosing with diverse clinical pictures (arrhythmias, myocarditis, and heart failure). Finally, virus can reach central nervous system causing central (acute cerebrovascular diseases, impairment of consciousness) and peripheral complications. The evolution of infection from early detection severe complications and death (shaded arrow). As reported, molecular and serological, as well as imaging tests, are useful depending on disease evolution: real-time PCR applied to nasopharyngeal swabs, venous blood as well as conjunctival swabs can track disease ongoing, while early-released IgM and late-released IgG might assess for immune response, in line with cytokine storm panel (IL6, TNF α , IFN γ , and IL10) typifying tissue/organ complications.

release, cSrc, FAK, MAPK, and PI3K) occur upon Spike2–RGD–integrin interaction.⁷ A “cytokine storm” is locally released (IL1 β , IL6, IL8, TNF α , MIP1 α , and VEGF), as first observed in patients showing fatal complications.⁵ This specific panel was used to screen patients requiring prompt intervention to avoid acute respiratory distress syndrome (ARDS).⁶ In a recent study, candidate drug targets for nonstructural proteins (3-chymotrypsin–like protease, papain-like protease, RNA-dependent RNA polymerase), viral access, and related immuno regulatory pathways have been prospected for evaluation.^{6,8,9} A wide range of pulmonary manifestations can be observed, varying from mild respiratory symptoms (cough or sore throat) to severe pneumonia, up to a sudden development of respiratory failure.¹⁰ Silent hypoxemia is a peculiar aspect frequent in frail and elderly patients that usually precedes the onset of an overt acute and severe respiratory syndrome.^{11,12} Chest CT imaging is strongly recommended for an early diagnosis of novel coronavirus pneumonia.^{13,14} CT findings, including patterns associated

with less frequent signs, eg, lobular, bronchial, pleural, and subpleural involvement, as well as pleural lymphadenopathy and pericardial effusion, have been described.¹⁵ SARS-CoV2 initially causes airspace exudates, interstitial edema, hyaline membranes, and inflammatory infiltrates in the alveoli.¹⁶ Other than the deleterious lung effects, systemic SARS-CoV2 has a significant impact on the hematopoietic system and tissue homeostasis.¹⁷ Initially, lymphopenia showed interesting prognostic value, for both neutrophil:lymphocyte and platelet:lymphocyte ratios in severe SARS-CoV2 cases. Lymphocyte parameters (count dynamics), some inflammatory indices (LDH, CRP, and IL6), and some recent circulating biomarkers (high serum procalcitonin and ferritin) have been suggested for identifying cases with poor prognosis (prompt intervention and improved outcomes). As observed, blood hypercoagulability, high D-dimer levels (particularly associated with disease worsening), protraction of both prothrombin (PT) time, activated partial thromboplastin time (aPTT), and disseminated intravascular coagulation

require constant surveillance to allow prompt intervention. In addition to upper-airway contact, conjunctivitis may be an ocular manifestation of SARS-CoV2 infection, if quickly detected.¹⁸ In December 2019, a Chinese ophthalmologist reported an unusual viral conjunctivitis. To date, several Internet articles and scientific reports have documented the potential use of eye swabs as a tool to screen virus infection, although contrasting data are available, most probably related to progression of infection and virus detection.¹⁹ In January 2020, a worldwide expert in infectious diseases referred to conjunctivitis during an inspection of Wuhan and tested positive for SARS-CoV2, but quickly recovered from infection. This led to the idea of “eye infection” as a possible alternative route of SARS-CoV2 transmission, alternative to the respiratory one.²⁰ Ocular secretion might represent a reservoir of virus at the early stages of contagious.¹⁸ When pinkeye occurs as a sign of conjunctivitis, a differential diagnosis can be of great utility to screen symptomatic and even presymptomatic individuals.²¹

Genetic Background, Individual Responses, and SNP Association

Recently, pharmacogenomics (the effects of a single genetic marker) and pharmacogenetics (the collective influence of variability across the genome to modulate an individual's drug response) have received great attention for their abilities to provide a new way to select drugs for personalized therapy (optimal dosing for maximizing drug efficacy or minimizing the risk of toxicity).^{22,23} Through drug therapy, pharmacogenetics might influence both pharmacokinetics and pharmacodynamics with respect to dosing, formulation sensitivity, and adverse drug reactions (ADRs), as well as drug-hypersensitivity reactions (allergic, pseudoallergic, and exaggerated pharmacological reactions to medications), determining an enhanced immunologic reaction or inflammatory response (side effects).²⁴ Genetic assessment can predict the occurrence of drug-related toxic effects. Single-nucleotide polymorphisms (SNPs) are the most common type of polymorphism found in the human genome, and represent the main reason for 90% of all types of genetic variations among individuals. An example of an ADR is the hypersensitivity reaction occurring in SNP carriers of the HLA-B*5701 allele who receive the antiviral abacavir for treatment of HIV.^{25,26} Covid-19 therapy is wide-ranging and multiple, and risk factors for ADRs can occur. Therefore, optimal doses, duration of treatment, side

effects, and long-term outcomes are critical aspects of Covid-19 therapy.²⁷ CoV-mediated inflammation may be counteracted by anti-inflammatory cytokines, including IL1 family members, IL6, and TNF α .²⁸ Since no specific drug/therapy for Covid-19 treatment has been US Food and Drug Administration (FDA)-approved, an array of drugs approved for other diseases and under investigation (including off-label and biological drugs) have been included in clinical trials.^{29,30} As observed, the metabolic pathways of these drugs included various polymorphic cytochrome P450 enzymes, strongly suggesting genotyping for the CYP2D6*2, CYP2D6*3, CYP2D6*4, and CYP2D6*10 alleles.^{31,32} As an example, no predictability in the metabolic function of the CYP3A5*3 allele can result in alternative mRNA splicing with a trunked protein, due to the formation of an untimely stop codon. Moreover, haplotype CYP3A5*3 has been related to a reduced clearance of both ritonavir and lopinavir (substrates) (Table 1). Of interest is the association between polymorphisms in *ABCC* and therapy efficacy, as the drug transporters are one of the primary mechanisms related to subtherapeutic antiretroviral-drug concentrations.³³ Prominent research has highlighted the relationship between the *ABCB1* polymorphism (3435 C>T) and hepatotoxicity risk after antiviral treatments, and few additional studies were found regarding other nucleoside analogues.³³ More recently, the presence of grade 3–4 hyperbilirubinemia is directly proportional to the homozygosity, heterozygosity, and wild-type genotyping for the UGT1A1*28 allele in patients who receive ritonavir and lopinavir.³⁴ Therefore, the attempt of this literature review coupled with in silico analysis was to provide a selected screening of drugs showing efficacy and toxicity effects useful for counteracting Covid-19 infection.

Methods

An extensive literature review of papers published until May 10, 2020 was performed based on a standard procedure (Medline, Embase, International Pharmaceutical Abstracts, PharmGKB, and Google Scholar).³⁵ Search terms were “Covid-19”, “novel coronavirus”, “SARS-CoV2”, “pharmacogenetics”, “treatment/s”, “adverse side effects”, “therapy”, “lung”, “ocular”, “pulmonary infection”, “drugs”, “drug response”, “virus”, “candidate drugs”, “potential inhibitors”, “protease inhibitors”, “personalized medicine”, “individual therapy”, “pneumonia”, “ACE”, “heparin”, “vasculitis”, “conjunctivitis”, “rhinitis”, “hematological complication” and “main metabolic

Table I The Most Promising and Repurposed Drugs

Drug (alias)	Main Metabolic Routes	Variants/rs for Toxicity	Variants/rs for Efficacy
Chloroquine	CYP2D6 and CYP3A4 substrate	Variants associated with deficit in G6PD	Not described
Hydroxychloroquine	CYP2D6, CYP3A4, CYP3A5, and CYP2C8 substrate	Variants associated with deficit in G6PD	Not described
Ritonavir	CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer; Pgp substrate; UGT1A1 inducer	rs8175347 INDEL (TA)6/(TA)6, rs17863778, rs7586110, rs429358, rs2854117, rs1042640, rs2854116, rs8330, rs3806596, rs5128, rs717620, rs17868323, rs2853826, rs10929303, rs7412	rs1045642, rs212091
Lopinavir	CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 inducer; Pgp substrate; UGT1A1 inducer	rs717620, rs2853826	rs1045642, rs212091, rs8187710
Ribavirin	CYP3A4 inhibitor and substrate; CYP2D6 substrate; CYP1A2, CYP2C9;	rs7270101, rs1127354, rs1544410, rs11854484, rs6051702	rs2228570, rs760370, rs4803217, rs8105790, rs3828913, rs12819210, rs7248668, rs10846744
Umifenovir	CYP3A4, monitor with strong inducers/inhibitors	Not described	Not described
IFN α and - β	Cleaved by serum esterase	rs2291858, rs1448673, rs10819043, rs2205986	rs12044852, rs3133084, rs760316, rs10494227, rs10760397
Nitazoxanide	UGT1A1 and GSTP1 substrates		Not described
Azithromycin	Biliar excretion, predominantly unchanged; CYP2C9 inhibitor	Not described	Not described
Heparin	XIIa, IXa, XIa, Xa, and IIa low molecular-weight heparin	risk of thrombosis caused by deficit of coagulation factors rs1799963, rs118203907, rs1800595, rs6025, rs1801133, rs1801131, rs1799889, rs5985, rs5918, rs1800790	Not described
Investigational drugs			
Remdesivir	CYP27B inducer	Not described	Not described
Favipiravir	CYP2C8 and aldehyde oxidase inhibitor	Not described	Not described
Atazanavir	CYP3A complex CYP3A5 inducer	rs8175347 INDEL (TA)6/(TA)6, rs17863778, rs7586110, rs1042640, rs8330, rs3806596, rs717620, rs17868323, rs10929303	rs887829, rs2740574
Darunavir	CYP3A4	Not described	rs8027174
Adjunctive experimental therapies			
Tocilizumab	Cleaved by serum esterase	Not described	rs4329505, rs12083537, rs11265618, rs11052877, rs396991, rs4910008

(Continued)

Table 1 (Continued).

Drug (alias)	Main Metabolic Routes	Variants/rs for Toxicity	Variants/rs for Efficacy
Sarilumab	Cleaved by serum esterase	Not described	rs4329505, rs12083537, rs11265618, rs11052877, rs396991, rs4910008
Bevacizumab	Cleaved by serum esterase	rs6929249, rs834576, rs9381299, rs3734704	Not described
Hydrocortisone	CYP3A complex, CYP2B6 inducer	rs6977967, rs8667	Not described
Methylprednisolone	11 β -hydroxysteroid dehydrogenases and 20-ketosteroid reductases	Not described	Not described
Dexamethasone	CYP3A4, CYP2C8 inducer	rs4553808	Not described
Prednisolone	11 β -hydroxysteroid dehydrogenases and 20-ketosteroid reductases (approved for veterinary use only)	rs738409	Not described
Captopril	CYP2A4 and CYP2D6 inducer, ACE inhibitor	Not described	rs1799752, rs4291, rs2106809, rs5186

routes”, either alone or in combination. From this manually performed analysis, drugs reported in at least two studies or in a clinical trial were included. Ongoing clinical trials and the index of studies of Covid-19 were identified using the search term “coronavirus infection” on [ClinicalTrials.gov](https://clinicaltrials.gov) and the Chinese Clinical Trial Registry (<http://www.chictr.org/enindex.aspx>). In silico analysis of genetic variants related to each drug was performed on dedicated databases, such as PharmGKB (Table 2), Ensembl Genome Browser, www.drugs.com, and SNPedia. The allelic frequency of each variant average in all populations was based on data from the 1000 Genomes Project phase 3. We considered SNPs related to both efficacy and toxicity response with allele frequencies

$\geq 5\%$, as already described in previous studies.^{36,37} The quality of each study was assured, and resulting information included study design, baseline characteristics of disease, treatment regimens, and allelic frequencies of the genetic variant.

Results

Drugs in use as routine therapy or in clinical trials for Covid-19 include steroids and antiviral and biological humanized neutralizing antibodies against some pro-inflammatory cytokines, such as IL1, IL6, IFN, and TNF α , in addition to supportive measures and symptomatic treatment, according to the severity of the disease.³⁸ Data analysis on registered clinical trials of Covid-19 in the

Table 2 Overview of PharmGKB

• PharmGKB	Is one of the foremost worldwide resources for PGx knowledge, and the organization has been adapting and refocusing its mission along with the current revolution in genomic medicine.
	Annotates drug labels containing pharmacogenetic information approved by the US Food and Drug Administration, European Medicines Agency Swiss Agency for Therapeutic Products, Pharmaceuticals and Medical Devices Agency (Japan) and Health Canada.
	Attempts to interpret the level of action implied in each label with the “PGx level”.
• PharmGKB website provides a diverse array of PGx information, from annotations of the primary literature to guidelines for adjusting drug treatment based on genetic information.	
• PharmGKB online pharmacogenomics knowledge resource maintains a list of very important pharmacogene summaries (www.pharmgkb.org/view/vips.jsp), which (until March 2020) describes 22,919 allelic variant annotation in which allelic variation has been shown to significantly influence drug metabolism, drug transport, drug-target response, expression of genes encoding drug-metabolizing enzymes, or risk of adverse drug reactions.	

US is available at <https://clinicaltrials.gov>. Nowadays, a great number of agents have been evaluated for potential use in Covid-19 management, and only a few have been included within international and/or local protocols.³⁸ According to the US National Institutes of Health, no pharmacological agent has earned approval for safe and effective use yet, mainly because of the lack of evidence in favor or against these agents (<https://covid19treatmentguidelines.nih.gov>). One important aspect of a therapeutic approach consists in the choice of the right drugs throughout the natural history of disease. Indeed, a three-phase pathogenetic model has been proposed, with different clinical and laboratory features, each requiring a specific treatment based on the changing role over time, of direct viral damage and host inflammatory response in the disease course. This model describes an early stage (stage I), coinciding with incubation and/or mild flulike symptoms, during which antiviral drugs might reach high effectiveness, a moderate stage (stage II) characterized by pulmonary involvement without IIa or with IIb hypoxia, which may benefit from the use of antivirals and anti-inflammatory therapy (including steroids), and lastly a severe stage (stage III), in which a dysregulated, systemic hyperinflammatory response takes place, thus requiring the administration of immunomodulating agents, several of which are currently under investigation, and in some cases already in use within management protocols.³⁷

Gene variants associated with pharmacological responses to drugs are reported in a dedicated database — PharmGKB (<https://www.pharmgkb.org>) — allowing the identification of relationships between genetic variations (eg, SNPs, indels, repeats, haplotypes) and individual drug responsiveness.^{40,41} Herein, *in silico* pharmacogenetic analysis shows the potential clinical efficacy and/or toxicity of the major drugs selected for Covid-19 treatment. The main drugs proposed for Covid-19 treatments and reference sequence (rs) related to ADRs and efficacy are shown in Table 1. Genes and related SNPs (rs) associated with drug effects and their study annotation are summarized in Table 3.^{42–64} Major clinical information regarding “variant drug” responsiveness (clinical annotations) is highlighted. Bloodstream fluidity requires a tidy balance among factors favoring flow of blood and thrombosis. Any modification in this physiological balance triggers pathological conditions: deficit of coagulation factors favor bleeding, while genetic mutations of coagulation factors can determine a thrombotic risk framework characterized by differences in genetic variants of coagulation

(Table 4). All drugs used as therapeutic options and their study annotation based on pharmacogenetic data are discussed.

The Most Promising and Repurposed Drugs

Chloroquine (Cq) and Hydroxychloroquine (Hcq)

Cq is used for chemoprophylaxis of malaria and amebiasis, while Hcq is used to treat autoimmune disease.⁸ The mechanism of action includes the blocking of viral entry through the inhibition of glycosylation of host receptors, proteolytic processing, and endosomal acidification.⁶⁵ Effects of immunomodulation on cytokine production and inhibition of autophagy/lysosomal activity have been also reported.^{65–67} Several randomized controlled trials (RCTs) are currently investigating Cq and Hcq in Covid-19 treatment (<https://clinicaltrials.gov>). Based on current data, both drugs are recommended for treatment of unhospitalized Covid-19 patients, and the effects of cardiotoxicity in immunosuppressed subjects or patients with kidney or liver problems are known. Recommendations for oral administration in Covid-19 treatment are 500 mg twice a day and 400 mg twice a day, followed by 200 mg twice a day for Cq and Hcq, respectively.⁶⁸ Blood monitoring is required, as hemolytic anemia might occur, particularly when the drug is delivered in association with other drugs that cause hemolysis.⁶⁹ It should not be underestimated the extent to which both drugs may cause hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient individuals. Of note, about 39% of Covid-19 patients suffering from lupus have failed to respond or were even intolerant to Hcq.⁷⁰ Moreover, long-term Cq–Hcq treatment induces retinal toxicity, and particularly when Hcq-related retinopathy is diagnosed, the retinal damage endures, even after cessation of therapy.⁷¹ High doses or prolonged administration of Hcq, even at recommended doses, may increase the risk of ocular toxicity (paracentral scotomas, color-vision changes, corneal/ciliary body/conjunctival as well as retinal abnormalities), and visual disturbances (retinal and macular toxicity).⁷² This would imply that accurate eye screening for confirming SARS-CoV2 presence in early conjunctivitis or monitoring ocular structure during Covid-19 therapy is recommended to counteract early or even prevent eventual signs of ocular drug toxicity, including the retinopathy.⁷³

Lopinavir/Ritonavir

The oral combination of these two agents (FDA-approved and currently authorised as anti-HIV medicine) demonstrate

Table 3 List of Genes and Reference SNPs (Rs: Reference Sequences) Associated with Drug Effects. Study Annotation Based on Data from Pharmgkb.org HGVS: Human Genome Variation Society (<http://varnomen.hgvs.org>)

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference
Antiretrovirals	UGT1A1	c.*238-6785_*238-6786insTA	rs8175347	Patients with the (TA)6/(TA)7 (UGT1A1*1/*28) or (TA)7/(TA)7 (UGT1A1*28/*28) genotype have increased levels of bilirubin leading to an increased likelihood for hyperbilirubinemia when treated with atazanavir and ritonavir.	982047507	40
		c.*339G>C	rs1042640	Patients with the GG genotype may be at increased risk of nephrolithiasis when treated with atazanavir and ritonavir as compared to patients with the CG or CC genotypes.	1185000362	41
		c.*440G>C	rs8330	Patients with the GG genotype may be at increased risk of nephrolithiasis when treated with atazanavir and ritonavir as compared to patients with the CG or CC genotypes.	1185000369	41
		c.*211T>C	rs10929303	Patients with the TT genotype may be at increased risk of nephrolithiasis when treated with atazanavir and ritonavir as compared to patients with the CC or CT genotypes.	1185000350	41
		c.*238-7110C>T	rs887829	Patients with the CC or CT genotype who are treated with atazanavir may have a decreased risk of hyperbilirubinemia and bilirubin-related drug discontinuation compared to patients with the TT genotype.	1183863836	44
	UGT1A7	c.391C>A	rs17863778	Patients with the AA genotype may be more likely to develop hyperbilirubinemia when administered atazanavir and ritonavir as compared to patients with the AC or CC genotypes. Please note: the AA genotype was significantly associated with likelihood of hyperbilirubinemia only when it was part of a haplotype with four other UGT1A variants: rs7586110 GG, rs17868323 GG (UGT1A7), rs3806596 CC (UGT1A3), and UGT1A1*28/*28.	1448097587	45
		c.855+44504T>G	rs7586110	Patients with the GG genotype may be more likely to develop hyperbilirubinemia when administered atazanavir and ritonavir as compared to patients with the GT or TT genotypes. Please note: the GG genotype was significantly associated with likelihood of hyperbilirubinemia only when it was combined with the rs17868323 GG, rs17863778 AA (UGT1A7), rs3806596 CC (UGT1A3), and UGT1A1*28/*28 genotypes.	1448097556	46
		c.387T>G	rs17868323	Patients with the GG genotype may be more likely to develop hyperbilirubinemia when administered atazanavir and ritonavir. Please note: the GG genotype was significantly associated with likelihood of hyperbilirubinemia only when it was combined with the rs7586110 GG and rs17863778 AA (UGT1A7), rs3806596 CC (UGT1A3), and UGT1A1*28/*28.	1448097574	46

(Continued)

Table 3 (Continued).

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference
Antiretrovirals	UGT1A3	c.*237+11029T>C	rs3806596	Patients with the CC genotype may be more likely to develop hyperbilirubinemia when administered atazanavir and ritonavir. Please note: the CC genotype was significantly associated with likelihood of hyperbilirubinemia only when it was part of a haplotype with 4 other UGT1A variants: rs17868323 GG and rs17863778 AA, rs7586110 GG (UGT1A7), and UGT1A1*28/*28.	1448097600	46
	APOE	c.466T>C	rs429358	Patients with the CC or CT genotype who are treated with antiretrovirals such as ritonavir or combinations may be at increased risk for elevated plasma lipids compared to patients with the TT genotype.	655384666	47
		c.604C>T	rs7412	Patients with the TT or CT genotype may be at increased risk of elevated triglycerides in response to ritonavir containing antiretroviral therapy compared to patients with the CC genotype. Patients with the TT or CT genotype who are treated with antiretroviral regimens containing ritonavir may be at increased risk of hypertriglyceridemia compared to patients with the CC genotype.	981203709	47
	APOC3	Regulatory region variant g.116829426T>C	rs2854117	Patients with the TT or TC genotype who are treated with ritonavir may have higher triglyceride levels (increased risk of hypertriglyceridemia) than patients with the CC genotype.	655385082	47
		Regulatory region variant g.116829453C>T	rs2854116	Patients with the TT genotype who are treated with ritonavir may have increased severity of triglyceride elevation as compared to patients with the CT or TT genotypes.	655385087	48
		c.*40G>C	rs5128	Patients with the CC genotype who are treated with ritonavir may be at increased risk of triglyceride elevation as compared to patients with the CG or GG genotypes.	655385092	48
	ABCC2	c.-24C>T	rs717620	Patients with the TT or CT genotype who are treated with atazanavir, lopinavir, ritonavir, or tenofovir may be at increased risk for drug toxicity compared to patients with the TT genotype.	1447982779	49
		c.4544G>A	rs8187710	Patients with the AA or AG genotype who are treated with lopinavir may have a higher accumulation of lopinavir in peripheral blood mononuclear cells and reduced ABCC2-mediated efflux of lopinavir compared to patients with the GG genotype.	1183491026	50
	ABCB1	c.3243A>G	rs1045642	Patients with the AG or GG genotype may be at increased risk of virological failure when receiving highly active antiretroviral therapy (HAART), with lamivudine, lopinavir, ritonavir or zidovudine as compared to patients with the AA genotype.	1183690892	51

(Continued)

Table 3 (Continued).

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference	
	ABCC1	c.*1512T>C	rs212091	Patients with the CC or CT genotype may be at increased risk of virological failure when treated with highly active antiretroviral therapy (HAART) with lamivudine, lopinavir, ritonavir, or zidovudine compared to patients with the TT genotype.	1444673130	51	
	ITPA	c.124+21A>C	rs7270101	Patients with the AA genotype may be at increased risk of anemia but a decreased risk of thrombocytopenia compared to patients with the AC and CC genotype who are taking PEG-IFN-IFN α_{2b} and ribavirin. Studies have looked at the composite genotypes of rs1127354 CC and rs7270101 AA to identify "normal" vs "deficient" ITPase activity. Normal ITPase activity is associated with increased risk of anemia and possibly decreased risk of thrombocytopenia compared to deficient activity. Patients with the CC or AC genotype may be at decreased risk of anemia but at increased risk of thrombocytopenia.	1446905703	38	
		c.43C>A	rs1127354	Patients with the AA or AC may be at decreased risk of anemia but at increased risk of thrombocytopenia when compared to patients with the CC genotype. Patients with the chronic CC genotype may be at increased risk of anemia. but at decreased risk of thrombocytopenia.	1446905691	38	
		c.2651-716A>C	rs6051702	Patients with the AA genotype who are treated with ribavirin may be at increased risk of anemia as compared to patients with the CC or AC genotype.	1444703777	38	
	VDR	c.*1026+283G>A	rs1544410	Patients with the AA genotype may be at increased risk of anemia when treated with PEG-IFN α_{2a} and ribavirin compared to patients with the GG or GA	1444700867	38	
		c.152A>G	rs2228570	Patients with the AA or AG genotype may have an increased likelihood of sustained virological response when treated with PEG-IFN α_{2b} and ribavirin compared to patients with the GG genotype.	1448102550	38	
	SLC28A2	c.65C>T	rs11854484	Patients with the TT genotype may be at increased risk of anemia when treated with protease inhibitors plus ribavirin and PEG-IFN compared to patients with the CC or CT genotype.	1445401427	38	
	Antiretrovirals	IFNL3	Intergenic variant g.39241861T>C	rs8105790	Patients with the TT genotype may have increased likelihood of sustained virological response when treated with PEG-IFN α and ribavirin compared to patients with the CC or CT genotype.	1448102470	38
			c.*52G>T	rs4803217	Patients with the TT genotype may have higher response rates (SVR) to triple therapy (telaprevir, PEG-IFN $\alpha_{2a/b}$ and ribavirin) than patients with the GG or GT genotype.	1448102490	38

(Continued)

Table 3 (Continued).

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference
		Intergenic variant g.39253181G>A	rs7248668	Patients with the GG genotype may have an increased likelihood of sustained virological response when treated with PEG-IFN α and ribavirin as compared to patients with the AA or AG genotype.	1448102463	50
	MICB	c.27+3023C>A	rs3828913	Patients with genotype CC may have higher rate of sustained virological response (SVR) treated with PEG-IFN plus ribavirin (PEG-IFN/RBV) therapy as compared to patients with genotype AA or AC.	1444843493	38
	OASL	c.1509C>T	rs12819210	Patients with the TT genotype may have increased SVR (sustained virological response) when treated with PEG-IFN α_{2b} and ribavirin compared to patients with the CC or CT genotype.	1183680570	38
	SCARB1	c.127-10172C>G	rs10846744	Patients with the CC or CG genotype may have increased sustained virological response (SVR) when treated with peginterferon alpha and ribavirin as compared to patients with genotypes GG.	1448264186	38
	SLC29A1	c.1260-201A>G	rs760370	Patients with the GG genotype may be more likely to have rapid virological response when treated with pegylated interferon-ribavirin therapy as compared to patients with the AA or AG genotype.	1448101202	38
	ND3	c.340A>G	rs2853826	Patients with the G allele may have a greater decline in adiponectin when treated with antiretroviral therapy (lopinavir, Nucleoside and nucleotide reverse transcriptase inhibitors or ritonavir) as compared to patients with the A allele.	1447963057	38
	CYP3A4	Intergenic variant g.99784473C>T	rs2740574	Patients with the CC or CT genotype may have decreased clearance of atazanavir as compared to patients with the TT genotype.	1448617757	53
	SLCO3A1	c.646+25149G>T	rs8027174	Genotypes GG is associated with increased clearance of darunavir in people as compared to genotypes GT + TT.	1184137368	55
Interferon- α and - β	GAPVDI	c.*3757A>G	rs2291858	Patients with the AA or AG genotype may have a decreased response to treatment with interferon-beta as compared to patients with the GG genotype.	1447959738	55
		c.-150+13007C>T	rs10819043	Patients with the CC genotype may have a decreased response to treatment with interferon-beta as compared to patients with the TT genotype.	1447959731	55
		g.125370928T>C	rs10760397	Allele C is associated with increased response to interferon beta-1a and interferon beta-1b in as compared to allele T.	1447959700	55

(Continued)

Table 3 (Continued).

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference
	NONE	intergenic variant g.17565446A>G	rs1448673	Patients with the AA genotype may have a decreased response to treatment with interferon-beta as compared to patients with the GG or AG genotype.	1447959724	55
	IRF6	c.-307+4490G>A	rs2205986	Patients with the AG or GG genotype may be at increased risk of developing drug-induced liver injury following treatment with interferon beta as compared with the AA genotype.	1449713231	56
Interferon- α and - β	CD58	c.71-553G>T	rs12044852	Patients with the AA or AC may have a better response to treatment with interferon beta 1a/1b as compared to patients with the CC genotype.	1445402209	57
	NONE	Regulatory region variant g.126157578A>G	rs3133084	Patients with the AA or AG genotype may have an increased response to treatment with interferon-beta as compared to patients with the GG genotype.	1447959752	55
	ZNF697	Regulatory region variant g.119594822A>G	rs10494227	Patients with the AA or AG genotype may have an increased response to treatment with interferon-beta as compared to patients with the GG genotype.	1447959700	55
	FHIT	c.104-99089C>T	rs760316	Patients with the CC genotype may have an increased response to treatment with interferon-beta as compared to patients with the TT genotype.	1447959717	55
Tocilizumab	IL6R	c.1067-5190T>C	rs4329505	Patients with the TT genotype who are treated with tocilizumab may have increased response to tocilizumab as compared to patients with the CT or TT genotypes.	1444704366	38
	IL6R	c.85+2913A>G	rs12083537	Patients with the AG genotype who are treated with tocilizumab may have increased response to tocilizumab as compared to patients with the AA or GG genotypes.	1444700767	38
	IL6R	c.1067-7518C>T	rs11265618	Patients with the CC genotype may have a better response when treated with tocilizumab as compared to patients with the CT or TT genotypes.	1448112486	38
	CD69	c.*387T>C	rs11052877	Patients with the AA or AG genotype may have an increased response to tocilizumab compared to patients with the GG genotype.	1448112486	38
	FCGR3	c.526T>A	rs396991	Patients with AA genotype may have an increased response to tocilizumab as compared to patients with the AC or CC genotypes.	1450371701	38
	GALNT18	c.236-9383G>A	rs4910008	Patients with CC genotype may have an increased response to tocilizumab as compared to patients with the CT or TT genotypes.	1448112493	38

(Continued)

Table 3 (Continued).

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference
Bevacizumab	HSP90AB1	Regulatory region variant g.44235246A>G	rs6929249	Patients with the AG or GG genotype may be at increased risk of developing hypertension as a result of bevacizumab treatment as compared to patients with the AA genotype.	1449564196	58
	HSP90AB1	Regulatory region variant g.44238042C>A	rs834576	Patients with the AA or AC genotype may be at increased risk of developing hypertension as a result of bevacizumab treatment as compared to patients with the CC genotype.	1449564202	58
	PRKCA	Intergenic variant g.44244130T>C	rs9381299	Patients with the CC genotype be at increased risk of developing hypertension as a result of bevacizumab treatment as compared to patients with the TT genotype.	1449564208	58
	HSP90AB1	TF-binding site g.44234210A>C	rs3734704	Patients with the CC genotype be at increased risk of developing hypertension as a result of bevacizumab treatment as compared to patients with the AA genotype.	1449564190	58
Hydrocortisone Prednisolone Dexamethasone	ATF5	c.*22G>A prime UTR variant	rs8667	Genotypes AA + AG is associated with increased likelihood of diarrhea when treated with asparaginase, cytarabine, hydrocortisone and prednisone as compared to genotype G.	1450044679	59
	MIR3683	Noncoding transcript-exon variant g.7067005A>G	rs6977967	Genotype GG is associated with increased likelihood of mucositis when treated with asparaginase, cyclophosphamide, cytarabine, daunorubicin, hydrocortisone, prednisone and vincristine as compared to genotypes AA + AG.	1450044669	59
	CTNNB1	Intergenic variant g.203866282A>G	rs4553808	Patients with the AA who are treated with dexamethasone and prednisone may have a later onset of bortezomib-induced peripheral neuropathy as compared to patients with the AG or GG genotype.	1043880851	60
	PNPLA3	c.432C>G	rs738409	Patients with the CG genotype may have increased risk of hepatotoxicity when treated with remission induction therapy as compared to patients with genotype CC.	1448632697	61
Captopril	ACE	Intron variant c.584-105_584-104ins	rs1799752	Patients with the ATACAGTCACTTTTTTTTTTTT TTTGACGGAGTCTCGCTCTGTGCCCC/del genotype and conditions such as heart failure, chronic obstructive pulmonary disease and Type 2 diabetes may have an increased response when treated with captopril as compared to patients with the del/del genotype, or a decreased response compared to patients with the ATACAGTCACTTTTTTTTTTTTTTTTGGACGGAGTCTCGCTCTGTGCCCC/ATACAGTCACTTTTTTTTTTTT TTTTGGACACGGAGTCTCGCTCTGTGCCCC genotype. Responses were also tested within healthy individuals in one study	982047862	62

(Continued)

Table 3 (Continued).

Drug/biological Agent	Enzyme Involved	Genetic Variant HGVS Name	Reference SNP	Clinical Annotation	PharmGKB ID	Reference
		Regulatory region variant g.63476833T>A	rs4291	Patients with the AA genotype not experience increasing creatinine levels when taking captopril compared to patients with the AT and TT genotypes.	1448259106	62
	ACE2	c.*264+788A>G	rs2106809	Patient with the AA and AG genotype and hypertension may have a smaller decrease in diastolic blood pressure when treated with captopril as compared to patient with the GG genotype.	1183612731	62
	AGTRI	c.*86A>C	rs5186	Patients with the CC and CA genotype have an increased response when treated with captopril as compared to patients with the AA genotype.	1043858965	62

Notes: This table shows all drugs and biological agents considered in our study, and for each the genes and respective sequence variants of pharmacogenetic interest have been listed. All variants were named following the sequence-variant nomenclature suggested by the Human Genome Variation Society (<http://varnomen.hgvs.org>).⁴² Each variant report show the reference SNP (refSNP) cluster ID numbers (rs#), a code by which each SNP can be queried from the dbSNP website (<https://www.ncbi.nlm.nih.gov/snp>) and through which further information is available (such as functional analysis, population-specific allele frequencies, validation information, or clinical significance).⁴³ Furthermore, for each variant, a summary of PharmGKB clinical annotations with respective identification codes (phenotype for any given genotype) is reported. Using the access codes for dbSNP and PharmGKB, it is thus possible to find more information for the sequence variants and the respective variant-drug responsiveness associations. Finally, the last column shows the most significant bibliographic reference concerning the association between the genetic variant reported and individual drug responsiveness.

activity against other novel coronaviruses.^{74,75} Several RCTs examining lopinavir/ritonavir in Covid-19 are in progress.⁷⁶ Recommendations for administration in Covid-19 treatment is 400 mg/100 mg twice daily for up to 14 days.⁷⁷ Adverse effects of lopinavir/ritonavir include several gastrointestinal complaints, such as nausea, vomiting, and diarrhea, and hepatotoxicity, pancreatitis, and cardiac conduction abnormalities.⁷⁸ These adverse effects are increased in 20%–30% of Covid-19 patients with elevated transaminases.⁷⁹ Previous studies have shown that these ADRs with lopinavir–ritonavir combination are related to several polymorphisms present in the genes *UGT1A1*, *UGT1A7*, *APOE*, and *APOC3* (Table 1).

Ribavirin

This antiviral drug (guanine analogue) inhibits viral RNA-dependent RNA polymerase. Ribavirin activity against Covid-19 disease is limited and requires high doses or combination therapy to be effective in humans. No evidence exists for inhaled ribavirin for Covid-19 treatment — no benefit over enteral or intravenous administration⁷⁹ — though several studies have demonstrated possible harm due to adverse effects (hematologic and liver toxicity).⁸⁰ Ribavirin causes severe dose-dependent hematologic toxicity.⁸¹ The inconclusive efficacy and toxicity results suggest that ribavirin has limited value in treatment of Covid-19. Case–control pharmacogenetic association studies indicate different polymorphisms in the *ITPA*, *VDR*, and *SLC28A2*

genes that are related to toxicity and adverse effects, while an increased pharmacological response is associated when some variants of the *VDR*, *SLC29A1*, *IFNL3*, and *MICB–OASL* genes are present. It must be noted that numerous studies have undertaken pharmacogenetic evaluations on populations undergoing ribavirin therapy combined with PEG-IFN α .⁸²

Umifenovir

This is an antiviral agent that exerts a mechanism of action targeting the S protein–ACE2 interaction, inhibiting membrane fusion of the viral envelope.⁸³ The recommendation for umifenovir oral dose (200 mg every 8 hours, 7–14 days) for influenza treatment was studied for Covid-19 therapy (NCT04260594). In Covid-19 patients treated with umifenovir, adverse effects include allergic-reaction gastrointestinal upset and elevated transaminases, although there are no studies that describe an association of these episodes with genetic variants.^{27,83}

Miscellaneous Agents

IFN α / β

IFN α and β have been studied for novel CoVs.⁸⁴ Several studies reported clinical outcomes in combination with ribavirin and/or lopinavir/ritonavir.⁸⁵ Adverse effects have been described in almost every organ, clearly dose-dependent.^{84,85} Several toxic mechanisms for IFN α / β have

Table 4 List of Coagulation Factors with Relative Protein Localization, Pathway, Function, Nucleotide Variants, and Reference SNPs (Reference Sequences) Involved in Thrombophilic Disorders

	Protein Localization	Gene	Pathway/function	Genetic Variant HGVS Name	Reference SNP
Factor II (prothrombin)	Plasm protein	<i>F2</i>	Common pathway, converted to fibrin (insoluble weblike substance of clot)	c. G20210A	rs1799963
Factor V	Plasm protein	<i>F5</i>	Common pathway, functions as a cofactor	c.A5279G	rs118203907
				c.A4070G	rs1800595
Factor V Leiden				c.G1691A	rs6025
Methylenetetrahydrofolate reductase	Cytoplasmic protein	<i>MTHFR</i>	Catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate	c.C677T	rs1801133
				c.A1298C	rs1801131
Serpin family E member PAI1	Plasma protein	<i>SERPINE1</i>	Common pathway, endothelial plasminogen-activator inhibitor	(-675 I/D, 5G/4G)	rs1799889
Factor FXIII	Plasma protein	<i>F13A1</i>	Common pathway, cross-links fibrin	c.G103T	rs5985
Integrin subunit $\beta 3$ or CD61	Integral cell-surface protein	<i>ITGB3</i>	Participates in cell adhesion and cell surface-mediated signaling	c.T1565C	rs5918
Fibrinogen β	Plasma protein	<i>FGB</i>	Common pathway, forms fibrin	c.-455 G>A	rs1800790

Notes: In Covid-19 patients, prescreening of coagulation factors is essential to highlight genetic predisposition related to thrombophilia, as those subjects with thrombophilic mutations (based on the degree found) are at greater risk of thrombotic complications and clinical aggravation causing worsening and death.

been investigated in recent years. Much remains still to be elucidated, although most side effects disappear on dose reduction or interruption of treatment. Previous genome-wide association studies on the response to IFN β in neurological degenerative diseases suggest an increase in therapeutic response with the presence of several SNPs in the genes *CD58*, *ZNF697*, and *FHIT*. In parallel, ADRs have been observed with the presence of variants of the *GAPVD1* and *IRF6* genes. As of now, the use of interferons to treat Covid-19 disease is controversial.⁸⁶

Nitazoxanide/Camostat Mesylate

Although an antihelminthic agent, nitazoxanide has shown antiviral activity with a favorable safety profile.^{87,88} Camostat mesylate prevents novel CoV-cell entry through inhibition of the host surface transmembrane protease/serine (TMPRSS2), as observed by in vitro studies.⁸⁹ Neither drug has pharmacogenetic studies regarding efficacy or toxicity effects associated with genetic variants.

Azithromycin

This macrolide antibiotic is used extensively in patients with viral infections to prevent severe respiratory tract

infections. Azithromycin-Hcq combination shows a synergistic effect on Covid-19 disease in vitro at concentrations comparable with that observed in human lung,⁹⁰ and has been found useful in combination with remdesivir, lopinavir/ritonavir and IFN β . To date, the interaction between this macrolide and genetic factors is unknown. However, due to the potential risk of prolonged QT interval, remarkably increased by the mutual interaction between these two agents, their concomitant use is not recommended by several guidelines, unless within the setting of controlled trials (<https://covid19treatmentguidelines.nih.gov>).

Low Molecular-Weight Heparin

This anticoagulant is used to reduce thromboembolic events in patients with Covid-19 infection. As known, the SARS-CoV2 pandemic is characterized by the development of ARDS that results from acute inflammation within the alveolar space and prevention of normal gas exchange. Indeed, huge deposits of fibrin in the lung parenchyma and air spaces have been reported. The raising of proinflammatory cytokines within the lung leads to recruitment of leukocytes, increasing the local

inflammatory response, and since the coagulation route contributes to reducing pathogen invasion by improving compartmentalization, this anticoagulant treatment has potential risk in those Covid-19 patients with no significant coagulopathy. The drug enoxaparin can be started as soon as the day of Covid-19 diagnosis and continued over 14 days, after baseline assessment and monitoring of PT, aPTT, complete blood-cell count, and creatinine levels. Clinical aggravation causing worsening and death in Covid-19 inpatients appears to be thrombotic. Therefore, special attention should be devoted to both risks and benefits of using heparin in Covid-19 patients. Prescreening is essential to highlight genetic predisposition related to thrombophilia, as these subjects with thrombophilic mutations (based on the degree found) are at greater risk of thrombotic complications.

Investigational Drugs

Remdesivir

This is an RNA-polymerase inhibitor (GS-5734), a retroviral drug belonging to the class of nucleotide analogues, and a monophosphate prodrug that was discovered during a screening study of antimicrobials with antiviral activity, showing promise against the Ebola virus.^{91,92} Recently approved by the FDA for the treatment of patients with Covid-19, remdesivir is recommended as a single 200 mg dose, followed by 100 mg daily infusion.⁹³ Besides the drug's clinical use in the treatment of Ebola, several clinical trials are ongoing to evaluate the antiviral activity of remdesivir in patients with Covid-19 (NCT04292899, NCT04292730, NCT04257656, NCT04252664, and NCT04280705).⁹¹ No pharmacogenetic indications are present, allowing modulation of dosage for therapy. Due to its toxicity, remdesivir is not currently FDA-approved, and must be obtained via compassionate use, expanded access, or enrollment in a clinical trial.

Favipiravir

Favipiravir ribofuranosyl-5'-triphosphate is a retroviral drug acting as an inhibitor of viral replication (RNA-polymerase inhibitor T705). This agent demonstrates broad activity against Ebola infection and other RNA viruses.⁹⁴ Favipiravir is recommended at a dose of 2,400–3,000 mg every 12 hours (two doses) followed by maintenance doses of 1,200–1,800 mg every 12 hours. Favipiravir is overall well tolerated, although a mild adverse-event profile for higher-dose regimens has been observed.^{95–97} The high doses used result in hyperuricemia, diarrhea, elevated

transaminases, and reduction in neutrophil count, but nothing is known about any pharmacogenetic correlations. Favipiravir presents efficacy in the treatment of Covid-19 disease, but to date limited clinical experience has reported support for its use. No pharmacogenetic indications are present, allowing modulation of dosage for therapy using this drug.

Atazanavir and Darunavir

These drugs are well-known protease inhibitors used for the treatment of AIDS, with good efficacy and safety profiles. While atazanavir is combined with other antiretrovirals, darunavir is used in a fixed-dose combination with cobicistat, a new pharmacokinetic enhancer. With respect to the other protease inhibitors, atazanavir is less likely to cause lipodystrophy and is preferentially used in combination with other antiviral agents (ritonavir), providing antiviral potency equivalent to lopinavir, although concomitant use of ritonavir decreases the efficacy of atazanavir. Valid pharmacogenetic correlations of the efficacy of these antivirals can be deduced from studies carried out on HIV patients in which the efficacy of polymorphisms in the *UGT1A1*, *CYP3A4*, *CYP3A5*, and *SLCO3A1* genes has been demonstrated. In contrast, cases of toxicity and ADRs are related to sequence variants in the *UGT1A1*, *UGT1A7*, *UGT1A3*, *APOE*, and *APOC3* genes.^{44–48,51,55,56,98} In some settings, darunavir–cobicistat may be used in the presence of tolerability or availability of the lopinavir–ritonavir combination (<https://covid19.treatmentguidelines.nih.gov>). Concerning the metabolism of Azatavir, the variants *CYP3A5*1*, *CYP3A5*3*, *CYP3A5*6*, *CYP3A5*7* in *CYP3A5* (rs776746) have been reported. Briefly, individuals carrying one or two copies of the *1 allele may metabolize atazanavir more rapidly than individuals with one or more copies of the *3, *6, or *7 alleles.⁹⁸

Adjunctive Experimental Therapies

Anticytokine or Immunomodulatory Agents (Tocilizumab, Sarilumab, and Bevacizumab)

Monoclonal antibodies directed against key inflammatory cytokines represent another potential class of adjunctive anti-Covid-19 therapies.^{99,100} IL6 is a key driver of this dysregulated inflammation.¹⁰⁰ The use of monoclonal antibodies against IL6 shows a dampening of this process and improves clinical outcomes. Tocilizumab, a monoclonal antibody IL6-receptor antagonist, is used in severe Covid-19 cases with success. Adult doses are 400 mg or

8 mg/kg in one or two doses, with second dose 8–12 hours after the first if response is inadequate.¹⁰¹ Sarilumab is another IL6-receptor antagonist approved for rheumatoid arthritis. It is being studied in multiple centers for hospitalized patients with severe Covid-19 (NCT04315298; www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneration-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19). Other monoclonal antibodies or immunomodulatory agents in several clinical trials are available for expanded access, such as bevacizumab (anti-VEGF medication; NCT04275414), fingolimod (immunomodulator approved for multiple sclerosis; NCT04280588) and eculizumab (antibody inhibiting terminal complement; NCT04288713). ADRs have been reported in subjects carrying variants in the *IL6R*, *CD69*, *FCGR3*, and *GALNT18* genes.

Corticosteroids (Hydrocortisone, Prednisolone/Methylprednisolone, and Dexamethasone)

Corticosteroids are used to reduce lung inflammatory responses that in many cases evolve into acute lung injury and ARDS. At present, the effects of corticosteroids in patients affected by Covid-19 have been poorly described, so our considerations are based on observations in other viral pneumonia types, such as SARS and MERS.¹⁰² These previous studies do not indicate any association between corticosteroid use and increased survival, but slower viral clearance in the respiratory and blood tracts, hyperglycemia (high blood sugar), vascular necrosis, and psychotic episodes.¹⁰³ Data are still unclear in patients with SARS-CoV2 infection. Although it remains controversial, the possibility of using corticosteroid treatment in patients with moderate or severe ARDS can be useful to reduce mortality. Low (ie, 25 mg/day) and moderate (ie, 140 mg/day) doses of corticosteroids reduce mortality in patients with acquired pneumonia,¹⁰⁴ but at present the risk of secondary infections, excessive persistence of viral load, and long-term complications using high-dose corticosteroids cannot be excluded. Dexamethasone is a potent CYP3A4 inducer. To date, the main studies on the pharmacogenetic aspects of steroid drugs have indicated a correlation between adverse events and variants of the *ATF5*, *MIR3683*, *CTNBN1*, and *PNPLA3* genes.^{61–63}

ACE Inhibitors

As stated, SARS-CoV2 has the ability to introduce and infect the host cell using the ACE2 receptor.⁵ This has alarmed several researchers, who hypothesized how ACE

inhibitors and angiotensin-receptor blockers could interfere negatively or positively with the viral infection process.^{89,105} Since ACE inhibitors upregulate ACE2 receptors, possible worsening of disease under ACE inhibitor therapy has been hypothesized. By contrary, angiotensin-receptor blockers could theoretically prevent the entry of the virus at the cellular level.¹⁰⁶ Some RCTs specific for captopril used alone or in combination in patients with Covid-19 with severe pneumonia are currently under investigation in order to understand ARDS (NCT04355429, <https://clinicaltrials.gov>). Since ACE inhibitors are among the most frequently used drugs in medical practice, consequent knowledge on related pharmacogenetic aspects is now widely known. The polymorphisms that modulate the activity of these drugs in *ACE*, *ACE2*, and *AGTR1* genes have been widely studied and described in several recent studies.

Discussion

The Covid-19 pandemic is due to the novel pathogenic coronavirus SARS-CoV2, which emerged in China and spread quickly worldwide.^{1,2} Therapeutic options for Covid-19 are wide-ranging, and some drugs have gained emergency-use authorization from the FDA and/or European Medicines Agency. At present, patients are treated with symptomatic therapy and vital support in severe cases. Several international efforts are aimed at the investigation and development of antiviral agents, other immunotherapies, and vaccine strategies. Pharmacogenomics might be a promising tool in the development of more appropriate therapies (including drug management) and the prevention of fatal-complication onset due to ADRs.²⁷ Pharmacogenomics can predict from the beginning the effect of a specific drug formulation in terms of efficacy/toxicity with respect to individual genetic background and minimize exposure to drugs potentially less/ineffective other than toxic (precision medicine).^{22,23} As known, drug formulations can elicit different cell/tissue responses depending on individual genetic background. This is possible because each subject can have variations in nucleotide sequences belonging to genes encoding for enzymes involved in the activity of the drug that has been considered for therapy.^{22–24} This aspect appears of great importance in patients having several comorbidities or simply “fragile” old patients.

As there is no specific cure for Covid-19, we reviewed all the therapies (drugs) actually in use to counteract SARS-CoV2 effects and the related adverse effects to certain drugs

(antiviral, antimalarial, and several biological humanized agents able to reduce the levels of some cytokines belonging to the cytokine storm), as reported by RCTs.^{29–34,38–41} Response to these drugs was extremely complex, and numerous cases of toxicities and antiretroviral drug resistance (viral mutations) have been reported.³⁸ A possible explanation of this variability might be the presence of factors that modify pharmacokinetics/pharmacodynamics and the activity of the virus itself (viral pharmacodynamics).⁴⁰ In addition, viral pharmacodynamics and mutagenesis are still unclear with regard to Covid-19 drug resistance.³⁸

Genetic factors might account at least in part for the unpredictability of therapy among Covid-19 patients.³⁸ Merely, a significant number of SNPs in genes encoding proteins implicated in the transport and metabolism of drugs may be responsible for the wide variability in drug pharmacokinetics and toxicity.³² Consistently, this review, coupled with a wide *in silico* analysis on the relevance of identification of SNPs involved in drug metabolism, provides a list of specific drug-associated SNPs associated with efficacy (green) or toxicity (red), useful in predicting individual response to therapy in Covid-19 patients. This would imply the possibility of checking variants in biological samples collected and evaluated before the beginning of therapy with the aim of predicting the outcome of a single or combined Covid-19 therapy. To our knowledge, although a considerable number of ADR episodes in Covid-19 patients have to date been described in the literature, there has been no pharmacogenetic study attempting to correlate the clinical outcomes of drug treatment with gene variants.²⁷ The identification of gene variants is only the first step in a complex process prior to applicability into clinical practice. In fact, the clinical application of pharmacogenetic analysis requires previous studies confirming its validity and usefulness. To support this, essential measures applied to genetic tests are required: analytical and clinical validity and clinical utility. While analytical validity defines test accuracy, sensitivity, and specificity, guaranteeing that a “positive” or “negative” result corresponds with the real presence or absence of the sequence variant investigated, clinical validity represents the ability to identify the clinical phenotype of interest, evaluating clinical sensitivity and specificity, and positive or negative predictive values, or in other cases, the association measured as a risk or odds ratio.^{107,108} Of note, clinical utility is related to the evidence that genetic testing can provide useful information for the diagnostic process, better measures for clinical outcomes, and odds

ratios for patient-management decision-making (precision medicine).^{107,108} As such, a pharmacogenetic test — potentially useful for patient treatment — must improve clinical outcomes. Evidence on the clinical utility of a pharmacogenetic assay is obtained by experimental studies, preferably RCTs. A valid method to evaluate clinical utility is the use of prospective trials on randomized subjects undergoing genetic testing or not to compare the same treatment between the two groups. Similarly, prospective trials on genetically stratified groups are also mandatory to comparing treatment outcomes between different groups.^{108,109} In other cases, clinical utility is determined by a “chain of indirect evidence” linking the results of a genetic test to intermediate data that are associated with improved clinical outcomes.^{108,110} However, pharmacogenetic research remains an expanding field, and to date there is no unanimous consensus on the best appropriate study designs to uniquely evaluate drug–response variability related to genetic variations.¹⁰⁹ Finally, several national drug agencies are carefully evaluating risk:benefit ratios in individual cases, carefully considering the concomitant pathologies (long QT syndrome, major arrhythmias, liver or kidney failure, electrolyte disorders), pharmacological associations (in particular for drugs that increase the QT), and above all the clinical anamnesis and identification with genetic diagnosis of favism (G6PD deficiency).

In our opinion, this is the first study to suggest the application of personalized medicine tools during the treatment of SARS-CoV2 infection. All identified SNPs, including allelic efficacy/toxicity, selected from an accurate *in silico* analysis have been identified for the most promising and repurposed drugs, and the investigational and adjunctive experimental drugs have been reported in both tables and figures.^{42–64} Particularly, in [Figure 2](#) we graphically represent the frequency of SNP alleles related to an efficacy response (green bars) or toxicity (red bars), useful in predicting individual response to therapy with the main therapies used for Covid-19 patients. In this study, tocilizumab showed varying efficacy, while inside the antiviral group a divergent response was observed. Therefore, to understand from the beginning specific susceptibility (efficacy/toxicity) to a drug, as displayed by the presence of specific functional clusters in the genetic background of the patient under treatment, might assist the specialist toward a more “specific” selection of therapeutic agent. This would result in a more appropriate therapeutic response, with fewer ADRs. As reported in other therapies, this individualized approach

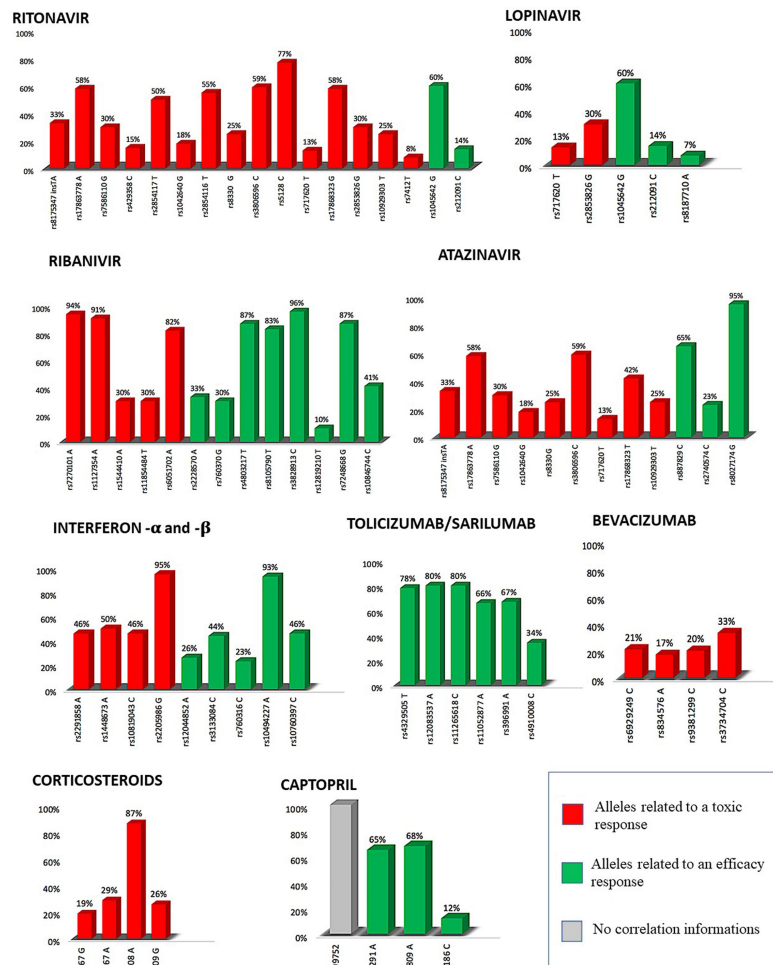


Figure 2 Graphical representation of the frequency of SNPs alleles related to toxicity (red bars) and efficacy (green bars) response, useful in predicting individual response to therapy with the main drugs used for the therapy of Covid-19 patients. Allelic frequencies have been recovered by 1000 Genomes Project (<https://www.internationalgenome.org/home>), Ensemble (<http://www.ensembl.org/index.html>), dbSNPs (<https://www.ncbi.nlm.nih.gov/snp/>), gnomAD v2.1.1 (<https://gnomad.broadinstitute.org/>). The gray bar refers to SNP rs1799752 for which there is no correlation information. The information for SNP rs8027174 refers to both Atazanavir and Darunavir.

appears of great utility, and particularly for the Covid-19 pandemic could improve the choice of more efficient therapy. The screening is less invasive for the patient, as it is possible by venous blood or buccal-cell swab using real-time PCR analysis.

Conclusion

Any attempt to find more suitable tests, identify asymptomatic/presymptomatic and/or confirm symptomatic subjects, and therapeutic agents/strategies to sustain therapeutic decisions in Covid-19-affected patients appears mandatory. Herein, we performed a wide in silico study of genetic variants associated with the main drugs in use for Covid-19 therapy, providing a list of genetic variants of efficacy/toxicity. This study highlights the clinical utility of a pharmacogenetic tool in planning personalized

treatments that are likely to become essential in the pharmacological management of Covid-19 patients.

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Author Contributions

CC, AR, AM, RP, and SP conceived the study and participated in its design and coordination. CC, AR, AM, and RP contributed to data collection and analysis. All authors made a significant contribution to the work reported, whether in its conception, study design, execution, acquisition of data, analysis and interpretation, or all these areas, took part in drafting, revising, or critically reviewing the article, gave final approval to the version to be published, have agreed on the

journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest and report no conflicts of interest for this work.

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