Adverse drug reactions in SARS-CoV-2 inpatients: a case-series with a focus on drug-drug interactions

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Abstract

Background and aim: The search for early and emergency effective treatments for COVID-19 infection may have led to loss of sight of treatments safety. In addition, characteristics of drug-drug interactions (DDIs)-related adverse drug reactions (ADRs) in COVID-19 patients have not yet been studied in depth. The aim of the present case-series study is to describe clinical and pharmacological characteristics of SARS-CoV-2 inpatients, focusing on ADRs, particularly those related to DDIs. Methods: We evaluated all reports of COVID-19 medications-related ADRs collected within the COVID-19 Units of Careggi University Hospital, Florence (Italy), between January 1st and 31st May 2020. Information regarding COVID-19 medications, patients' demographic and clinical characteristics, concomitant drugs, ADRs description and outcome, were collected. Each case was evaluated for the causality assessment and to identify the presence of DDIs. Results: During the study period, 23 Caucasian patients (56.5% males, mean age 76.1 years) experienced one or more ADRs. The majority of them were exposed to polypharmacy and 17.4% presented concomitant conditions. ADRs were referred to cardiovascular, psychiatric and gastrointestinal disorders. The most frequently reported preferred term was QT prolongation (mean QT interval 496.1 msec). ADRs improved or resolved completely in 60.8% of cases. For all patients, a case-by-case evaluation revealed the presence of one or more DDIs, especially those related to pharmacokinetic interactions. Conclusions: Despite the small number of patients, our evidence underline the clinical burden of DDIs in SARS-CoV-2 inpatients and the risk of unexpected and uncommon psychiatric ADRs.

1. Introduction

Since the outbreak of COVID-19 epidemic, clinicians started a real "gold rush" to find the best therapeutic option among those currently available for infectious and inflammatory diseases [1]. Waiting for a vaccine, the study of COVID-19 clinical characteristics proved effective in directing towards meaningful medical choices.

Three main stages represent COVID-19 infection clinical course. In the first phase, the virus replicates within the host cells and patients may experience symptoms as dry cough, fever, and general weakness and malaise [2]. In the second phase, the progression of the disease is characterised by the development of a bilateral interstitial pneumonia and by morphological changes in host's lungs [3]. Respiratory symptoms, which could be stable in the first phase of pneumonia, could worsen, due to both direct effects of the virus and host's immune response, leading to clinical instability and severe hypoxemia [4]. Only in a limited number of

cases (third phase), patients experience a "cytokine storm" and following hyper-inflammatory state, with local and systemic consequences [5]. Among them, at the lung level, arterial and venous vasculopathy, with thrombosis of the small vessels and evolution towards serious and sometimes permanent lung lesions. A progressive alteration of inflammatory and coagulation parameters, such as C-reactive Protein (PCR), ferritin, pro-inflammatory cytokines, consumption of clotting factors, and increased levels of the fragments of fibrin degradation (D-dimer), have been observed [6, 7].

In this complex scenario, therapeutic strategies have focused on viral growth containment in the first and second phase of the disease, and on inflammation and coagulation control, in the second and third phases (**Table 1**) [8]. When COVID-19 pandemic spread to Italy, the Italian Medicines Agency (AIFA) approved the off-label use of the antiviral combinations lopinavir/ritonavir and darunavir/cobicistat, the use of antimalarials chloroquine and hydroxychloroquine (HCQ), the antibiotic azithromycin, and the anticoagulant enoxaparin [9]. Clinical experience also suggested the use of tocilizumab, a humanized monoclonal antibody against interleukin (IL)-6 receptor [10].

However, the search for early and emergency effective treatments for COVID-19 infection may have led to loss of sight of treatments safety. From the beginning of COVID-19 pandemic, concerns about HCQ efficacy and safety raised [11] and subsequently AIFA suspended its use in SARS-CoV-2 patients out of clinical trials on May 29th 2020 [12]. Moreover, based on available evidence concerning the efficacy and safety of fixed associations darunavir/cobicistat and lopinavir/ritonavir, AIFA also suspended their use out of clinical trials on July 17th 2020 [13, 14].

Prevalence of adverse drug reactions (ADRs) in COVID-19 patients has not yet been deeply evaluated, but results from observational studies suggest that its frequency could be high in this population [15]. The majority of ADRs includes gastrointestinal and liver system disorders. Nevertheless, potential harmful ADRs should be closely monitored, and pharmacovigilance monitors', toxicologists' and clinical pharmacologists' support in COVID-19 Units should be carefully considered in order to better manage COVID-19 therapies [16]. In particular, good quality information regarding drug-drug interactions (DDIs)-related ADRs are still lacking.

In this context, the aim of the present case-series study is to describe clinical and pharmacological characteristics of SARS-CoV-2 inpatients, focusing on ADRs, particularly those related to DDIs.

2. Methods

In the present observational study, we considered and evaluated all reports of suspected ADRs collected in the COVID-19 Units of Careggi University Hospital, Florence (Italy), between January 1st and 31st May 2020. All suspected ADRs were collected from the clinical charts after a consultation performed by the Toxicology Unit on request of clinicians working in COVID-19 Units.

Following the Italian pharmacovigilance legislation [17], a multidisciplinary team composed by experts in pharmacovigilance (GC, AV, NL) and clinical toxicology (VB, CL, AB, AI, GM) provided their consultation and filled out the specific report form [18, 19], collecting information on: (1) patients' demographic characteristics (age, gender, ethnic group); (2) patients' clinical status; (3) suspected drugs and concomitant medications (for each one, administration route, therapy duration, dosages, and therapeutic indication were recorded); (4) ADRs description; (5) ADRs outcome (improvement, complete resolution, unchanged or worsened event, resolution with sequelae, death). A "suspected drug" is defined as a drug which is potentially associated with the observed ADR, while a "concomitant medication" is a drug the patient is exposed to at the time of ADR occurrence. A concomitant medication may not necessarily be associated to the ADR.

For each case included in the analysis the experts performed a medical evaluation in order to assess the causality relationship between the suspected drugs and their related ADRs according to the Naranjo's scale [20]. Moreover, each case was evaluated with the aim of identifying the presence of DDIs, which may have contributed to ADRs. DDIs were identified using two different validated tools: (1) the open access Drug Interaction Checker [21], and (2) the drug interaction software Micromedex Drug-REAX System (Thomson

Reuters Healthcare Inc., Greenwood Village, Colorado, United States), available online with restricted access. As reported in the Micromedex [22] and Drug Interaction [21] tools, DDIs were classified as mild, moderate, or major, depending on their clinical impact on patient.

Suspected drugs and concomitant medications were classified according to the Anatomical Therapeutic Chemical (ATC) classification system. ADRs description according to diagnosis and symptoms was coded using the Medical Dictionary for Regulatory Activities (MedDRA) and organized by Preferred Term (PT) [23, 24].

Data are presented as number and percentages or, for continuous variables, as mean and standard deviation (SD).

3. Results

Between January 1st and May 31st 2020, among patients hospitalised in the COVID-19 Units of Careggi University Hospital, Florence (Italy), clinicians requested a consultation for a total of 23 patients who experienced one or more ADRs.

All patients were Caucasian with a mean age of 76.1 (SD **Table 2**).

Table 3 shows a case-by-case description of evaluated ADR reports. One patient presented an elevation of transaminases, 3 patients experienced gastrointestinal (GI) ADRs (nausea, diarrhoea, vomiting and GI pain), 18 patients showed cardiovascular (CV) ADRs (ECG QT prolongation), one patients presented a prolongation of the QT interval along with symptoms of major depression, and one patient reported psychotic symptoms. The 19 patients who experienced an ECG QT prolongation, showed a mean prolongation of QT interval of 496.1 (SD ±14.4) msec (**Table 2**).

Table 4 shows all moderate and major DDIs observed in our sample between COVID-19 treatments and patients' concomitant medications. The application of tools for interactions revealed that all patients presented at least one DDI. Among 82 different DDIs, 53 (64.4%) were moderate, and 32 (39%) increased the risk of QT prolongation. Many others DDIs (n=112) were identified between medications other than COVID-19 treatments (**Supplementary Table 1**).

4. Discussion

This study aimed to describe the clinical and pharmacological characteristics of SARS-CoV-2 inpatients who experienced one or more ADRs, with a focus on DDIs. Based on the evidence herein reported, the majority of ADRs occurred in elderly patients exposed to polypharmacy.

Off-label drug utilisation and DDIs are well known causes of ADRs in the general population [2524]. In the case of COVID-19 pandemic, lacking of specific pharmacological treatments forced clinicians and regulatory agencies to resort to currently available drugs. Thus, *off-label* drug utilisation could not be avoided. On the contrary, a patient's complete anamnesis, in particular regarding comorbidities and concomitant medications, may help in avoiding the occurrence of ADRs, often due to DDIs.

In our sample, according to the case-by-case clinical evaluation, most frequently reported ADRs were Cardiac, Psychiatric and nervous system, and Gastrointestinal and hepatic disorders.

Cardiac disorders

We observed 19 cases of CV ADRs, in particular "QT prolongation". In these cases, the most frequently reported suspected COVID-19 medications were HCQ, azithromycin, lopinavir/ritonavir and darunavir/cobicistat, which are, based on their pharmacokinetic and pharmacodynamic properties, commonly associated to CV events.

HCQ acute toxicity occurs most frequently when therapeutic or high doses are administered rapidly through parenteral routes. HCQ doses of >5 g given parenterally usually are fatal. Toxic manifestations relate primarily to the CV system, including hypotension, suppressed myocardial function, arrhythmias, and eventual

cardiac arrest. Due to its long elimination half-life (>40 days) [26], prolonged treatment with high doses may also cause ADRs such as widening of the QRS interval, and T-wave abnormalities. In fact, it is well known that HCQ inhibits human ether-a-go-go related gene (hERG) potassium channels. Inhibition of hERG can block the outward flow of potassium, which leads to intracellular accumulation of potassium and ventricular repolarization and results in QT prolongation and torsade de pointes (TdP) [27]. These complications usually disappear shortly after the drug withdrawal. HCQ may also inhibit CYP2D6, interacting with a variety of different COVID-19 and non-COVID-19 medications.

The macrolide azithromycin is a weak inhibitor of CYP3A4. In this case, in connection with its effect on QT prolongation, the potential for DDIs is associated to azithromycin pharmacodynamic characteristics. As such, caution should always be observed when combining azithromycin with other molecules that increase the QT interval, such as HCQ. In particular, QT prolongation seems to be significantly higher in patients who received the two medications concomitantly [28]. The exact mechanism by which azithromycin and other macrolides prolong the QT interval is through a blockade of the rapid component, IKr, of the delayed rectifier potassium current IK, which is encoded by the hERG [29], similarly to HCQ.

Special caution must be used when administering protease inhibitors, such as lopinavir/ritonavir, due to their potential of inducing QT interval prolongation, particularly when used in combination with other pro-arrhythmic medications, such as HCQ and azithromycin. In fact, lopinavir/ritonavir may increase concentrations of the co-administered medicinal products and this may result in an increase of their associated cardiac ADRs. This can be explained by the ability of lopinavir/ritonavir to modulate enzymes, in particular CYP3A4 and P-glycoprotein (P-gp). Lopinavir/ritonavir may also inhibit BCRP and OATP1B1 transporters [30]. These pharmacokinetic characteristics were also observed for darunavir/cobicistat [31], leading to a comparable profile in terms of DDIs and potentially related CV ADRs.

In general, attention should be exercised when COVID-19 treatments are combined with drugs known to increase the PR or QT intervals, as they also cause conduction and repolarization disorders by themselves. Considering that QT prolongation could be an asymptomatic and potentially fatal event, it should be always strictly monitored. The risk factors for QT prolongation and TdS are female sex, older age, heart disease, exposure to QT interval prolonging drugs or metabolic inhibitors, bradycardia, and electrolyte disturbance [28]. The cornerstone of the management of acquired QT prolongation includes the identification and discontinuation of any suspected drug and the prompt correction of any metabolic abnormalities [32]. Short-term treatment includes the administration of intravenous magnesium sulphate and potassium chloride to manage a possible hypomagnesemia or hypokalemia. Thus, ECG and serum potassium levels should be frequently checked.

Psychiatric and nervous system disorders

We observed two cases of psychiatric disorders, in particular “major depression syndrome” and “psychotic crisis”, accompanied by agitation, delirium, and aggressiveness. In these cases, the suspected COVID-19 medications were HCQ, darunavir/cobicistat, and, for one patient, tocilizumab. Considering the presence of co-administered antidepressants, antipsychotics, and hypnotic and sedative agents, for these patients a COVID-19 drugs-related reduction of the activity of central nervous system medications could not be excluded. At the same time, psychological and social distress linked to COVID-19 infection should be taken into consideration [33, 34]. In fact, a recent systematic review and meta-analysis confirmed that SARS-CoV-2 might cause depression, anxiety, neuropsychiatric syndromes, and delirium in a significant proportion of patients in the acute stage [35]. Of notice, psychiatric ADRs are not commonly associated to HCQ [36], darunavir/cobicistat [37], and tocilizumab [38].

Cases of episodes of manic behaviour with psychotic features, persecutory delusions, anxiety, and reality detachment triggered by chloroquine were described [39-43]. Considering that HCQ and chloroquine have similar pharmacological properties, their toxicity profiles could be considered comparable. A meta-analysis [44] and a pharmacovigilance study on registry [45] confirmed the association between HCQ and psychiatric events. The mechanisms responsible for the psychiatric ADRs following HCQ exposure are not fully

clarified. Among proposed hypotheses, there are the cholinergic imbalance related to the inhibition of acetylcholinesterase, prostaglandin E antagonism, the accumulation of HCQ toxic metabolites in lysosomes, and the down-regulation of Glycoprotein-P in the blood-brain barrier [46]. Moreover, HCQ seems to inhibit the serotonin transporter, increasing its levels in the synapsis, and to act as N-methyl-d-aspartate agonist and γ-aminobutyric acid antagonist [46]. In general, psychiatric ADRs resolution follows HCQ withdrawal.

Among psychiatric ADRs, only "abnormal dreams" are reported in darunavir/cobicistat summary of product characteristics (SPC) [37], and, to date, literature is lacking evidence on this topic. In general, protease inhibitors have limited central nervous system penetration and therefore less-pronounced neurological and psychiatric ADRs [47]. Among this group, ritonavir alone or in combination is more likely to produce psychiatric ADRs, in particular mood changes, agitation, and anxiety. In a clinical trial, HIV patients were randomized to darunavir/ritonavir or darunavir/ritonavir in combination with two nucleoside/nucleotide reverse transcriptase inhibitors [48]. After 48 weeks of therapy, grade 1-4 nervous system and psychiatric ADRs were seen in 16% and 9% of patients in each treatment arm. Researchers reported the following psychiatric manifestations: anxiety, depression, obsessive-compulsive disorder, and psychotic crisis. Considering that cobicistat is a CYP3A4 inhibitor and recommendations reported in its SPC suggest reducing the dosages of concomitant central nervous system medications, actually, there is no possibility of a drug therapeutic failure of antipsychotics driven by the pharmacokinetic properties of suspected protease inhibitors. Therefore, psychiatric ADRs observed in our sample may have been mainly related to high-dose HCQ and to underlying psychiatric comorbidities.

After a literature search, we ascertained the lack of evidence on psychiatric ADRs related to tocilizumab [38]. Nowadays, the association between tocilizumab and psychiatric ADRs cannot be fully explained. As for protease inhibitors, particularly darunavir/cobicistat, psychiatric ADRs may have been mainly related to high-dose HCQ and to pre-existing psychiatric disorders.

When diagnosis of a psychiatric ADRs is made, the best solution is to discontinue any suspected drug. Based on our clinical experience, depending on psychiatric clinical manifestation and on QT interval values, the administration of specific antipsychotic medications (i.e., chlorpromazine) could be considered. Usually, patient's mental status reverts to normal in a few days. In case of emergencies, emotional distress is ubiquitous, but some groups may be more vulnerable than others. In particular, people at heightened risk for COVID-19, those who contract the disease, and people with pre-existing medical or psychiatric conditions are at increased risk for adverse psychosocial outcomes [49]. Particular attention should also be given to mental health of people in conditions of increased risk, such as women during pregnancy [50] or post-partum [51].

Gastrointestinal and hepatic disorders

We observed four cases of GI and hepatic disorders, in particular "nausea", "vomiting", "diarrhoea" and "hypertransaminasemia". In these cases, all classes of COVID-19 medications were involved and GI intolerance often led to pharmacological switching between the associations lopinavir/ritonavir and darunavir/cobicistat. This kind of non-specific ADRs is frequently (*common* or *very common*) observed for all medication classes, including that of COVID-19 treatments [30, 36-38, 52]. The evaluation of causality assessment for GI and hepatic disorders must take into consideration the presence of concomitant medications and the underlying SARS-CoV-2 infection, which is commonly associated with GI symptoms [53].

5. Conclusions

Despite the small number of patients, the evidence reported in the present analysis confirms that the clinical burden of DDIs in SARS-CoV-2 inpatients is relevant. Moreover, the risk of unexpected and uncommon ADRs, such those referred to psychiatric disorders, was highlighted. In this population, COVID-19 treatments should be used with extreme caution, especially in fragile and polymedicated patients. Although living in the context of a global emergency and looking for an effective therapeutic treatment, drug safety should never be overlooked, especially in the presence of DDIs.

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Data Availability Statement

Data will be available upon reasonable request.

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Table 1. Indication of use and mechanism of action of principal SARS-CoV-2 medications in Italy.

SARS-CoV-2 infection phase	**Medication**	**Indication**	**Mechanism of action**	**AIFA authorization**
Phase I and II Viral growth containment	Darunavir/cobicistat Lopinavir/ritonavir	HIV treatment	Inhibition of viral replication by the binding and inactivation of the 3CLpro and PL2pro proteases	Off-label use restricted to RCTs *(last update July 17th 2020)*
	Hydroxychloroquine Chloroquine	Antimalarials, antirheumatics	Increasing of endosomal pH crucial for virus-cell fusion	Off-label use restricted to RCTs *(last update July 22th 2020)*
	Remdesivir*	Ebola virus	In vitro and in vivo activity against SARS-CoV-2, MERS-CoV and SARS-CoV	Compassionate use
	Ribavirin*	Chronic HCV and RSV infections	Guanosine analogue that interferes with the replication of RNA and DNA viruses	Compassionate use
Phase III Inflammation and coagulation control	Azithromycin	Antibacterial for systemic use	Downregulation of adhesion molecules of cell surface, reduction of pro-inflammatory cytokines production	Authorized out of RCTs only in SARS-CoV-2 positive adult patients with bacterial infections *(last update May 5th 2020)*

Canakinumab*	Arthritis, autoinflammatory fever, Still's disease (IL-1 β antibody)	Reduction of SARS-CoV-2 induced pneumonia and inflammation	Compassionate use
Enoxaparin	Prophylaxis of venous thromboembolism	Containment of thrombotic phenomena from the pulmonary circulation	Off-label use
Tocilizumab	RA (IL-6 receptor antibody)	Reduction of SARS-CoV-2 induced pneumonia and inflammation	Off-label use
Ruxolitinib*	Myelofibrosis (inhibitor of JAK1 and JAK2 kinases)	Reduction of SARS-CoV-2 induced pneumonia and inflammation	Compassionate use
Solnatide*	Pseudo-hypoaldosteronism 1B	In study to treat pulmonary permeability edema in Austria and Germany	Compassionate use

* Compassionate use. AIFA: Italian Medicines Agency; CoV: coronavirus; HCV: hepatitis virus C; HIV: Human Immunodeficiency Viruses; MERS: Middle East Respiratory Syndrome; RA: rheumatoid artritis; RCT: randomized clinical trial; RSV: Respiratory syncytial virus; SARS: Severe Acute Respiratory Syndrome.

Table 2. Patients' characteristics.

Cases characteristics	**No. of Cases N=23 (%)**
Patient age, years	
19-64	4 (17.4)
65-79	5 (21.7)
	14 (60.9)
Mean ± standard deviation	76.1±14.40
Gender	
Male	13 (56.5)
Female	10 (43.5)
No. of suspected drugs	
2	10 (43.5)
3	8 (34.8)
	5 (21.7)
No. of concomitant medications	
None	3 (13.2)
1-5	4 (17.4)
6-10	11 (47.7)
	5 (21.7)
No. of concomitant conditions	
None	5 (21.7)
1-5	14 (60.9)
	4 (17.4)

Outcome	
Improvement	14 (60.8)
Death	5 (21.7)
Unchanged or worsened event	3 (13.2)
Complete resolution	1 (4.3)
Causality assessment	
Certain	-
Probable	17 (73.9)
Possible	6 (26.1)
Not classifiable	-
QT prolongation (19 patients), msec	
Mean ± standard deviation	496.1±36.64

Table 3. Case-by-case clinical description of all evaluated reports.

Case	Age (years)	M/F	Adverse Drug Reactions (PT)	Outcome	Suspected drugs	Concomitant medications	Concomitant conditions
1	36	F	Nausea, vomiting, abdominal pain, drug level modification	Improvement	Tacrolimus Darunavir/cobicistat	None	Renal transplant
2	80	M	ECG QT prolonged, atrial flutter, hemiplegia, hypokalaemia, major depression	Improvement	HCQ Risperidone	Sertraline, olanzapine, lorazepam, ceftriaxone, enoxaparin, lopinavir/ritonavir*, darunavir/cobicistat*	None
3	61	M	Hypertransaminasemia	Improvement	Lopinavir/ritonavir Darunavir/cobicistat Tocilizumab HCQ	Azithromycin, bisoprolol, pantoprazole, enoxaparin, lorazepam, atorvastatin	Atrial fibrillation
4	52	F	Diarrhoea, vomiting	Complete resolution	Darunavir/cobicistat HCQ Azithromycin	None	None
5	78	F	ECG QT prolonged, hypokalaemia	Improvement	HCQ Lopinavir/ritonavir	Darunavir/cobicistat*	Cardiomyopath and pacemaker
6	84	M	ECG QT prolonged, vomiting	Improvement	HCQ Lopinavir/ritonavir Azithromycin	None	Pancreatic lesions

7	56	M	ECG QT prolonged	Improvement	HCQ Lopinavir/ritonavir Azithromycin	Darunavir/cobicistat, enoxaparin, acetylsalicylic acid, candesartan, losartan, betamethasone, amoxicillin	Hypertension*
8	93	F	ECG QT prolonged	Improvement	HCQ Citalopram	Simvastatin, levothyroxine, bromazepam, trazodone, enoxaparin, azithromycin, ceftriaxone	None
9	82	F	ECG QT prolonged	Improvement	HCQ Lopinavir/ritonavir Azithromycin	Sevelamer, pantoprazole, bisoprolol, furosemide, methylprednisolone, piperacillin/tazobactam, linezolid, epoetin alpha	Renal failure, anaemia, hypertension
10	80	M	ECG QT prolonged	Unchanged event	HCQ Sertraline Azithromycin	Valsartan, esomeprazole, pantoprazole, lorazepam, amlodipine, mesalamine, tamsulosin, loperamide, piperacillin/tazobactam, acetylsalicylic acid, enoxaparin, furosemide	None
11	67	F	ECG QT prolonged	Unchanged event	HCQ Lopinavir/ritonavir Azithromycin Haloperidol Levomepromazine Zuclopenthixol	Valproic acid, atorvastatin, lorazepam, fondaparinux	Paranoid schizophrenia, hypercholester

12	85	M	ECG QT prolonged	Unchanged event	Lopinavir/ritonavir HCQ	Piperacillin/tazobactam, magnesium sulphate, linezolid, fluticasone propionate/vilanterol, bisoprolol, pantoprazole, thiamazole, allopurinol, acetylsalicylic acid, ursodeoxycholic acid, calcium carbonate, calcitriol	Bleeding, failure, hyperthyroidism, BPH, heart failure
13	70	F	ECG QT prolonged	Death	HCQ Darunavir/cobicistat Azithromycin Amiodarone	Warfarin, furosemide, potassium chloride, atorvastatin, amoxicillin/clavulanate, acetaminophen, enoxaparin, ruxolitinib, aclidinium bromide	COPD, hypothyroidism, atrial fibrillation, renal failure
14	86	M	ECG QT prolonged	Improvement	HCQ Lopinavir/ritonavir	Furosemide, apixaban, atorvastatin, nitroglycerine, clonidine, potassium chloride, darunavir/cobicistat*, enoxaparin	None

15	93	M	ECG QT prolonged	Death	Lopinavir/ritonavir HCQ Azithromycin	Ceftriaxone, furosemide, bisoprolol, tamsulosin, dutasteride, ramipril, enoxaparin, insulin, gliclazide, vildagliptin, metformin, perindopril, barnidipine, simvastatin	Diabetes, hypertension, BPH, vascular encephalopathy, lower limbs obliterating arteriopathy
16	80	M	ECG QT prolonged	Death	Lopinavir/ritonavir HCQ Azithromycin Haloperidol	Verapamil, lansoprazole, acetylsalicylic acid, macrogol, enoxaparin	Alzheimer and Parkinson's diseases, hypertension, right carotid stenosis, renal failure, hepatic steatosis
17	85	M	ECG QT prolonged, hypokalaemia	Improvement	HCQ Magnesium sulphate	Tamsulosin, bisoprolol, warfarin, atorvastatin, bicalutamide, rabeprazole, meropenem, vancomycin, potassium chloride	Hypertension, hypercholesterolemia, neuropathic pain, prostatic cancer, mitral valve intervention, hypokalaemia and hypomagnesem
18	71	M	ECG QT prolonged	Improvement	HCQ Darunavir/cobicistat	Simvastatin, allopurinol, olmesartan, nebivolol, rivaroxaban, potassium chloride	Hypertension, dyslipidaemia, atrial fibrillation, pulmonary emphysema, obesity

19	89	M	ECG QT prolonged	Initial improvement of QT prolongation and death	Lopinavir/ritonavir HCQ Azithromycin Citalopram	Pantoprazole, bisoprolol, clopidogrel, atorvastatin, quetiapine, promazine, piperacilline/tazobactam, enoxaparin, olanzapine	Mild mental retardation, Parkinson's disease, past severe head injury with subdural hematoma, chronic dysphagia, thrombocytopenia, anaemia, hypertension, dyslipidaemia, chronic renal failure
20	65	M	Psychosis, agitation, delirium, aggressiveness	Improvement	HCQ Darunavir/cobicistat Tocilizumab	Dutasteride, allopurinol, propofol, risperidone, valproic acid, clonazepam, ramipril, amlodipine, midazolam, spironolactone, dexmedetomidine, olanzapine	Overweight, hyperuricemia, prostatic hypertrophy
21	81	F	ECG QT prolonged	Improvement	HCQ Darunavir/cobicistat	Thiamazole, pantoprazole, folic acid, potassium chloride, bisoprolol, furosemide, warfarin, potassium canrenoate, alprazolam, enoxaparin and iron, vitamin C and vitamin B12 supplementation	Atrial fibrillation, hypertension, hyperthyroidism, osteoporosis, mitral valve disease

22	89	F	ECG QT prolonged	Death	HCQ Trazodone	Ceftriaxone, methylprednisolone, acetylsalicylic acid, acetaminophen/codeine, alprazolam, omeprazole, valproic acid, morphine, enoxaparin, calcium and vitamin D3 supplementations	Cognitive impairment, chronic subcortical vascular encephalopathy, kidney heteroplasia, hypertension, osteoporosis, osteoarthritis, anxiety-depressive syndrome
23	88	F	ECG QT prolonged	Improvement	HCQ Darunavir/cobicistat Haloperidol	Promazine, enoxaparin, potassium chloride	Alzheimer's disease

BPH: benign prostatic hyperplasia; COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; F: female; HCQ: hydroxychloroquine; M: male.

* This medication was not administered simultaneously with the suspected drugs. In particular, the patient was not exposed to this medication at the time of ADR occurrence.

Table 4. Major and moderate drug-drug interactions between COVID-19 treatments and patients' concomitant medications.

Interacting drugs	**Interacting active principles**	**In**
COVID-19 medication with other COVID-19 therapies	HCQ-azithromycin	Mo
	HCQ-lopinavir/ritonavir	Ma
	HCQ-tocilizumab	Mo
	Lopinavir/ritonavir-azithromycin	Mo
	Lopinavir/ritonavir-darunavir/cobicistat	Mo
COVID-19 medication with CNS medications	Azithromycin-citalopram	Ma
	Azithromycin-haloperidol	Ma
	Azithromycin-olanzapine	Mo
	Azithromycin-promazine	Mo
	Azithromycin-quetiapine	Mo
	Azithromycin-trazodone	Mo
	Darunavir/cobicistat-alprazolam	Mo
	Darunavir/cobicistat-clonazepam	Mo
	Darunavir/cobicistat-midazolam	Ma
	Darunavir/cobicistat-risperidone	Mo
	Darunavir/cobicistat-sertraline	Mo
	Enoxaparin-citalopram	Mo
	Enoxaparin-sertraline	Mo
	HCQ-citalopram	Ma
	HCQ-codeine	Mo
	HCQ-haloperidol	Ma

	HCQ-olanzapine
	HCQ-promazine
	HCQ-quetiapine
	HCQ-risperidone
	HCQ-sertraline
	HCQ-trazodone
	Lopinavir/ritonavir-citalopram
	Lopinavir/ritonavir-haloperidol
	Lopinavir/ritonavir-olanzapine
	Lopinavir/ritonavir-promazine
	Lopinavir/ritonavir-quetiapine
	Lopinavir/ritonavir-risperidone
	Lopinavir/ritonavir-sertraline
	Lopinavir/ritonavir-valproic acid
	Tocilizumab-amlodipine
	Tocilizumab-clonazepam
	Tocilizumab-midazolam
COVID-19 medication with CV medications	Azithromycin-atorvastatin or simvastatin
	Azithromycin-sertraline
	Azithromycin-warfarin
	Darunavir/cobicistat-amiodarone
	Darunavir/cobicistat-amlodipine
	Darunavir/cobicistat-apixaban
	Darunavir/cobicistat-atorvastatin or simvastatin
	Darunavir/cobicistat-nebivolol
	Darunavir/cobicistat-rivaroxaban
	Darunavir/cobicistat-warfarin
	Enoxaparin-amiodarone
	Enoxaparin-apixaban
	Enoxaparin-clopidogrel
	Enoxaparin-losartan or valsartan
	Enoxaparin-perindopril
	Enoxaparin-warfarin
	HCQ-amiodarone
	HCQ-atorvastatin or simvastatin
	Lopinavir/ritonavir-apixaban
	Lopinavir/ritonavir-atorvastatin or simvastatin
	Lopinavir/ritonavir-bisoprolol
	Lopinavir/ritonavir-verapamil
	Tocilizumab-atorvastatin
COVID-19 medication with other medications	Azithromycin-loperamide
	Darunavir/cobicistat-betamethasone
	Darunavir/cobicistat-clopidogrel
	Darunavir/cobicistat-dutasteride
	Darunavir/cobicistat-ruxolitinib
	HCQ-bicalutamide
	HCQ-fluticasone propionate/vilanterol
	HCQ-gliclazide
	HCQ-linezolid
	HCQ-loperamide
	Lopinavir/ritonavir-betamethasone

	Lopinavir/ritonavir-clopidogrel	Ma
	Lopinavir/ritonavir-dutasteride	Mo
	Lopinavir/ritonavir-fluticasone propionate/vilanterol	Ma
	Lopinavir/ritonavir-gliclazide	Mo
	Lopinavir/ritonavir-insulin	Mo
	Lopinavir/ritonavir-levothyroxine	Mo
	Lopinavir/ritonavir-metformin	Mo
	Lopinavir/ritonavir-methylprednisolone	Ma
	Lopinavir/ritonavir-tamsulosin	Ma
	Lopinavir/ritonavir-vildagliptin	Mo

CNS: central nervous system; CV: cardiovascular; ECG: electrocardiogram; HCQ: hydroxychloroquine.

Supplementary table 1 . Major and moderate DDIs between concomitant medications reported in patients' anamnesis.

Interacting drugs	**Interacting active principles**	**Interaction severity**	**Interaction e**
CNS medications	Alprazolam-codeine or morphine	Major	Increased risk
	Alprazolam-furosemide	Moderate	Increased risk
	Alprazolam-omeprazole	Moderate	Increased bloo
	Alprazolam-trazodone	Moderate	Increased risk
	Citalopram-promazine	Major	Increased risk
	Citalopram-quetiapine	Major	Increased risk
	Clonazepam-dexmedetomidine	Moderate	Increased risk
	Clonazepam-spironolactone	Moderate	Increased risk
	Clonazepam-propofol	Moderate	Increased risk
	Clonazepam-risperidone	Moderate	Increased risk
	Codeine-morphine	Major	Increased risk
	Codeine-trazodone	Moderate	Increased risk
	Codeine-valproic acid	Moderate	Increased risk
	Dexmedetomidine-amlodipine	Moderate	Increased risk
	Dexmedetomidine-midazolam	Moderate	Increased risk
	Dexmedetomidine-olanzapine	Moderate	Increased risk
	Dexmedetomidine-propofol	Moderate	Increased risk
	Dexmedetomidine-ramipril	Moderate	Increased risk
	Dexmedetomidine-risperidone	Moderate	Increased risk
	Dexmedetomidine-spironolactone	Moderate	Increased risk
	Haloperidol-verapamil	Moderate	Increased risk
	Lorazepam-bisoprolol	Moderate	Increased risk
	Lorazepam-furosemide	Moderate	Increased risk
	Lorazepam-haloperidol	Moderate	Increased risk
	Lorazepam-olanzapine	Major	Increased CNS
	Lorazepam-risperidone	Moderate	Increased CNS
	Lorazepam-tamsulosin	Moderate	Increased risk
	Midazolam-propofol	Moderate	Increased risk
	Midazolam-spironolactone	Moderate	Increased risk
	Morphine-trazodone	Moderate	Increased risk
	Olanzapine-amlodipine	Moderate	Increased risk
	Olanzapine-bisoprolol	Moderate	Increased risk
	Olanzapine-citalopram	Moderate	Increased risk
	Olanzapine-clonazepam	Major	Increased risk

	Olanzapine-midazolam	Major	Increased risk
	Olanzapine-promazine	Moderate	Increased risk
	Olanzapine-propofol	Moderate	Increased risk
	Olanzapine-quetiapine	Moderate	Increased risk
	Olanzapine-spironolactone	Moderate	Increased risk
	Promazine-bisoprolol	Moderate	Increased risk
	Promazine-quetiapine	Moderate	Increased risk
	Quetiapine-bisoprolol	Moderate	Increased risk
	Risperidone-amlodipine	Moderate	Increased risk
	Risperidone-olanzapine	Moderate	Increased risk
	Risperidone-midazolam	Moderate	Increased risk
	Risperidone-propofol	Moderate	Increased risk
	Risperidone-spironolactone	Moderate	Increased risk
	Sertraline-furosemide	Moderate	Increased risk
	Sertraline-loperamide	Moderate	Increased risk
	Sertraline-lorazepam	Moderate	Increased CNS
	Sertraline-olanzapine	Moderate	Increased risk
	Sertraline-risperidone	Moderate	Increased risk
	Sertraline-tamsulosin	Moderate	Increased bloo
	Trazodone-citalopram	Major	Increased risk
	Valproic acid-clonazepam	Moderate	Increased risk
	Valproic acid-haloperidol	Moderate	Increased risk
	Valproic acid-dexmedetomidine	Moderate	Increased risk
	Valproic acid-morphine	Moderate	Increased risk
	Valproic acid-olanzapine	Moderate	Increased risk
	Valproic acid-propofol	Moderate	Increased bloo
	Valproic acid-risperidone	Moderate	Increased bloo
	Valproic acid-trazodone	Moderate	Increased risk
CV medications	Acetylsalicylic acid-amlodipine	Moderate	Increased risk
	Acetylsalicylic acid-enoxaparin	Major	Increased risk
	Acetylsalicylic acid-betamethasone or methylprednisolone	Moderate	Reduced serum
	Acetylsalicylic acid-candesartan	Moderate	Increased risk
	Acetylsalicylic acid-citalopram	Moderate	Increased risk
	Acetylsalicylic acid-losartan or valsartan	Moderate	Increased risk
	Acetylsalicylic acid-sertraline	Moderate	Increased risk
	Acetylsalicylic acid-verapamil	Moderate	Increased bloo
	Acetylsalicylic acid-verapamil	Moderate	Increased risk
	Amiodarone-furosemide	Major	Increased risk
	Amiodarone-warfarin	Major	Increased risk
	Atorvastatin-amiodarone	Moderate	Increased bloo
	Atorvastatin-bicalutamide	Moderate	Increased bloo
	Atorvastatin-pantoprazole	Moderate	Increased bloo
	Bisoprolol-alprazolam	Moderate	Increased risk
	Bisoprolol-gliclazide	Moderate	Increased risk
	Bisoprolol-furosemide	Moderate	Increased risk
	Bisoprolol-linezolid	Moderate	Increased risk
	Bisoprolol-methylprednisolone	Moderate	Increased risk
	Candesartan-enoxaparin	Moderate	Increased risk
	Candesartan-betamethasone	Moderate	Increased risk
	Clopidogrel-atorvastatin	Moderate	Decreased effic
	Clopidogrel-citalopram	Moderate	Increased risk

	Losartan-betamethasone	Moderate	Increased risk
	Olmesartan-potassium chloride	Major	Increased risk
	Perindopril-furosemide	Moderate	Increased risk
	Perindopril-glicazide	Moderate	Increased risk
	Perindopril-insulin	Moderate	Increased risk
	Perindopril-metformin	Moderate	Increased risk
	Perindopril-vildagliptin	Moderate	Increased risk
	Ramipril-allopurinol	Major	Increased risk
	Ramipril-clonazepam	Moderate	Increased risk
	Ramipril-olanzapine	Moderate	Increased risk
	Ramipril-risperidone	Moderate	Increased risk
	Ramipril-spironolactone	Major	Increased risk
	Ramipril-vildagliptin	Moderate	Increased risk
	Warfarin-amoxicillin/clavulanate	Moderate	Increased risk
	Warfarin-rabeprazole or pantoprazole	Moderate	Increased risk
Other interactions	Fluticasone propionate/vilanterol-linezolid	Moderate	Increased risk
	Furosemide-ceftriaxone	Moderate	Increased risk
	Furosemide-gliclazide	Moderate	Increased risk
	Furosemide-insulin	Moderate	Increased risk
	Furosemide-linezolid	Moderate	Increased risk
	Furosemide-methylprednisolone	Moderate	Increased risk
	Furosemide-pantoprazole or esomeprazole	Moderate	Increased risk
	Furosemide-vildagliptin	Moderate	Increased risk
	Gliclazide-furosemide	Moderate	Increased risk
	Insulin-gliclazide	Moderate	Increased risk
	Insulin-vildagliptin	Moderate	Increased risk
	Vildagliptin-gliclazide	Moderate	Increased risk

CNS: central nervous system; CV: cardiovascular; ECG: electrocardiogram.