A comprehensive review of adverse events to drugs used in COVID-19 patients: Recent clinical evidence

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Abstract
Background: Since the breakthrough of the pandemic, several drugs have been used to treat COVID-19 patients. This review aims to gather information on adverse events (AE) related to most drugs used in this context.

Methods: We performed a literature search to find articles that contained information about AE in COVID-19 patients. We analysed and reviewed the most relevant studies in the Medline (via PubMed), Scopus and Web of Science. The most frequent AE identified were grouped in our qualitative analysis by System Organ Class (SOC), the highest level of the MedDRA medical terminology for each of the drugs studied.

Results: The most frequent SOCs among the included drugs are investigations (n = 7 drugs); skin and subcutaneous tissue disorders (n = 5 drugs); and nervous system disorders, infections and infestations, gastrointestinal disorders, hepatobiliary disorders, and metabolism and nutrition disorders (n = 4 drugs). Other SOCs also emerged, such as general disorders and administration site conditions, renal and urinary disorders, vascular disorders and cardiac disorders (n = 3 drugs). Less frequent SOC were eye disorders, respiratory, thoracic and mediastinal disorders, musculoskeletal and connective tissue disorders, and immune system disorders (n = 2 drugs). Psychiatric disorders, and injury, poisoning and procedural complications were also reported (n = 1 drug).

Conclusions: Some SOCs seem to be more frequent than others among the COVID-19 drugs included, although neither of the studies included reported causality analysis. For that purpose, further clinical studies with robust methodologies, as randomised controlled trials, should be designed and performed.

KEYWORDS
Adverse drug events, Pharmacovigilance, SARS-CoV-2, Therapeutic drug monitoring
1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in late December 2019 in Wuhan, China, and it is responsible for coronavirus disease 2019 (COVID-19). COVID-19 was classified as a pandemic by the World Health Organization (WHO) on 11 March 2020. As of 16 February 2022, there were more than 412 million confirmed cases of COVID-19, with 5,821,004 confirmed deaths.

A minimal set of therapeutic approaches with real effectiveness and clinical safety is available for specific stages of the disease. Several additional therapeutic possibilities are already under study in multiple countries. The most used approach has been investigating drugs already available on the market with approved indications for other diseases—‘drug repurposing’, to bypass the limiting factor in the process of drug development: time. Although attention has been focused on the drugs’ potential effectiveness, the safety window is also one of the most important aspects in a clinical context. Several studies have reported a substantial set of adverse events (AE) where imputation of causality to a drug is difficult. For instance, approximately 20%–30% of patients have elevated transaminases during COVID-19 infection. This exacerbation may be due to therapy, viral infection or a combination of both. Recent literature shows that the most commonly reported AE with COVID-19 treatments, in decreasing order of frequency, were QT-prolonged electrocardiogram, diarrhea, nausea, hepatitis, vomiting and upper abdominal pain. These data are particularly important for health professionals who treat COVID-19 patients; particular attention should be paid to the early detection and reporting of AE.

The most recent descriptive analysis published with data from the VigiBase—the adverse drug reactions database of the WHO—supports the importance of studying AE in COVID-19 therapy. This report describes AE in COVID-19 patients worldwide, with individual analysis for a set of selected drugs. 4739 reports were received from 6 WHO regions, 50.1% of which were from the European region. Of the total reports, 51.5% were classified as ‘serious’. However, many of these reported cases did not include the seriousness criterion of the reactions. Besides, it is well recognised that there is a global underreporting of AE, and for these reasons, the problem is probably much more serious than the data show.

This review aims to gather current and comprehensive information on AE related to drugs used in COVID-19 patients, which might help to support clinical decisions. The selection of drugs to include in this review was based on reports of use in the clinical context of COVID-19—clinical trials or healthcare assistance practice—even considering off-label use (more detailed information in the Methods section).

1.1 | Therapeutics

Several investigational agents and drugs approved for other indications are currently being studied in clinical trials to treat patients with COVID-19 and associated complications. Currently, seven drugs are already approved in Europe for use in patients with COVID-19: remdesivir (RDV), dexamethasone (DM), anakinra, regdanvimab, tocilizumab, and casirivimab/imdevimab and sotrovimab.

The antiviral RDV was the first treatment officially approved by the US Food and Drug Administration (FDA) and then by the European Medicines Agency (EMA), for the treatment of COVID-19 patients requiring hospitalisation, as long as they are adults or paediatric patients, 12 years of age and older and weighing at least 40 kg. Subsequently, these authorities approved the corticosteroid DM as a treatment for COVID-19 patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation). Five other pharmacological approaches of interest for this disease were recently approved, although they are not yet being used widely in most health services worldwide.

These decisions have been supported by studies showing improvement in some outcomes in very specific clinical contexts, although some studies have reported contradictory data. A meta-analysis that included 15 studies with patients with coronavirus infections (e.g., COVID-19, SARS and MERS) and a retrospective
review of critically ill patients with COVID-19\textsuperscript{16} suggest an increased risk of multiorgan dysfunction as a result of treatment. The results of these studies should be interpreted with caution, as they are retrospective and present methodological limitations typical of this type of study. On the other hand, when used during outbreaks of other coronavirus infections (i.e., MERS and SARS), corticosteroids (CS) therapy was associated with delayed virus clearance.\textsuperscript{17,18} The Randomised Evaluation of COVID-19 Therapy—RECOVERY study, a multicentre, randomised, open-label trial in hospitalised patients with COVID-19, showed that in the group of patients randomised to receive DM, the mortality from COVID-19 was lower than in the group who received the standard of care.\textsuperscript{19} Also, the length of hospital stay seems to decrease with RDV (from 15 to 11 days), with no evidence of reducing mortality.\textsuperscript{20} The decrease in mortality seems to bring an added benefit to DM when compared to RDV (evidenced by a 35% reduction in mortality in patients with invasive mechanical ventilation and 20% in patients with oxygen support without mechanical ventilation). The benefit was most significant in patients with symptoms for more than seven days and requiring mechanical ventilation. Conversely, there was no benefit (but possibly harm) among patients with shorter symptom duration and no supplemental oxygen requirement.\textsuperscript{19}

Other classes of drugs are being evaluated, as other antivirals (e.g., lopinavir–ritonavir [LPV/r], oseltamivir and favipiravir), antiparasitic drugs (e.g., chloroquine [CQ] and hydroxychloroquine [HCQ], ivermectin [IVM]), antibodies (e.g., convalescent plasma, hyperimmune immunoglobulins), non-steroidal anti-inflammatory drugs (NSAIDs), targeted immunomodulatory therapies (including interleukin-6 inhibitors as tocilizumab [TCB], sarilumab [SAR] and ruxolitinib [RX]), anticoagulants (e.g., heparin) and antifibrotics (e.g., tyrosine kinase inhibitors).\textsuperscript{14,21–25} Some of these drugs have also been studied in combination with other drugs, such as HCQ plus azithromycin (AZM).\textsuperscript{26} Except for RDV and DM, all of these drugs should be seen in clinical practice as off-label use in COVID-19 patients.\textsuperscript{27}

In the therapeutic arsenal for COVID-19 patients, inhaled nitric oxide has been considered in refractory hypoxia cases,\textsuperscript{28,29} but there are still no reliable results to support its use in clinical practice. Moreover, no agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) are recommended by the international scientific authorities.\textsuperscript{30}

The use of drugs always depends on a risk-benefit balance by the clinical team, but the effects of most drug interventions against COVID-19 are currently highly uncertain, with insubstantial evidence to support benefits and/or harms for any outcomes. However, data from randomised controlled trials (RCT), prospective and retrospective observational cohorts, case–control and case series studies are rapidly emerging.

2 | METHODS

2.1 | Search strategy and selection criteria

The research team performed a literature search to find articles that contained information about AE related to drugs used in COVID-19 patients regardless of the type of clinical study. We searched Medline (via PubMed), Scopus and Web of Science, using the search terms: ADR, adverse drug reactions, adverse drug events, adverse drug effects, adverse events and pharmacovigilance, in combination with the terms: severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 and COVID-19. We also manually searched for additional references to articles related to the clinical use of drugs against COVID-19. Inclusion criteria were all clinical studies targeting COVID-19 patients and with results on AE and other safety issues. We have not established any exclusion criteria concerning study design, funding, date of publication or language of the articles to be included. Exceptionally, some unpublished references related to study reports publicly available by the pharmaceutical companies or available in preprints platforms were also considered. The core of the research was performed until September 2021, but has been continuously updated. Authors reviewed abstracts and potentially relevant full texts independently, with any conflict resolved by consensus. Our research strategy followed the main steps required for narrative reviews suggested by Baethge et al. in SANRA—a scale for the quality assessment of narrative review articles.\textsuperscript{31}

For the purpose of this review, we categorised the drugs according to the ‘COVID-19 treatment guidelines’ presented by the National Institutes of Health\textsuperscript{30} even if it does not correspond to their official pharmacotherapeutic classification.

3 | RESULTS AND DISCUSSION

3.1 | Antiviral therapeutics

3.1.1 | Chloroquine and hydroxychloroquine

CQ and HQC are approved for the treatment of malaria and amoebiasis, and have demonstrated virucidal activity against SARS\textsuperscript{32} and SARS-CoV-2\textsuperscript{33} in in vitro studies, simulation pharmacokinetic analysis and animal models.
However, subsequent clinical studies have shown that the efficacy in COVID-19 patients was not as expected.\textsuperscript{34-38} Indeed, the RECOVERY trial was suspended after an interim analysis showing no efficacy (primary outcome being 28-day mortality).\textsuperscript{39} Also relevant, HCQ was associated with a higher incidence of AE than the usual care group.\textsuperscript{40} An early Cochrane systematic review further strengthened this view.\textsuperscript{41} The authors concluded that the efficacy of CQ or HCQ against COVID-19 was inconsistent, but overall, there was no benefit in mortality, symptom resolution or clinical deterioration/development of acute respiratory distress syndrome (ARDS). More recently, another Cochrane systematic review\textsuperscript{37} concluded that there was little or no effect of HCQ on the risk of death or on the progression to mechanical ventilation and that the incidence of AE was higher than that of a placebo, although very few serious AE were found.

CQ and HCQ have a similar toxicological profile.\textsuperscript{42} Cardiotoxicity was a concern ever, namely because of prolonged QT and/or ventricular tachycardia, including Torsade-des-Points and conduction disorders (atrioventricular and bundle-branch blocks) and heart failure.\textsuperscript{43-47} Two recent retrospective studies highlighted AZM as a factor of increased risk for HCQ-associated cardiotoxicity in patients with rheumatoid arthritis\textsuperscript{48} or other clinical condition,\textsuperscript{49} which should be considered when translating to the treatment of COVID-19 patients. Indeed, high doses of CQ\textsuperscript{42} were associated with serious heart rhythm problems in critically ill COVID-19 patients also receiving AZM (due to the hospital protocol). Also, there is currently robust evidence in COVID-19 patients that the concomitant use of HCQ and AZM increases the risk of QTc prolongation.\textsuperscript{41,46,49} Although the risk of arrhythmic toxicity from HCQ is likely to be low given the short duration of therapy in COVID-19, the Heart Rhythm Society published guidelines suggesting caution on patients who are taking QT-prolonging medications (e.g., macrolide antibiotics, antiarrhythmics, antipsychotics and antifungals).\textsuperscript{50,51} A retrospective study of 1438 hospitalised COVID-19 patients concluded that patients who received HCQ alone or with AZM are more likely to experience cardiac arrest when compared to patients on conventional therapy. However, there were no differences in mortality or abnormal electrocardiogram (ECG) recordings compared to those who did not receive any of these drugs.\textsuperscript{44} Based on the evidence of the cardiotoxic potential of drug interactions, the American College of Cardiology recommends additional monitoring—in baseline and follow-up—for patients taking the combination of HCQ plus AZM.\textsuperscript{52} Tang et al. reported diarrhoea, blurred vision and thirst as AE in 30% of patients in his study, and two of them reported severe AE due to disease progression to upper respiratory tract infection.\textsuperscript{53}

Among symptomatic non-hospitalised adults, HCQ (5-day regimen) was associated more frequently with AE, of which gastrointestinal symptoms were the most prevalent, namely upset stomach or nausea, abdominal pain, diarrhoea or vomiting.\textsuperscript{54} Mild types of AE were reported in hospitalised COVID-19 patients, such as rash, headache, blurred vision, diarrhoea, nausea, vomiting and rash.\textsuperscript{53,55,56} A case report also highlighted the risk of hepatotoxicity associated with HCQ, which unusually coursed with a marked increase in serum transaminase levels that normalised after HCQ discontinuation.\textsuperscript{57}

The use of HCQ has also been studied in asymptomatic patients with household or occupational exposure to a person with confirmed COVID-19 for PEP. Nausea, loose stools and abdominal discomfort were the most common AE,\textsuperscript{58} corroborating the evidence previously described in COVID-19 patients with a confirmed diagnosis.

Overall, despite the initial optimism supporting the use of HCQ and CQ, these drugs should not be used in this disease, as the risk-benefit balance is not favourable. Some authors support the idea that future investments in studies with these drugs for COVID-19 should not be made.\textsuperscript{37}

3.1.2 | Ivermectin

IVM is an FDA-approved antiparasitic drug used to treat several neglected tropical diseases, including onchocerciasis, helminthiasis and scabies.\textsuperscript{59} Reports from in vitro studies suggest that IVM acts by inhibiting the host importin α/β-1 nuclear transport proteins, suppressing the host’s antiviral response.\textsuperscript{60,61} Although more recent studies demonstrate therapeutic ineffectiveness in COVID-19, initial studies suggested that IVM (single 200 μg/kg dose eventually repeated after 7 days) was associated with significantly lower mortality among patients with more severe manifestations of COVID-19.\textsuperscript{62} In vitro assays showed antiviral efficacy against SARS-CoV-2\textsuperscript{63} but suggested that the plasma concentrations necessary for the antiviral activity would be 50 to 100 times higher than the dose that is approved for use in humans.\textsuperscript{64,65} Although IVM has shown to be safe in healthy adults at doses up to 120 mg,\textsuperscript{64} subsequent studies have shown uncertainty regarding the benefit and safety of treatment with this drug in different settings, such as outpatient, hospital or post-exposure prophylaxis.\textsuperscript{66-68}

Currently, there are very few data on the safety profile of this drug in COVID-19. A recent RCT found dizziness and blurred vision more prevalent in the group taking IVM than placebo, but no difference for confusion, drowsiness or pruritus.\textsuperscript{69} Another recent double-blind RCT with 400 subjects found a very similar AE pattern between the IVM and the placebo arms.\textsuperscript{70} Dizziness, diarrhoea,
nausea, abdominal pain, vision disorders, tremor, skin rash, skin discolouration and less frequently, swelling and vomiting were reported, although the headache was the most reported. We recognise this latest clinical trial as one of the most complete studies with the best methodological quality published to date.

Studies before COVID-19 arose reported headache, dysmenorrhea, upper respiratory infection symptoms, diarrhoea, nausea, vomiting, stomach pain, skin rash (some severe cases requiring hospitalisation), painful skin oedema (especially of the limbs and face), pruritus, arthralgia (mostly in knees, ankles and elbows), bone pain, thoracic pain, malaise, painful and tender glands in neck, thralgia (most in knees, ankles and elbows), bone pain, oedema (especially of the limbs and face), pruritus, arthralgia (some severe cases requiring hospitalisation), painful skin rash, skin discoloration and less frequently, swelling and vomiting were reported, although the headache was the most reported. We recognise this latest clinical trial as one of the most complete studies with the best methodological quality published to date.

Fever,71–78 sudden drop in blood pressure, liver injury (hepatitis) and thoracic pain, malaise, painful and tender glands in neck, thralgia (mostly in knees, ankles and elbows), bone pain, oedema (especially of the limbs and face), pruritus, arthralgia (some severe cases requiring hospitalisation), painful skin rash, skin discoloration and less frequently, swelling and vomiting were reported, although the headache was the most reported. We recognise this latest clinical trial as one of the most complete studies with the best methodological quality published to date. The EMA's official position regarding the use of IVM in the prevention and treatment of this disease is clear, and it is not recommended in either the prevention or treatment of COVID-19, unless in the context of a properly designed clinical trial.79 Even so, the putative benefit and safety profile of IVM have not been adequately studied to prevent or treat COVID-19.

3.1.3 Lopinavir–Ritonavir

Lopinavir (LPV) and ritonavir are aspartic acid protease inhibitors developed for the treatment of HIV.80 Lopinavir is mainly metabolised by CYP3A4 (90%), while ritonavir is a substrate with marked inhibitory activity on CYP3A4.81 As such, LPV is co-formulated with a low dose of ritonavir (LPV/r) to boost the pharmacokinetics and half-life of LVP through inhibition of CYP450.80 An association between PF-07321332 and ritonavir was recently submitted to the EMA for a marketing authorisation.11 The AE most frequently reported with LPV/r are gastrointestinal signs/symptoms, such as nausea, vomiting and/or diarrhoea.30,82–86 Abnormal liver function tests,30,85 hepatobiliary disorders83,87 and elevated lipase levels,97 dyslipidaemias (hypertriglyceridaemia and hypercholesterolaemia)87,88 and hypokalemia94 have also been reported. An RCT also reported a loss of appetite among patients hospitalised with mild/moderate COVID-19.85 Concerning the AE of LPV/r on liver function, information is controversial; early studies suggest that patients treated with LPV/r commonly experience an elevation of transaminases,86,89 but one clinical trial found no differences in liver enzyme levels—alanine aminotransferase (ALT) and aspartate transaminase (AST)—between the LPV/r group and standard care group of COVID-19 patients.82 Another study showed 18.6% of liver injuries after treatment with LPV/r, suggesting possible drug-induced liver damage in COVID-19 patients.90 Anyway, these findings on liver function agree with previous studies in HIV patients on LVP/r therapy: clinically significant liver injury appears to be rare and resolves with drug removal.91

Although rare, cardiotoxicity has also been a concern associated with LVP/r. Early in the COVID-19 pandemic, the French Network of Pharmacovigilance Centers estimated the incidence of these AE (among a time period of 8 weeks) between 12.5%92 and 14.2%,93 from spontaneous reports of COVID-19 patients. On average, the AE occurred on day 4 ± 3 of treatment.92 All cases were notified as serious and comprised death, three life-threatening situations, prolongation of hospitalisation, among other serious medical situations.92 These studies show an incidence of LPV/r-associated cardiotoxicity much higher than that of the pre-COVID-19 period and highlight the need for rational drug use, especially in those with congenital QTc prolongation.88,92 However, the occurrence of cardiac AE may be facilitated by COVID-19, as for SARS-CoV-2-induced hypokalemia94 or cardiomyopathy.95

An important aspect to consider when evaluating these drugs’ safety profiles is the genetic variations (polymorphism) observed across patients, particularly those associated with loss of function of CYP3A4,96 which can affect drug efficacy or expose the patients to metabolic toxicity.97 Also, co-administering LPV/r with medications also metabolised by CYP3A4 may increase the concentrations of those medications, resulting in concentration-related toxicity.98 This is particularly evident with lurasidone, quetiapine and ziprasidone, and can lead to an increased risk of serious AE, including prolongation of QTc interval.98 Nevertheless, screening for these susceptibilities is not practical in the setting of short-duration treatment for SARS-CoV-2.99

Despite reports of ocular toxicity from chronic use of ritonavir (monotherapy) in HIV patients, retinal toxicity caused by short-term use of LPV/r seems unlikely in COVID-19 patients.100

As ritonavir is co-administered with lopinavir to favour pharmacokinetics, there is a significant potential for drug-drug interactions even in the short-term use of the clinical setting of COVID-19 patients. A recent review focused on the interactions between LPV/r and cardiac medications, with recommendations not to use concomitantly or to switch to another molecule within the group/class.101 This is true in the case of co-prescription of cardiac (e.g., ranolazine, dronedarone, colchicine, simvastatin and sildenafil) and antiviral therapies, resulting in increased potential for toxicity and, consequently, severe drug interactions.101 Although these interactions have not been studied in COVID-19 patients, it is expected that AE may still arise.
Gastrointestinal upset and potential drug-drug interactions are the primary concerns with LPV/r. Although the evidence is still minimal for clinical use, some hospitals worldwide have used these drugs in COVID-19 patients. Observational cohort studies from the clinical records of COVID-19 patients should be considered.

3.1.4 | Remdesivir

RDV was initially developed to treat Ebola haemorrhagic fever, and the clinical trial is still ongoing; as such, it has not been approved globally for any therapeutic indication. RDV was associated with hypotension (during infusion of the loading dose) and neurologic complications (clinical trial, phase I) reported in patients with Ebola virus infections.

Early in the COVID-19 pandemic period, RDV started to be used off-label and transient gastrointestinal AE were reported in three COVID-19 patients in the United States of America (USA), namely nausea, vomiting, gastroparesis, rectal bleeding and elevated levels of transaminases (1–5 days after initiating RDV). The initial reports of the off-label use of RDV in COVID-19 patients were small case series. Additionally, poorly robust clinical study designs (e.g., non-randomised clinical trials), low-quality data and poorly characterised information constitute other limitations in interpreting the findings.

The first randomised, double-blind, placebo-controlled clinical trial assessing the effect of intravenous (IV) RDV in adults admitted to hospital with severe COVID-19 (n = 237) had the dosing stopped prematurely by the investigators due to the occurrence of AE. AE were similar in both the trial’s arms (RDV vs. placebo), although with a higher proportion in the RDV arm. The most common AE were hyperbilirubinaemia, hypokalaemia, anaemia, thrombocytopenia, rash, increased blood glucose and increased total bilirubin. Other RCT have also identified nausea, diarrhoea, pyrexia, constipation, (acute) respiratory failure, increased ALT, decreased glomerular filtration rate (GFR), decreased haemoglobin level, decreased lymphocyte count, increased blood creatinine level and rashess (including maculopapular rash). The most common serious AE have been multiple-organ-dysfunction syndrome, septic shock, acute kidney injury, hypotension, respiratory failure or ARDS and cardiopulmonary failure, essentially in patients with invasive ventilation. The length of RDV treatment seems not to influence the incidence of AE, although a slight variation was found between 5-day and 10-day treatment with RDV concerning laboratory abnormalities, with marked decreased creatinine clearance being more frequently observed in the 10-day treatment group than in the 5-day treatment group.

According to the marketing authorisation holder, renal function should be monitored in patients before and during RDV treatment. Furthermore, RDV is not recommended for patients with an estimated GFR <30 ml/min. The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA considers that, so far, there is no evidence that kidney problems are associated with RDV, but will continue to monitor it carefully.

Elevation of liver transaminases has also been reported and can be considered a serious AE depending on the magnitude of the increase. These increases have been associated with RDV in either healthy volunteers or COVID-19 patients, partially excluding the hypothesis that they directly affect the infection. RDV may need to be discontinued if ALT levels increase to >10 times the upper limit of normal and should be discontinued if an increase in ALT level and signs or symptoms of liver inflammation are observed. The hepatic AE of RDV in COVID-19 patients were further characterised in a pharmacovigilance analysis from VigiBase—the WHO’s individual case safety reports database. Until 15 June 2020, there were 387 reports with RDV in COVID-19 patients (1–11 days of treatment), of which 34% presented hepatic AE. Reports originated from the USA and Europe involved mostly men (81.62%), with a mean age of 54.9 years. Most cases were serious (94.72%), resulting in hospitalisation or a prolonged hospital stay, and occurred within a mean of 5.4 days after starting RDV. Hepatotoxicity is mainly reflected as an increase in hepatic enzymes (AST, ALT and bilirubin). RDV was associated with a more increased risk of reporting hepatic AE than HCQ/CQ, lopinavir/ritonavir or TCB. This study reports real-world data, which overcomes the barrier of small and selected samples from clinical trials and gives stronger support to the need for further pharmacoepidemiological studies to support clinical decisions. However, despite the hepatic AE described for RDV in COVID-19 patients, it is still unclear whether these laboratory changes are due to the drug itself or the virus because a third of critically COVID-19 patients also presents liver dysfunction. Still, regarding interactions, CQ or HCQ may decrease the antiviral activity of RDV, so the coadministration of these drugs is not recommended.

Data on the safety of RDV during pregnancy are scarce. In a study among pregnant and postpartum women hospitalised with severe COVID-19 who received RDV, the therapy was well tolerated, with a low rate of serious AE and no new safety issues. A case report of a woman by the third trimester of pregnancy treated for severe COVID-19 showed no adverse outcomes apart from transiently elevated transaminases, which could also be ascribed to the
viral infection.\textsuperscript{117} A clinical trial is currently evaluating the pharmacokinetics of RDV in children (<18 years old).\textsuperscript{118}

Several clinical trials that are evaluating RDV for the treatment of COVID-19 are currently underway or in development.\textsuperscript{119} Since it is an authorised drug on the market for COVID-19, further post-authorisation studies should be initiated to generate real-world evidence.

As a conclusion, the evidence shows that the odds of having severe AE are less among the RDV group than the placebo group though the odds for the development of overall AE among two groups are not statistically significant.\textsuperscript{120}

3.2 | Immunomodulating therapeutics

3.2.1 | Corticosteroids

Patients with severe COVID-19 can develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction. CS are a class of drugs with potent anti-inflammatory activity (e.g., DM, prednisone, methylprednisolone and hydrocortisone), which have been claimed to reduce the harmful inflammatory damage COVID-19 patients. However, a recent meta-analysis concluded that there were no survival benefits with the use of CS along with delayed recovery and longer hospital stay, and the mortality risk increases with the use of CS.\textsuperscript{121}

Given the number of ongoing or completed clinical trials in COVID-19, it is already possible to analyse some consistent data on AE associated with CS.\textsuperscript{122–124} Registered clinical trials found that include at least one CS are DEXA-COVID-19, COVID-19 Dexamethasone (CODEX), Community-Acquired Pneumonia: Evaluation of Corticosteroids (CAPE_COD), COVID STEROID, a Randomised, Embedded, Multi-factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and Steroids-SARI. Some of the AE reported in COVID-19 patients under CS have been hyperglycaemia,\textsuperscript{125,126} secondary infections/superinfections\textsuperscript{125,126} (namely bacteraemia\textsuperscript{126} and fungemia\textsuperscript{127}), barotrauma,\textsuperscript{125} neuropathy\textsuperscript{127} and COVID-19-associated pulmonary aspergillosis.\textsuperscript{128} A case series has also reported avascular necrosis,\textsuperscript{129} although already with evidence prior to this infection.\textsuperscript{130} Although overall AE varied across clinical trials, there was no suggestion that the risk of serious AE was higher in patients assigned to CS than usual care or placebo.

The CAPE_COD trial\textsuperscript{131} identified three serious AE: cerebral vasculitis, cardiac arrest and intra-abdominal haemorrhage. However, these events are possibly related to SARS-CoV-2 infection, pulmonary embolism and anticoagulant therapy for pulmonary embolism respectively. Also, in the REMAP-CAP trial,\textsuperscript{127} AE unrelated to the treatment were identified: pneumonia, pulmonary embolism, elevated serum troponin, postoperative haemorrhage, intracranial haemorrhage, thrombocytopenia, ventricular tachycardia and hypoglycaemia.

Well-known side effects of CS such as hyperglycaemia and superimposed infections have been previously reported in other coronavirus diseases.\textsuperscript{17,132} Furthermore, prolonged use of systemic CS may also increase the risk of reactivation of latent infections (e.g., hepatitis B virus, strongyloidiasis and tuberculosis).\textsuperscript{133,134} This is also critical in COVID-19 patients who had previously had other infections, given the compromised functional status. Over the years, the medical literature has reported some neuropsychiatric effects in patients undergoing CS treatment, so the appearance of these clinical profiles in COVID-19 patients can be predicted.\textsuperscript{135–137}

In postmortem studies of COVID-19 patients, diffuse alveolar disruption with large vessel thrombi and microthrombi were seen.\textsuperscript{138,139} DM (6 mg per day, as recommended) tends to increase clotting factor and fibrinogen concentration. Thus, it is plausible for exogenous glucocorticoids to favour clinical thrombosis.\textsuperscript{140} Moreover, previous studies in non-COVID-19 patients reported AE in long-term treatment with CS, such as myopathy, neuromuscular weakness and psychiatric symptoms. Although the current guidelines for COVID-19 recommend short treatments (about 10 days), these AE should be considered.\textsuperscript{135,141}

DM is one of the drugs approved for the treatment of COVID-19. DM is a potent CS with predominantly glucocorticoid effects and low mineralocorticoid action. This drug is a moderate cytochrome P450 (CYP) 3A4 inducer, so it may interfere with the concentration and potential efficacy of concomitant drugs that are CYP3A4 substrates (e.g., RDV also used in association with DM).\textsuperscript{142}

Further pharmacoepidemiologic studies are necessary to ascertain short, medium and long-term AE of CS in COVID-19 patients. The relationship between the different variables should be privileged through multivariate analysis and the study of population subgroups.

3.2.2 | Interferons

Interferon (IFN)-α and IFN-β are endogenous signalling proteins produced by virus-infected cells and released in response to infection or inflammation.\textsuperscript{143} There are currently insufficient data to recommend for or against either of them for the treatment of COVID-19.\textsuperscript{30}

This class of drugs is closely related to significant AE, even when used as a short-term therapy. Although data on COVID-19 patients are still limited, a recent RCT\textsuperscript{144}
on the use of IFN-β1a on severe COVID-19 patients reported hypersensitivity reactions, IFN-related infection reactions (namely fever, chills, myalgia and headache), neuropsychiatric problems and indirect hyperbilirubinemia. The most common gastrointestinal AE were nausea, vomiting and abdominal pain. Another phase 2 clinical trial identified headache as slightly more frequent AE in the arm that received IFN than the placebo arm (15% and 10% respectively). Another clinical trial reported reactions at the administration site and flu-like syndrome, again being as frequent in the group that received IFN as in the control group.145 Injection site reactions at the administration site and flu-like arm (15% and 10% respectively). Another clinical trial identified headache as slightly more frequent AE in the arm that received IFN than the placebo arm (15% and 10% respectively). Another clinical trial identified headache as slightly more frequent AE in the arm that received IFN than the placebo arm (15% and 10% respectively).

Previous safety data reported injection site reactions, flu-like symptoms (fever, myalgias, and headaches), nausea, weight loss, haematological toxicities, elevated transaminases, regulation of autoimmunity and decreased blood counts (associated with a decrease in all three haematopoietic lineages).148–150 Neuropsychiatric problems have also been reported, such as fatigue, irritability, agitation and sleep disturbances (‘neurovegetative symptoms’) and significant symptoms comprising depression and cognitive impairment.151 Cases of pulmonary arterial hypertension using IFN (α and β) are also described in the literature.152–154 However, and although there are slight variations in AE that can be seen with IFN-α or IFN-β, it seems that IFN-β is better tolerated than IFN-α.155,156 Retrospective data suggest no increase in the risk of spontaneous abortion or congenital anomalies in women exposed to IFN-β during pregnancy,157 just as it did not influence the birthweight, height or head circumference of the newborn.158

It has been one of the classes of drugs that have been studied to include the therapeutic arsenal, although a well-characterised set of AE has been reported in the literature and the safety databases.

3.2.3 | Interleukins

*Interleukin-1 Inhibitors*

Anakinra is an antagonist of the human recombinant interleukin-1 (IL-1) and is approved by the FDA to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes.159 On 17 December 2021, the EMA authorised an extension of indication for the treatment of COVID-19.160

Recently, several studies on the use of anakinra in COVID-19 have been published, giving strength to the decision of its approval by the EMA.161–166 According to Huet et al. (2020), a case–control study with 52 patients observed an increase in ALT levels and thromboembolic events, but the frequency was similar to that in the control group and was not related to anakinra, as was found for bacterial infections. Also, in a singlecentre, retrospective cohort study with 29 patients, Cavalli et al. (2020) reported that a high dose of anakinra was well-tolerated, although it was discontinued in 7 (24%) patients due to bacteremia by Staphylococcus epidermidis (14%) and increases in serum liver enzymes (10%). However, these findings were also found in the control group.164 The SAVE-MORE trial found a smaller proportion of patients in the anakinra arm experienced secondary infections, including ventilator-associated pneumonias, than in the placebo arm (8.4% vs. 15.9%; p = .01).162 The CORIMUNO-ANA-1 trial found that serious AE occurred in 46% of patients in the anakinra arm compared to 38% in the usual care arm; 11 of 59 patients (18.6%) in the anakinra arm experienced bacterial or fungal infections compared to 4 of 55 patients (7.3%) who received usual care.161 Finally, a case series with nine patients described a mild transient increase of transaminase and triglyceride levels; however, this type of study does not formally test a hypothesis and does not have a control group, so causal relationships should be made cautiously. Once approved, real-life data are expected for more realistic analyses of effectiveness and safety in clinical practice.

*Interleukin-6 Inhibitors*

IL-6 is a proinflammatory cytokine involved in several physiological processes, such as activation of T lymphocytes, induction of immunoglobulins and acute-phase proteins, and stimulation of haemopoiesis. It has been implicated in the pathogenesis of inflammatory diseases, like the SARS-CoV infection, which triggers the production of IL-6 from bronchial epithelial cells, but that then, unusually, compromises the immune response and perpetuates the damage.167

TCB has been the IL-6 inhibitor for which more data have been reported. The AE reported in COVID-19 patients taking TCB included bacteremia and fungal infections; gastrointestinal complaints, often associated with gastrointestinal perforation; hypersensitivity/allergic reactions, like cutaneous rash, kidney function deterioration; and drug-induced liver injury, with an increase in liver enzymes (ALT, AST,
A multicentre, randomised, double-blind trial compared oral baricitinib 4 mg daily with placebo, both given in combination with RDV IV, to COVID-19 patients. This study identified 25 grade 3 or 4 AE in 207 patients (40.7%) in the combination group and 238 (46.8%) in the control group. The most common serious AE (observed in at least 5% of all patients) were hyperglycaemia, anaemia, decreased lymphocyte count and acute kidney injury.

RX has also been the drug of interest among the community of clinical experts. A small, single-blind, randomised, controlled phase 2 trial was performed in patients with COVID-19 to compare RX with placebo. The total number of AE of any grade in haematological, nonhaematological toxicities and chemical laboratory abnormalities was similar between groups (16 patients [80%] in the RX group; and 15 patients [71.4%] in the control group), with anaemia being the most prevalent event, followed by the ALT increase. One patient in the RX group developed grade 3 lymphocytopenia.

### 3.3 | Others

#### 3.3.1 | Antithrombotic/anticoagulant therapy

The treatment of patients with antithrombotic agents varies a lot according to the clinical context, being quite frequent in patients requiring invasive procedures. In COVID-19, several studies have reported different incidences of venous thromboembolism, so prophylaxis with antithrombotic agents can be considered in patients who have an incident thromboembolic event or are highly likely to trigger an event as patients requiring extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters. However, COVID-19 has also been associated with inflammation and a prothrombotic
TABLE 1  Summary of evidence found in the literature about AE in COVID-19 patients. Only AE with a suggestive relationship with the drug reported by the authors were described in the table and grouped by System Organ Class (SOC), the highest level of the MedDRA medical terminology.

| Drug                     | Main AE grouped by SOC                                                                 | Research context                                                                 | References |
|--------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------|
| Chloroquine and hydroxychloroquine | Cardiac disorders: ▪ Prolonged QT and/or ventricular tachycardia, including Torsade-des-Points, atrioventricular and bundle-branch blocks, and heart failure ▪ Increased cardiotoxicity with azithromycin combination | 4 Observational studies 1 Case series 1 Systematic Review and Meta-analysis | 33, 37-40, 43 |
|                          | Eye disorders: ▪ Blurred vision ▪ Increased cardiotoxicity with azithromycin combination | 1 Observational study 1 Randomised Clinical Trial                                  | 46, 47    |
|                          | Gastrointestinal disorders: ▪ Upset stomach or nausea ▪ Abdominal pain ▪ Loose stools ▪ Diarrhoea ▪ Vomiting | 4 Randomised Clinical Trial 1 Observational study                                  | 45-48, 178 |
|                          | Investigations: ▪ Increased serum transaminase levels                                   | 1 Case report                                                                      | 49        |
|                          | Nervous system disorders: ▪ Headache ▪ Dizziness ▪ Tremor                              | 2 Randomised Clinical Trial 2 Observation studies                                  | 46-48     |
|                          | Skin and subcutaneous tissue disorders: ▪ Rash                                       | 1 Randomised Clinical Trial                                                       | 48        |
| Ivermectin               | Eye disorders: ▪ Blurred vision                                                        | 2 Randomised Clinical Trial                                                       | 56, 57    |
|                          | Gastrointestinal disorders: ▪ Diarrhoea ▪ Nausea ▪ Abdominal pain ▪ Vomiting           | 1 Randomised Clinical Trial                                                       | 57        |
|                          | General disorders and administration site conditions: ▪ Swelling                      | 1 Randomised Clinical Trial                                                       | 57        |
|                          | Nervous system disorders: ▪ Dizziness ▪ Headache ▪ Tremor                             | 2 Randomised Clinical Trial                                                       | 56, 57    |
|                          | Skin and subcutaneous tissue disorders: ▪ Skin rash ▪ Skin discoloration               | 1 Randomised Clinical Trial                                                       | 57        |
| Lopinavir-Ritonavir      | Cardiac disorders: ▪ Cardiotoxicity, especially in those with congenital QTc prolongation ▪ Cardiomyopathy | 2 Observational study 1 Summary of product characteristics                        | 74, 79, 179 |
|                          | Gastrointestinal disorders: ▪ Nausea ▪ Vomiting ▪ Diarrhoea                             | 2 Randomised Clinical Trial 1 Case series 1 Health Authority (NIH guidelines)     | 28, 68, 70-72, 180 |
|                          | Hepatobiliary disorders:                                                               | 1 Expert opinion/commentary 2 Observational studies                               | 29, 76, 181 |
| Drug          | Main AE grouped by SOC                                                                 | Research context                              | References       |
|--------------|----------------------------------------------------------------------------------------|-----------------------------------------------|------------------|
|              | Investigations:                                                                        |                                               |                  |
|              | ▪ Abnormal liver function                                                              |                                               |                  |
|              | ▪ Elevated lipase levels                                                               |                                               |                  |
|              | ▪ Possibly increased transaminases (ALT and AST)                                       |                                               |                  |
|              | Metabolism and nutrition disorders:                                                    |                                               |                  |
|              | ▪ Hypokalaemia                                                                         |                                               |                  |
|              | ▪ Loss of appetite                                                                     |                                               |                  |
|              | ▪ Hypertriglyceridemia                                                                  |                                               |                  |
|              | ▪ Hypercholesterolemia                                                                  |                                               |                  |
| Remdesivir   | Blood and lymphatic system disorders:                                                  |                                               |                  |
|              | ▪ Anaemia                                                                              |                                               |                  |
|              | ▪ Thrombocytopenia                                                                     |                                               |                  |
|              | Gastrointestinal disorders:                                                            |                                               |                  |
|              | ▪ Nausea                                                                               |                                               |                  |
|              | ▪ Vomiting                                                                             |                                               |                  |
|              | ▪ Gastroparesis                                                                        |                                               |                  |
|              | ▪ Rectal bleeding                                                                       |                                               |                  |
|              | ▪ Constipation                                                                         |                                               |                  |
|              | General disorders and administration site conditions:                                  |                                               |                  |
|              | ▪ Pyrexia                                                                              |                                               |                  |
|              | ▪ Multiple-organ-dysfunction syndrome                                                   |                                               |                  |
|              | Hepatobiliary disorders:                                                                |                                               |                  |
|              | ▪ Hypalbuminaemia                                                                       |                                               |                  |
|              | Infections and infestations:                                                           |                                               |                  |
|              | ▪ Septic shock                                                                          |                                               |                  |
|              | Investigations:                                                                        |                                               |                  |
|              | ▪ Elevated levels of aminotransferase (ALT and AST)                                     |                                               |                  |
|              | ▪ Increased blood glucose                                                              |                                               |                  |
|              | ▪ Increased total bilirubin                                                             |                                               |                  |
|              | ▪ Decreased Glomerular Filtration Rate                                                 |                                               |                  |
|              | ▪ Decreased haemoglobin level                                                           |                                               |                  |
|              | ▪ Decreased lymphocyte count                                                           |                                               |                  |
|              | ▪ Increased blood creatinine level/ Decreased creatinine clearance                      |                                               |                  |
|              | Metabolism and nutrition disorders:                                                    |                                               |                  |
|              | ▪ Hypokalaemia                                                                          |                                               |                  |
|              | Renal and urinary disorders:                                                           |                                               |                  |
|              | ▪ Acute kidney injury                                                                   |                                               |                  |
|              | Respiratory, thoracic and mediastinal disorders:                                       |                                               |                  |
|              | ▪ (Acute) respiratory failure                                                           |                                               |                  |
|              | ▪ Acute respiratory distress syndrome                                                  |                                               |                  |
|              | ▪ Cardiopulmonary failure                                                               |                                               |                  |
|              | Skin and subcutaneous tissue disorders:                                                |                                               |                  |
|              | ▪ Skin rash, including maculopapular rash                                               |                                               |                  |
|              | Vascular disorders:                                                                    |                                               |                  |
|              | ▪ Hypotension                                                                          |                                               |                  |

TABLE 1 (Continued)
| Drug                      | Main AE grouped by SOC                                                                 | Research context                  | References       |
|--------------------------|----------------------------------------------------------------------------------------|-----------------------------------|------------------|
| Corticosteroids          | Infections and infestations:                                                           | 3 Randomised Clinical Trials      | 109-112          |
|                          | • Secondary infections/superinfections, namely bacteraemia and fungaemia               | 1 Case series                     |                  |
|                          | • COVID-19-associated pulmonary aspergillosis                                          |                                   |                  |
|                          | Injury, poisoning and procedural complications:                                         | 1 Randomised Clinical Trial       | 109              |
|                          | • Barotrauma                                                                            |                                   |                  |
| Metabolism and nutrition disorders: |                                               | 2 Randomised Clinical Trials      | 109, 110         |
|                          | • Hyperglycaemia                                                                       |                                   |                  |
| Musculoskeletal and connective tissue disorders: |                                              | 1 Case report                    | 113              |
|                          | • Avascular necrosis                                                                   |                                   |                  |
| Nervous system disorders: |                                               | 1 Randomised Clinical Trial       | 111              |
|                          | • Neuropathy                                                                           |                                   |                  |
| Respiratory, thoracic and mediastinal disorders: |                                              | 2 Case reports                   | 122, 123         |
|                          | • Diffuse alveolar disruption                                                          |                                   |                  |

| Interferons              | Gastrointestinal disorders:                                                             | 3 Randomised Clinical Trials      | 128, 131         |
|                          | • Nausea                                                                               | 1 Observational study            |                  |
|                          | • Vomiting                                                                             |                                   |                  |
|                          | • Abdominal pain                                                                       |                                   |                  |
|                          | • Diarrhoea                                                                            |                                   |                  |
|                          | • Oral pain                                                                            |                                   |                  |
| General disorders and administration site conditions: |                                              | 2 Randomised Clinical Trials      | 128-130          |
|                          | • Pyrexia                                                                              | 1 Observational study            |                  |
|                          | • Chills                                                                               |                                   |                  |
|                          | • Flu-like symptoms                                                                    |                                   |                  |
|                          | • Injection site reactions                                                             |                                   |                  |
| Hepatobiliary disorders: |                                               | 1 Randomised Clinical Trial       | 128              |
|                          | • Indirect hyperbilirubinemia                                                          |                                   |                  |
| Immune system disorders: |                                               | 1 Randomised Clinical Trial       | 128              |
|                          | • Hypersensitivity reactions                                                           |                                   |                  |
| Investigations:          |                                               | 1 Observational study            | 131              |
|                          | • Decreased oxygen saturation                                                          |                                   |                  |
| Musculoskeletal and connective tissue disorders: |                                              | 1 Randomised Clinical Trial       | 128              |
|                          | • Myalgia                                                                              |                                   |                  |
| Nervous system disorders: |                                               | 1 Randomised Clinical Trial       | 128, 131         |
|                          | • Headache                                                                             | 1 Observational study            |                  |
|                          | • Tremor                                                                               |                                   |                  |
|                          | • Cognitive impairment                                                                 |                                   |                  |
| Psychiatric disorders:   |                                               | 1 Randomised Clinical Trial       | 128              |
|                          | • Depression                                                                           |                                   |                  |
| Respiratory, thoracic and mediastinal disorders: |                                              | 1 Observational study            | 131              |
|                          | • Dry throat                                                                           |                                   |                  |
| Skin and subcutaneous tissue disorders: |                                              | 131                              |
|                          | • Night sweats                                                                         |                                   |                  |
| Drug                                      | Main AE grouped by SOC                                                                 | Research context                      | References |
|------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------|------------|
| **Interleukin-1 Inhibitors** *(Anakinra)* | Infections and infestations:                                                            |                                       |            |
|                                          | - Bacteraemia                                                                           | 1 Observational study                 | 145        |
|                                          | Investigations:                                                                        |                                       |            |
|                                          | - Elevated ALT levels/serum liver enzymes                                             | 2 Observational study                 | 144-146    |
|                                          | - Elevated triglyceride levels                                                        | 1 Case series                         |            |
|                                          | Vascular disorders:                                                                   | 1 Observational study                 | 144        |
|                                          | - Thromboembolic events                                                               |                                       |            |
| **Interleukin-6 Inhibitors**             | Blood and lymphatic system disorders:                                                 | 1 Observational study                 | 155        |
|                                          | - Anaemia *(in association with ribavirin)*                                           |                                       |            |
|                                          | Cardiac disorders:                                                                    | 1 Observational study                 | 155        |
|                                          | - QTc prolongation *(in association with HCQ)*                                         |                                       |            |
|                                          | Gastrointestinal disorders:                                                            | 1 Observational study                 | 150        |
|                                          | - Gastrointestinal complaints                                                          |                                       |            |
|                                          | - Gastrointestinal perforation                                                        |                                       |            |
|                                          | General disorders and administration site conditions:                                 | Press release from the promoter of a  | 160        |
|                                          | - Multiple-organ-dysfunction syndrome                                                  | Randomised Clinical Trial             |            |
|                                          | Immune system disorders:                                                              | 1 Observational study                 | 158        |
|                                          | - Cytokine release syndrome                                                            |                                       |            |
|                                          | Infections and infestations:                                                          | 2 Observational studies               | 148, 149   |
|                                          | - Bacteraemia                                                                          |                                       |            |
|                                          | - Fungal infections                                                                   |                                       |            |
|                                          | Investigations:                                                                        |                                       |            |
|                                          | - Increased liver enzymes *(ALT, AST, GGT)*                                           | 5 Observational studies               | 149, 151-157|
|                                          | - Neutropenia                                                                         | 2 Case report                         |            |
|                                          | - Thrombocytopenia                                                                    | 1 Randomised Clinical Trial           |            |
|                                          | Hepatobiliary disorders:                                                              | 1 Observational study                 | 158        |
|                                          | - Hepatic failure                                                                     |                                       |            |
|                                          | Skin and subcutaneous tissue disorders:                                               | 1 Observational study                 | 149, 151   |
|                                          | - Cutaneous rash                                                                      | 1 Randomised Clinical Trial           |            |
|                                          | Renal and urinary disorders:                                                          | 1 Case report                         | 152        |
|                                          | - Kidney function deterioration                                                       |                                       |            |
|                                          | Vascular disorders:                                                                   | Press release from the promoter of a  | 160        |
|                                          | - Hypotension                                                                         | Randomised Clinical Trial             |            |
| **Janus Kinase Inhibitors**              | Blood and lymphatic system disorders:                                                 | 1 Randomised Clinical Trial           | 163        |
|                                          | - Anaemia                                                                             |                                       |            |
|                                          | Investigations:                                                                        |                                       |            |
|                                          | - Lymphocytopenia                                                                     | 2 Randomised Clinical Trial           | 163, 164   |
|                                          | - ALT increase                                                                        |                                       |            |
|                                          | Metabolism and nutrition disorders:                                                   | 1 Randomised Clinical Trial           | 163        |
|                                          | - Hyperglycaemia                                                                      |                                       |            |
|                                          | Renal and urinary disorders:                                                          | 1 Randomised Clinical Trial           | 163        |
|                                          | - Renal kidney injury                                                                  |                                       |            |
| **Bruton’s Tyrosine Kinase Inhibitors**  | No data available in COVID-19 patients                                                 |                                       |            |
| **Antithrombotic/ anticoagulant therapy**| No data available in COVID-19 patients                                                 |                                       |            |
state, with increased fibrin levels, fibrin/fibrinogen degradation products, fibrinogen, D-dimers and lower prothrombin time activity and thrombin time.\(^{192}\)

Most of the studies on the use of antiaggregation/anti-coagulation drugs in COVID-19 patients were performed to study the prophylaxis and/or treatment of thrombotic events and not to evaluate their impact on the management of inflammation and/or viral load.\(^{190,193,194}\) Also, no study reported safety data for these drugs in the prophylaxis of thrombotic events in COVID-19 patients. However, we warn of potential interactions with other concomitant drugs as one of the primary causes of AE with these drugs. In this context, the University of Liverpool developed an open-access online tool with a list of drug interactions (Table 1).\(^{195}\)

4 | WEAKNESSES AND STRENGTHS

Our work constitutes an actual comprehensive review, covering a wide range of drugs and associated AE. Though the standards of systematic reviewing cannot be applied to a work of such breadth, we identify evidence using unbiased methods and describe all relevant evidence we found. The greatest strength of this work is to be considered a true hypothesis generator in daily clinical practice. Thus, all conclusions that readers can draw from the review should be seen in the light of the currently available evidence.

Our work has several strengths concerning AE of drugs used to treat COVID-19 patients. First, we only included clinical studies with COVID-19 patients, gathering the information on AE specifically in those patients and not from other clinical conditions. Also, we performed a comprehensive review, covering most/all drugs that have been used in COVID-19 patients, independently from the fact that they are approved, used off-label or experimentally, thus representing the real-word scenario. As a result, this document might be useful for every clinician in need (or interest) of information concerning the broad spectrum of drugs used in COVID-19 patients, supporting clinical decisions. This is an advantage since it gathers straight information on this field, which is otherwise scattered in the literature and, as so, difficult to find easily in the busy clinical setting.

This review has some limitations. First, due to the number of articles published in the last few months and the pace in which they continue to be published, there may be a divergence between the evidence at the time of the research and that at the time for the reader to contact with the manuscript. Also, and considering the available evidence on AE to some of these drugs, we seek to describe what is already known about the application of these drugs in other clinical contexts. The respective translation to COVID-19 must be done with caution.

5 | CONCLUDING REMARKS

The most frequent SOC among the included drugs are investigations; skin and subcutaneous tissue disorders; and nervous system disorders, infections and infestations, gastrointestinal disorders, hepatobiliary disorders, and metabolism and nutrition disorders. Other SOCs also emerged, such as general disorders and administration site conditions, general disorders and administration site conditions, renal and urinary disorders, vascular disorders and cardiac disorders. Since in the literature reporting AE in COVID-19 patients, there are no data on causality assessment, further experimental studies—RCTs—within robust methodologies are needed to provide new evidence on the causality of AE related to these drugs. Equally important, real-life studies (post-authorisation safety studies) would also be of critical relevance to present evidence outside the context of the RCTs.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

AUTHORS’ CONTRIBUTIONS

RFS participated in the concept and design, drafting and critical review of the manuscript. IRV, MM and JJP participated in the concept and design, critical review and supervision of the manuscript. All authors read and approved the final manuscript.

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