NARRATIVE REVIEW

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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).[1] 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.[2]

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',[3] 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.[4] 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.[5] Recent literature shows that the most commonly reported AE with COVID-19 treatments, in decreasing order of frequency, were QT-prolonged electrocardiogram, diarrhoea, nausea, hepatitis, vomiting and upper abdominal pain.[6] 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.[7] This report describes AE in COVID-19 patients worldwide, with individual analysis for a set of selected drugs. 4739 reports were received from six 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,[8] 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

Key points

- The different drugs used in COVID-19 patients are being extensively studied in clinical trials, producing evidence for safety data in this particular clinical condition.
- Remdesivir and dexamethasone, despite being the first drugs approved by regulatory authorities, have more robust safety data due to their use in the context of clinical practice. Most of the information regarding adverse events of drugs used in COVID-19 patients comes from clinical trials and much less from real-word data.
- Although several adverse events have been described for drugs used in COVID-19 patients, neither study reported data on causality assessment.

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.[9,10] 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).[11–13] 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,[14] 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)[15] and a retrospective

review of critically ill patients with COVID-19[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.[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.[19] Also, the length of hospital stay seems to decrease with RDV (from 15 to 11 days), with no evidence of reducing mortality.[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.[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).[14,21–25] Some of these drugs have also been studied in combination with other drugs, such as HCQ plus azithromycin (AZM).[26] Except for RDV and DM, all of these drugs should be seen in clinical practice as off-label use in COVID-19 patients.[27]

In the therapeutic arsenal for COVID-19 patients, inhaled nitric oxide has been considered in refractory hypoxia cases,[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.[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.[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[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[32] and SARS-CoV-2[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.[34–38] Indeed, the RECOVERY trial was suspended after an interim analysis showing no efficacy (primary outcome being 28-day mortality).[39] Also relevant, HCQ was associated with a higher incidence of AE than the usual care group.[40] An early Cochrane systematic review further strengthened this view.[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[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.[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.[43–47] Two recent retrospective studies highlighted AZM as a factor of increased risk for HCQ-associated cardiotoxicity in patients with rheumatoid arthritis[48] or other clinical condition,[43] which should be considered when translating to the treatment of COVID-19 patients. Indeed, high doses of CQ[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.[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).[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.[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.[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.[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.[54] Mild types of AE were reported in hospitalised COVID-19 patients, such as rash, headache, blurred vision, diarrhoea, nausea, vomiting and rash.[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.[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,[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.[37]

3.1.2 | Ivermectin

IVM is an FDA-approved antiparasitic drug used to treat several neglected tropical diseases, including onchocerciasis, helminthiases and scabies.[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.[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[62]. In vitro assays showed antiviral efficacy against SARS-CoV-2[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.[64,65] Although IVM has shown to be safe in healthy adults at doses up to 120 mg,[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.[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.[69] Another recent double-blind RCT with 400 subjects found a very similar AE pattern between the IVM and the placebo arms.[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, armpits or groin, neurologic AE (seizures, confusion), a sudden drop in blood pressure, liver injury (hepatitis) and fever.[71–78]

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 disorders[83,87] and elevated lipase levels,[87] dyslipidaemias (hypertriglyceridemia and hypercholesterolemia)[87,88] and hypokalemia[84] 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 LVP/r on liver function, information is controversial; early studies suggest that patients treated with LVP/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 LVP/r group and standard care group of COVID-19 patients.[82] Another study showed 18.6% of liver injuries after treatment with LVP/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 hypokalemia[94] 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 LVP/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.[102] 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.[103] RDV was associated with hypotension (during infusion of the loading dose)[104] and neurologic complications (clinical trial, phase I)[105] 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 aminotransferase (1–5 days after initiating RDV).[106] 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.[107] 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 hypoalbuminaemia, 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 rashes (including maculopapular rash).[108–111] 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.[107–110] 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.[110]

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.[112] 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.[113]

Elevation of liver transaminases has also been reported and can be considered a serious AE depending on the magnitude of the increase.[108,109] 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.[110] 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.[112] 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.[114] 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.[115] Still, regarding interactions, CQ or HCQ may decrease the antiviral activity of RDV, so the coadministration of these drugs is not recommended.[112]

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.[116] 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.[117] A clinical trial is currently evaluating the pharmacokinetics of RDV in children (<18 years old).[118]

Several clinical trials that are evaluating RDV for the treatment of COVID-19 are currently underway or in development.[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.[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.[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.[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,[125,126] secondary infections/superinfections[125,126] (namely bacteraemia[126] and fungemia[127]), barotrauma,[125] neuropathy[127] and COVID-19-associated pulmonary aspergillosis.[128] A case series has also reported avascular necrosis,[129] although already with evidence prior to this infection.[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[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,[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.[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).[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.[135–137]

In postmortem studies of COVID-19 patients, diffuse alveolar disruption with large vessel thrombi and microthrombi were seen.[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.[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.[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).[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.[143] There are currently insufficient data to recommend for or against either of them for the treatment of COVID-19.[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[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 have already been described for IFN-β1a.[146] A randomised, double-blind, placebo-controlled, phase 2 pilot trial with an inhaled nebulised formulation of IFN-β1a reported respiratory failure and pneumonia, but unlikely to be attributed to IFN.[147] This study also found cases of headache, decreased oxygen saturation, diarrhoea, dry throat, oral pain, night sweats, and tremor, but very low in frequency among participants in the IFN arm. Cough cases were more frequent in the treatment group.

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 single-centre, 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 bacteraemia 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[165]; 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 bacteraemia and fungal infections[168,169]; gastrointestinal complaints, often associated with gastrointestinal perforation[170]; hypersensitivity/allergic reactions, like cutaneous rash[169,171]; kidney function deterioration[172]; and drug-induced liver injury, with an increase in liver enzymes (ALT, AST,

GGT).[169,171,173–175] A case report was found of a 40-fold increase a day after TCZ administration, normalising in 10 days.[176] There are also reports of neutropenia[174] and thrombocytopenia described in the literature.[169,177] Other AE were also found, but as a possible result of the association of TCB with other drugs: anaemia with ribavirin and QT interval prolongation with HQC.[175] It is important to note that some of these AE have been reported only in the context of TCB's continuous dosing, that is in the treatment of chronic diseases. Despite the moderate evidence of this drug's safety profile in this infection, previous data in non-COVID-19 patients have already identified a pattern of hepatic, pancreatic and pulmonary events associated with prolonged use of TCB. Several cases of TCB-associated hepatic failure and the cytokine release syndrome (a clinical picture similar to the cytokine storm found in severe COVID-19 infection), two serious and unpredictable reactions were found in an observational retrospective analysis.[178]

Preliminary, unpublished data from a RCT failed to demonstrate TCB's efficacy in patients with COVID-19. One of these trials was the CONVACTA—a study to evaluate the safety and efficacy of TCB in patients with severe COVID-19 pneumonia—which did not publish details of the drug's safety. At week four, rates of infections were 38.3% and 40.6% in the intervention and placebo arms, respectively, and the rates of serious infections were 21.0% and 25.9% in the intervention and placebo arms, respectively.[179]

Other IL-6 inhibitors used in the clinical context of COVID-19 are SAR and siltuximab. There are limited, unpublished data describing AE associated with these two drugs in patients with COVID-19. A press release of a phase III clinical trial reported that 80% of patients on SAR had experienced AE as 77% of patients on placebo did. The serious AE that occurred more frequently in patients were multiorgan dysfunction syndrome (6% SAR vs. 5% placebo) and hypotension (4% SAR vs. 3% placebo).[180] We found a preprint clinical cohort study with preliminary data on the use of siltuximab in COVID-19 patients, but no reference was made to the safety profile of the drug.[181]

3.2.4 | Kinase inhibitors

Janus kinase inhibitors
Some Janus Kinase inhibitors are used to treat inflammatory diseases such as rheumatoid arthritis, and their anti-inflammatory effect might be useful to control the cytokine storm in patients with COVID-19. Also, some drugs in this class, for example baricitinib, can show antiviral activity by preventing viral entry and infection of susceptible cells.[182]

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.[183] 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.[183]

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.[184]

Bruton's tyrosine kinase inhibitors
Bruton tyrosine kinase (BTK) is a nonreceptor tyrosine kinase and a member of the Tec family.[185] BTK signalling is involved in innate immune responses and regulates the production of proinflammatory cytokines.[186]

Acalabrutinib and ibrutinib have been considered in clinical studies for the treatment of COVID-19. A retrospective case series of 19 patients with severe COVID-19 did not observe AE associated with the use of acalabrutinib.[187] On the other hand, an uncontrolled case series study with six COVID-19 patients receiving the ibrutinib for a condition other than COVID-19 suggests that the drug may protect against lung injury and even improve pulmonary function in hypoxic patients with COVID-19. Safety data were not considered in the analysis.[188]

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.[189] In COVID-19, several studies have reported different incidences of venous thromboembolism,[190] 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.[191] 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	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	2 Randomised Clinical Trial 1 Observational study	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 discolouration	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 2 Observational study 1 Case series Health Authority (NIH guidelines)	28, 68, 70-72, 180
	Hepatobiliary disorders:	1 Expert opinion/commentary 2 Observational studies	29, 76, 181

TABLE 1 (Continued)

Drug	Main AE grouped by SOC	Research context	References
	Investigations: ■ Abnormal liver function ■ Elevated lipase levels ■ Possibly increased transaminases (ALT and AST)	1 Randomised Clinical Trial Health Authority (NIH guidelines)	28, 71
	Metabolism and nutrition disorders: ■ Hypokalaemia ■ Loss of appetite ■ Hypertriglyceridemia ■ Hypercholesterolemia	2 Observational studies 1 Randomised Clinical Trial 1 Summary of product characteristics	70, 71, 74, 181
Remdesivir	Blood and lymphatic system disorders: ■ Anaemia ■ Thrombocytopenia	1 Randomised Clinical Trial	93
	Gastrointestinal disorders: ■ Nausea ■ Vomiting ■ Gastroparesis ■ Rectal bleeding ■ Constipation	3 Randomised Clinical Trials 2 Observational studies 1 Expert opinion/commentary	92-97
	General disorders and administration site conditions: ■ Pyrexia ■ Multiple-organ-dysfunction syndrome	3 Randomised Clinical Trials 2 Observational studies	93-97
	Hepatobiliary disorders: ■ Hypalbuminaemia	1 Randomised Clinical Trial	93
	Infections and infestations: ■ Septic shock	1 Observational study 1 Randomised Clinical Trial	93, 94
	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	3 Randomised Clinical Trials 2 Observational studies 1 Expert opinion/commentary	92-97
	Metabolism and nutrition disorders: ■ Hypokalaemia	1 Randomised Clinical Trial	93
	Renal and urinary disorders: ■ Acute kidney injury	1 Randomised Clinical Trial	93
	Respiratory, thoracic and mediastinal disorders: ■ (Acute) respiratory failure ■ Acute respiratory distress syndrome ■ Cardiopulmonary failure	3 Randomised Clinical Trials 2 Observational studies	93-97
	Skin and subcutaneous tissue disorders: ■ Skin rash, including maculopapular rash	3 Randomised Clinical Trials 2 Observational studies	93-97
	Vascular disorders: • Hypotension	2 Observational studies 2 Randomised Clinical Trials	93-96

(Continues)

TABLE 1 (Continued)

Drug	Main AE grouped by SOC	Research context	References
Corticosteroids	Infections and infestations: • Secondary infections/superinfections, namely bacteraemia and fungaemia • COVID-19-associated pulmonary aspergillosis	3 Randomised Clinical Trials 1 Case series	[109-112]
	Injury, poisoning and procedural complications: • Barotrauma	1 Randomised Clinical Trial	[109]
	Metabolism and nutrition disorders: • Hyperglycaemia	2 Randomised Clinical Trials	[109, 110]
	Musculoskeletal and connective tissue disorders: • Avascular necrosis	1 Case report	[113]
	Nervous system disorders: • Neuropathy	1 Randomised Clinical Trial	[111]
	Respiratory, thoracic and mediastinal disorders: • Diffuse alveolar disruption	2 Case reports	[122, 123]
Interferons	Gastrointestinal disorders: ■ Nausea ■ Vomiting ■ Abdominal pain ■ Diarrhoea ■ Oral pain	3 Randomised Clinical Trials 1 Observational study	[128, 131]
	General disorders and administration site conditions: ■ Pyrexia ■ Chills ■ Flu-like symptoms ■ Injection site reactions	2 Randomised Clinical Trials 1 Observational study	[128-130]
	Hepatobiliary disorders: ■ Indirect hyperbilirubinemia	1 Randomised Clinical Trial	[128]
	Immune system disorders: ■ Hypersensitivity reactions	1 Randomised Clinical Trial	[128]
	Investigations: ■ Decreased oxygen saturation	1 Observational study	[131]
	Musculoskeletal and connective tissue disorders: ■ Myalgia	1 Randomised Clinical Trial	[128]
	Nervous system disorders: ■ Headache ■ Tremor ■ Cognitive impairment	1 Randomised Clinical Trial 1 Observational study	[128, 131]
	Psychiatric disorders: ■ Depression	1 Randomised Clinical Trial	[128]
	Respiratory, thoracic and mediastinal disorders: ■ Dry throat	1 Observational study	[131]
	Skin and subcutaneous tissue disorders: ■ Night sweats		[131]

TABLE 1 (Continued)

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 ■ Elevated triglyceride levels	2 Observational study 1 Case series	144-146
	Vascular disorders: ■ Thromboembolic events	1 Observational study	144
Interleukin-6 Inhibitors	Blood and lymphatic system disorders: ■ Anaemia (in association with ribavirin)	1 Observational study	155
	Cardiac disorders: ■ QTc prolongation (in association with HCQ)	1 Observational study	155
	Gastrointestinal disorders: ■ Gastrointestinal complaints ■ Gastrointestinal perforation	1 Observational study	150
	General disorders and administration site conditions: ■ Multiple-organ-dysfunction syndrome	Press release from the promoter of a Randomised Clinical Trial	160
	Immune system disorders: ■ Cytokine release syndrome	1 Observational study	158
	Infections and infestations: ■ Bacteraemia ■ Fungal infections	2 Observational studies	148, 149
	Investigations: ■ Increased liver enzymes (ALT, AST, GGT) ■ Neutropenia ■ Thrombocytopenia	5 Observational studies 2 Case report 1 Randomised Clinical Trial	149, 151-157
	Hepatobiliary disorders: ■ Hepatic failure	1 Observational study	158
	Skin and subcutaneous tissue disorders: ■ Cutaneous rash	1 Observational study 1 Randomised Clinical Trial	149, 151
	Renal and urinary disorders: ■ Kidney function deterioration	1 Case report	152
	Vascular disorders: ■ Hypotension	Press release from the promoter of a Randomised Clinical Trial	160
Janus Kinase Inhibitors	Blood and lymphatic system disorders: ■ Anaemia	1 Randomised Clinical Trial	163
	Investigations: ■ Lymphocytopenia ■ ALT increase	2 Randomised Clinical Trial	163, 164
	Metabolism and nutrition disorders: ■ Hyperglycaemia	1 Randomised Clinical Trial	163
	Renal and urinary disorders: ■ Renal kidney injury	1 Randomised Clinical Trial	163
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/anticoagulation 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 the drugs in this disease, 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—with 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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REFERENCES
1. Zhu NA, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727–733. doi:10.1056/NEJMoa2001017
2. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. Accessed November 16, 2021. https://covid19.who.int/?gclid=CjwKCAiA8Jf-BRB-EiwAWDtEGrzwwPU_OzZBe01nimHAyQk_JkPo65wlzBS27YLZRzzNZECD5CbzBBoCZM0QAvD_BwE

3. Senanayake SL. Drug repurposing strategies for COVID-19. *Future Drug Discov*. 2020;2(2):fdd-2020-0010. doi:10.4155/fdd-2020-0010

4. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;323(18):1824–1836. doi:10.1001/jama.2020.6019

5. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934–943. doi:10.1001/jamainternmed.2020.0994

6. Zekarias A, Watson S, Vidlin SH, Grundmark B. Sex differences in reported adverse drug reactions to COVID-19 drugs in a global database of individual case safety reports. *Drug Saf*. 2020;43(12):1309–1314. doi:10.1007/s40264-020-01000-8

7. World Health Organization. Descriptive analysis of COVID-19-related spontaneous reports from VigiBase: interim results. 2020.

8. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. *Drug Saf*. 2006;29(5):385–396. doi:10.2165/00002018-200629050-00003

9. Sheikhpour M. The current recommended drugs and strategies for the treatment of coronavirus disease (COVID-19). *Ther Clin Risk Manag*. 2020;16:933–946. doi:10.2147/tcrm.S262936

10. Asili P, Mirahmad M, Tabatabaei-Malazy O, et al. Characteristics of published/registered clinical trials on COVID-19 treatment: a systematic review. *Daru*. 2021;29(2):449–467. doi:10.1007/s40199-021-00422-8

11. European Medicine Agency. Treatments and vaccines for COVID-19 Share Table of contents: authorised medicines. Accessed June 12, 2021. https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19

12. Administration USFaD. FDA Approves First Treatment for COVID-19. Accessed June 12, 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-covid-19

13. European Medicine Agency. First COVID-19 treatment recommended for EU authorisation. Accessed June 12, 2021. https://www.ema.europa.eu/en/news/first-covid-19-treatment-recommended-eu-authorisation

14. Siemieniuk RAC, Bartoszko JJ, Ge L, et al. Drug treatments for covid-19: living systematic review and network meta-analysis. *Article. BMJ. Jul 30*. 2020;370:m2980. doi:10.1136/bmj.m2980

15. Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect*. 2020;81(1):e13–e20. doi:10.1016/j.jinf.2020.03.062

16. Lu X, Chen T, Wang Y, Wang J, Yan F. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. *Crit Care*. 2020;24(1):241. doi:10.1186/s13054-020-02964-w

17. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Medicine*. 2006;3(9):e343. doi:10.1371/journal.pmed.0030343

18. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically Ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197(6):757–767. doi:10.1164/rccm.201706-1172OC

19. Group RC, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384(8):693–704. doi:10.1056/NEJMoa2021436

20. Health NIo. NIH Clinical Trial Shows Remdesivir Accelerates Recovery from Advanced COVID-19. Accessed June 12, 2021. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

21. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): a review. *JAMA*. 2020;324(8):782–793. doi:10.1001/jama.2020.12839

22. Rochwerg B, Agarwal A, Siemieniuk RA, et al. A living WHO guideline on drugs for covid-19. *BMJ*. 2020;370:m3379. doi:10.1136/bmj.m3379

23. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? *Ecancermedicalscience*. 2020;14:1023. doi:10.3332/ecancer.2020.1023

24. Nasonov E, Samsonov M. The role of Interleukin 6 inhibitors in therapy of severe COVID-19. *Biomed Pharmacother*. 2020;131:110698. doi:10.1016/j.biopha.2020.110698

25. Barlow A, Landolf KM, Barlow B, et al. Review of emerging pharmacotherapy for the treatment of coronavirus disease 2019. *Review. Pharmacotherapy*. 2020;40(5):416–437. doi:10.1002/phar.2398

26. Fiolet T, Guihur A, Rebeaud ME, Mulot M, Peiffer-Smadja N, Mahamat-Saleh Y. Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021;27(1):19–27. doi:10.1016/j.cmi.2020.08.022

27. World Health Organization. Off-label use of medicines for COVID-19. Accessed November 12, 2020. https://www.who.int/news-room/commentaries/detail/off-label-use-of-medicines-for-covid-19

28. Tavazzi G, Pozzi M, Mongodi S, Dammassa V, Romito G, Mojoli F. Inhaled nitric oxide in patients admitted to intensive care unit with COVID-19 pneumonia. *Crit Care*. 2020;24(1):508. doi:10.1186/s13054-020-03222-9

29. Longobardo A, Montanari C, Shulman R, Benhalim S, Singer M, Arulkumaran N. Inhaled nitric oxide minimally improves oxygenation in COVID-19 related acute respiratory distress syndrome. *Br J Anaesth*. 2021;126(1):e44–e46. doi:10.1016/j.bja.2020.10.011

30. Health NIo. Coronavirus Disease 2019 (COVID-19): Treatment Guidelines. Accessed November 17, 2020. https://www.covid19treatmentguidelines.nih.gov/whats-new/

31. Baethge C, Goldbeck-Wood S, Mertens S. SANRA—a scale for the quality assessment of narrative review articles. *Res Integrity Peer Rev*. 2019;4(1):5. doi:10.1186/s41073-019-0064-8.

32. Savarino A, Di Trani L, Donatelli I, Cauda R, Cassone A. New insights into the antiviral effects of chloroquine. *Lancet Infect Dis*. 2006;6(2):67–69. doi:10.1016/S1473-3099(06)70361-9

33. Al-Kofahi M, Jacobson P, Boulware DR, et al. Finding the dose for hydroxychloroquine prophylaxis for COVID-19: the desperate search for effectiveness. *Clin Pharmacol Ther*. 2020;108(4):766–769. doi:10.1002/cpt.1874

34. Arabi YM, Gordon AC, Derde LPG, et al. Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial.

Intensive Care Med. 2021;47(8):867–886. doi:10.1007/s00134-021-06448-5

35. Axfors C, Schmitt AM, Janiaud P, et al. Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials. *Nat Commun.* 2021;12(1):2349. doi:10.1038/s41467-021-22446-z

36. Consortium WHOST, Pan H, Peto R, et al. Repurposed antiviral drugs for Covid-19 - interim WHO solidarity trial results. *N Engl J Med.* 2021;384(6):497–511. doi:10.1056/NEJMoa2023184

37. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database Syst Rev.* 2021;2(2):CD013587. doi:10.1002/14651858.CD013587.pub2

38. Kamstrup P, Sivapalan P, Eklöf J, et al. Hydroxychloroquine as a primary prophylactic agent against SARS-CoV-2 infection: a cohort study. *Int J Infect Dis.* 2021;108:370–376. doi:10.1016/j.ijid.2021.05.076

39. Group RC, Horby P, Mafham M, et al. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020;383(21):2030–2040. doi:10.1056/NEJMoa2022926

40. Group RC, Horby P, Mafham M. et al. Effect of Hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med.* 2020;383(21):2030–2040. doi:10.1056/NEJMoa2022926

41. Elavarasi A, Prasad M, Seth T, et al. Chloroquine and hydroxychloroquine for the treatment of COVID-19: a systematic review and meta-analysis. *J Gen Intern Med.* 2020;35(11):3308–3314. doi:10.1007/s11606-020-06146-w

42. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *JAMA Network Open.* 2020;3(4):e208857. doi:10.1001/jamanetworkopen.2020.8857

43. Nguyen LS, Dolladille C, Drici M-D, et al. cardiovascular toxicities associated with hydroxychloroquine and azithromycin: an analysis of the World Health Organization pharmacovigilance database. *Circulation.* 2020;142(3):303–305. doi:10.1161/CIRCULATIONAHA.120.048238

44. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York State. *JAMA.* 2020;323(24):2493–2502. doi:10.1001/jama.2020.8630

45. Mahévas M, Tran VT, Roumier M, et al. Clinical efficacy of hydroxychloroquine in patients with covid-19 pneumonia who require oxygen: observational comparative study using routine care data. *BMJ.* 2020;369:m1844. doi:10.1136/bmj.m1844

46. Mercuro NJ, Yen CF, Shim DJ, et al. Risk of QT interval prolongation associated with use of hydroxychloroquine with or without concomitant azithromycin among hospitalized patients testing positive for coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020;5(9):1036–1041. doi:10.1001/jamacardio.2020.1834

47. Ramireddy A, Chugh H, Reinier K, et al. Experience with hydroxychloroquine and azithromycin in the coronavirus disease 2019 pandemic: implications for QT interval monitoring. *J Am Heart Assoc.* 2020;9(12):e017144. doi:10.1161/jaha.120.017144

48. Lane JCE, Weaver J, Kostka K, et al. Safety of hydroxychloroquine, alone and in combination with azithromycin, in light of rapid widespread use for COVID-19: a multinational, network cohort and self controlled case series study. 2020;doi:10.1101/2020.04.08.20054551

49. Bessière F, Roccia H, Delinière A, et al. Assessment of QT intervals in a case series of patients with coronavirus disease 2019 (COVID-19) infection treated with hydroxychloroquine alone or in combination with azithromycin in an intensive care unit. *JAMA Cardiol.* 2020;5(9):1067–1069. doi:10.1001/jamacardio.2020.1787

50. Lakkireddy DR, Chung MK, Gopinathannair R, et al. Guidance for cardiac electrophysiology during the COVID-19 pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association. *Circulation.* 2020;141(21):e823–e831. doi:10.1161/CIRCULATIONAHA.120.047063

51. Ko B, Garcia S, Mithani S, Tholakanahalli V, Adabag S. Risk of acute kidney injury in patients who undergo coronary angiography and cardiac surgery in close succession. *Eur Heart J.* 2012;33(16):2065–2070. doi:10.1093/eurheartj/ehr493

52. Cardiology ACo. Ventricular Arrhythmia Risk Due to Hydroxychloroquine-Azithromycin Treatment For COVID-19. Accessed February 23, 2021. https://www.acc.org/latest-in-cardiology/articles/2020/03/27/14/00/ventricular-arrhythmia-risk-due-to-hydroxychloroquine-azithromycin-treatment-for-covid-19

53. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ.* 2020;369:m1849. doi:10.1136/bmj.m1849

54. Skipper CP, Pastick KA, Engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19: a randomized trial. *Ann Intern Med.* 2020;173(8):623–631. doi:10.7326/M20-4207

55. Gautret P, Lagier J-C, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: a pilot observational study. *Travel Med Infect Dis.* 2020;34:101663. doi:10.1016/j.tmaid.2020.101663

56. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *medRxiv.* 2020:2020.03.22.20040758. doi:10.1101/2020.03.22.20040758

57. Falcao MB, de Goes Pamplona, Cavalcanti L, Filgueiras Filho NM, Antunes de Brito CA. Case report: hepatotoxicity associated with the use of hydroxychloroquine in a patient with COVID-19. *Am J Trop Med Hyg.* 2020;102(6):1214-1216. doi:10.4269/ajtmh.20-0276

58. Boulware DR, Pullen MF, Bangdiwala AS, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med.* 2020;383(6):517–525. doi:10.1056/NEJMoa2016638

59. Omura S, Crump A. Ivermectin: panacea for resource-poor communities? *Trends Parasitol.* 2014;30(9):445–455. doi:10.1016/j.pt.2014.07.005

60. Yang SNY, Atkinson SC, Wang C, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Res.* 2020;177:104760. doi:10.1016/j.antiviral.2020.104760

61. Arévalo A, Pagotto R, Pórfido J, et al. Ivermectin reduces coronavirus infection in vivo: a mouse experimental

model. *bioRxiv*. (2020). doi:10.1101/2020.11.02.363242doi:10.1101/2020.11.02.363242

62. Rajter JC, Sherman MS, Fatteh N, Vogel F, Sacks J, Rajter JJ. Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ivermectin in COVID nineteen study. *Chest*. 2021;159(1):85–92. doi:10.1016/j.chest.2020.10.009

63. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res*. 2020;178:104787. doi:10.1016/j.antiviral.2020.104787

64. Guzzo CA, Furtek CI, Porras AG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. *J Clin Pharmacol*. 2002;42(10):1122–1133. doi:10.1177/009127002401382731

65. Chaccour C, Hammann F, Ramon-Garcia S, Rabinovich NR. Ivermectin and COVID-19: keeping rigor in times of urgency. *Am J Trop Med Hyg*. 2020;102(6):1156–1157. doi:10.4269/ajtmh.20-0271

66. Popp M, Stegemann M, Metzendorf M-I, et al. Ivermectin for preventing and treating COVID-19. *Cochrane Database Syst Rev*. 2021;2021(7). doi:10.1002/14651858.CD015017.pub2

67. Vallejos J, Zoni R, Bangher M, et al. Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial. *BMC Infect Dis*. 2021;21(1):635. doi:10.1186/s12879-021-06348-5

68. Roman YM, Burela PA, Pasupuleti V, Piscoya A, Vidal JE, Hernandez AV. Ivermectin for the treatment of coronavirus disease 2019: a systematic review and meta-analysis of randomized controlled trials. *Clin Infect Dis*. 2021:ciab591. doi:10.1093/cid/ciab591

69. Chaccour C, Casellas A, Blanco-Di Matteo A, et al. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial. *EClinicalMedicine*. 2021;32:100720. doi:10.1016/j.eclinm.2020.100720

70. López-Medina E, López P, Hurtado IC, et al. Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial. *JAMA*. 2021;325(14):1426–1435. doi:10.1001/jama.2021.3071

71. Muñoz J, Ballester MR, Antonijoan RM, et al. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. *PLoS Negl Trop Dis*. 2018;12(1):e0006020. doi:10.1371/journal.pntd.0006020

72. Rothova A, van der Lelij A, Stilma JS, Wilson WR, Barbe RF. Side-effects of ivermectin in treatment of onchocerciasis. *Lancet*. 1989;1(8652):1439–1441. doi:10.1016/s0140-6736(89)90136-0

73. Hall AH, Spoerke DG, Bronstein AC, Kulig KW, Rumack BH. Human ivermectin exposure. *J Emerg Med*. 1985;3(3):217–219. doi:10.1016/0736-4679(85)90075-7

74. Campbell WC. Ivermectin as an antiparasitic agent for use in humans. *Annu Rev Microbiol*. 1991;45:445–474. doi:10.1146/annurev.mi.45.100191.002305

75. Chijioke CP, Okonkwo PO. Adverse events following mass ivermectin therapy for onchocerciasis. *Trans R Soc Trop Med Hyg*. 1992;86(3):284–286. doi:10.1016/0035-9203(92)90310-9

76. Food and Drug Administration US. FAQ: COVID-19 and Ivermectin Intended for Animals. Accessed November 29, 2020. https://www.fda.gov/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals

77. Chandler RE. Serious neurological adverse events after ivermectin-do they occur beyond the indication of onchocerciasis? *Am J Trop Med Hyg*. 2018;98(2):382–388. doi:10.4269/ajtmh.17-0042

78. Food and Drug Administration US. Ivermectin (STROMECTOL) [package insert]. Accessed November 28, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s026lbl.pdf

79. Agency EM. EMA advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials. Accessed January 13, 2022. https://www.ema.europa.eu/en/news/ema-advises-against-use-ivermectin-prevention-treatment-covid-19-outside-randomised-clinical-trials

80. Cvetkovic RS, Goa KL. Lopinavir/ritonavir: a review of its use in the management of HIV infection. *Drugs*. 2003;63(8):769–802. doi:10.2165/00003495-200363080-00004

81. Yeh RF, Gaver VE, Patterson KB, et al. Lopinavir/ritonavir induces the hepatic activity of cytochrome P450 enzymes CYP2C9, CYP2C19, and CYP1A2 but inhibits the hepatic and intestinal activity of CYP3A as measured by a phenotyping drug cocktail in healthy volunteers. *J Acquir Immune Defic Syndr*. 2006;42(1):52–60. doi:10.1097/01.qai.0000219774.20174.64

82. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382(19):1787–1799. doi:10.1056/NEJMoa2001282

83. Vecchio G, Zapico V, Catanzariti A, Carboni Bisso I, Las HM. Adverse effects of lopinavir/ritonavir in critically ill patients with COVID-19. *Medicina (B Aires)*. 2020;80(5):439-441. Efectos adversos de lopinavir/ritonavir en enfermedad grave por coronavirus (COVID-19).

84. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. *Int J Infect Dis*. 2020;95:183–191. doi:10.1016/j.ijid.2020.03.013

85. Li Y, Xie Z, Lin W, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. *Med (N Y)*. 2020;1(1):105–113 e4. doi:10.1016/j.medj.2020.04.001

86. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic features and clinical course of patients infected with SARS-CoV-2 in Singapore. *JAMA*. 2020;323(15):1488–1494. doi:10.1001/jama.2020.3204

87. Batteux B, Bodeau S, Gras-Champel V, et al. Abnormal laboratory findings and plasma concentration monitoring of lopinavir and ritonavir in COVID-19. *Br J Clin Pharmacol*. 2021;87(3):1547–1553. doi:10.1111/bcp.14489

88. Food and Drug Administration US. Lopinavir/Ritonavir [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021251s046_021906s039lbl.pdf

89. Mirjalili M, Shafiekhani M, Vazin A. Coronavirus disease 2019 (COVID-19) and transplantation: pharmacotherapeutic management of immunosuppression regimen. *Ther Clin Risk Manag*. 2020;16:617–629. doi:10.2147/TCRM.S256246

90. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province. *China. Allergy*. 2020;75(7):1742–1752. doi:10.1111/all.14309

91. Grayson ML, Cosgrove SE, Crowe S, et al. *Kucers' The Use of Antibiotics: A Clinical Review of Antibacterial, Antifungal,*

Antiparasitic, and Antiviral Drugs, Seventh Edition - Three Volume Set. CRC Press. 2017.

92. Fresse A, Viard D, Romani S, et al. Spontaneous reported cardiotoxicity induced by lopinavir/ritonavir in COVID-19. An alleged past-resolved problem. *Int J Cardiol*. 2021;324:255–260. doi:10.1016/j.ijcard.2020.10.028

93. Gerard A, Romani S, Fresse A, et al. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: a survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. *Therapie*. 2020;75(4):371-379. doi:10.1016/j.therap.2020.05.002

94. Chen D, Li X, Song Q, et al. Hypokalemia and Clinical Implications in Patients with Coronavirus Disease 2019 (COVID-19). *medRxiv*. 2020. doi:10.1101/2020.02.27.20028530

95. Guzik TJ, Mohiddin SA, Dimarco A, et al. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res*. 2020;116(10):1666–1687. doi:10.1093/cvr/cvaa106

96. Lopez Aspiroz E, Cabrera Figueroa SE, Iglesias Gomez A, Valverde Merino MP, Dominguez-Gil HA. CYP3A4 polymorphism and lopinavir toxicity in an HIV-infected pregnant woman. *Clin Drug Investig*. 2015;35(1):61–66. doi:10.1007/s40261-014-0245-7

97. Aspiroz EL, Cabrera Figueroa SE, Cruz R, et al. Toxicogenetics of lopinavir/ritonavir in HIV-infected European patients. *Per Med*. 2014;11(3):263–272. doi:10.2217/pme.14.7

98. Bishara D, Kalafatis C, Taylor D. Emerging and experimental treatments for COVID-19 and drug interactions with psychotropic agents. *Ther Adv Psychopharmacol*. 2020;10:2045125320935306. doi:10.1177/2045125320935306

99. Chary MA, Barbuto AF, Izadmehr S, Hayes BD, Burns MM. COVID-19: therapeutics and their toxicities. *J Med Toxicol*. 2020;16(3):284-294. doi:10.1007/s13181-020-00777-5

100. Bertoli F, Veritti D, Danese C, et al. Ocular findings in COVID-19 patients: a review of direct manifestations and indirect effects on the eye. *J Ophthalmol*. 2020;2020:1–9. doi:10.1155/2020/4827304

101. Agarwal S, Agarwal SK. Lopinavir-ritonavir in SARS-CoV-2 infection and drug-drug interactions with cardioactive medications. *Cardiovasc Drugs Ther*. 2021;35(3):427–440. doi:10.1007/s10557-020-07070-1

102. Liu W, Zhou P, Chen K, et al. Efficacy and safety of antiviral treatment for COVID-19 from evidence in studies of SARS-CoV-2 and other acute viral infections: a systematic review and meta-analysis. *CMAJ*. 2020;192(27):E734–E744. doi:10.1503/cmaj.200647

103. Hoenen T, Groseth A, Feldmann H. Therapeutic strategies to target the Ebola virus life cycle. *Nat Rev Microbiol*. 2019;17(10):593–606. doi:10.1038/s41579-019-0233-2.

104. Mulangu S, Dodd LE, Davey RT, et al. A randomized, controlled trial of ebola virus disease therapeutics. *N Engl J Med*. 2019;381(24):2293–2303. doi:10.1056/NEJMoa1910993

105. European Medicines Agency. Committee for Medicinal Products for Human Use. Medicinal products under development for the treatment of Ebola. 2016. https://www.ema.europa.eu/en/documents/referral/assessment-report-article-53-procedure-medicinal-products-under-development-treatment-ebola_en.pdf

106. Team C-I. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nat Med*. 2020;26(6):861–868. doi:10.1038/s41591-020-0877-5.

107. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395(10236):1569–1578. doi:10.1016/S0140-6736(20)31022-9

108. Antinori S, Cossu MV, Ridolfo AL, et al. Compassionate remdesivir treatment of severe Covid-19 pneumonia in intensive care unit (ICU) and Non-ICU patients: clinical outcome and differences in post-treatment hospitalisation status. *Pharmacol Res*. 2020;158:104899. doi:10.1016/j.phrs.2020.104899

109. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med*. 2020;382(24):2327–2336. doi:10.1056/NEJMoa2007016

110. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med*. 2020;383(19):1827–1837. doi:10.1056/NEJMoa2015301

111. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med*. 2020;383(19):1813–1826. doi:10.1056/NEJMoa2007764

112. Food and Drug Administration US. Remdesivir (VEKLURY) [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf

113. Agency EM. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC): PRAC reviews a signal with Veklury. Accessed July 12, 2021. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-february-2021

114. Montastruc F, Thuriot S, Durrieu G. Hepatic disorders with the use of remdesivir for coronavirus 2019. *Clin Gastroenterol Hepatol*. 2020;18(12):2835-2836. doi:10.1016/j.cgh.2020.07.050

115. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481. doi:10.1016/S2213-2600(20)30079-5

116. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe Covid-19. *Clin Infect Dis*. 2020;73:e3996–e4004. doi:10.1093/cid/ciaa1466

117. Maldarelli GA, Savage M, Mazur S, Oxford-Horrey C, Salvatore M, Remdesivir Marks KM. Treatment for severe COVID-19 in third-trimester pregnancy: case report and management discussion. *Open Forum Infect Dis*. 2020;7(9):ofaa345. doi:10.1093/ofid/ofaa345

118. ClinicalTrials.gov. Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN). Accessed November 17, 2020. https://www.ClinicalTrials.gov.ct2/show/NCT04431453

119. ClinicalTrials.gov. Remdesivir and COVID-19. Accessed November 17, 2020. https://clinicaltrials.gov/ct2/results?cond=&term=remdesivir+and+covid-19

120. Shrestha DB, Budhathoki P, Syed NI, Rawal E, Raut S, Remdesivir Khadka S. A potential game-changer or just a myth? A systematic review and meta-analysis. *Life Sci*. 2021;264:118663. doi:10.1016/j.lfs.2020.118663

121. Budhathoki P, Shrestha DB, Rawal E, Khadka S. Corticosteroids in COVID-19: is it rational? A systematic review and meta-analysis. *SN Compr Clin Med*. 2020;2(12):2600–2620. doi:10.1007/s42399-020-00515-6

122. Cano EJ, Fonseca Fuentes X, Corsini Campioli C, et al. Impact of corticosteroids in coronavirus disease 2019 outcomes: SYSTEMATIC review and meta-analysis. *Chest*. 2021;159(3):1019–1040. doi:10.1016/j.chest.2020.10.054

123. Group WHOREAfC-TW, Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. 2020;324(13):1330–1341. doi:10.1001/jama.2020.17023

124. Organization WH, Corticosteroids for COVID-19. 2020.

125. Villar J, Ferrando C, Martínez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8(3):267–276. doi:10.1016/S2213-2600(19)30417-5

126. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. 2020;324(13):1307–1316. doi:10.1001/jama.2020.17021

127. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324(13):1317–1329. doi:10.1001/jama.2020.17022

128. Wang J, Yang Q, Zhang P, Sheng J, Zhou J, Qu T. Clinical characteristics of invasive pulmonary aspergillosis in patients with COVID-19 in Zhejiang, China: a retrospective case series. *Crit Care*. 2020;24(1):299. doi:10.1186/s13054-020-03046-7

129. Agarwala SR, Vijayvargiya M, Pandey P. Avascular necrosis as a part of 'long COVID-19'. *BMJ Case Rep*. 2021;14(7):e242101. doi:10.1136/bcr-2021-242101

130. Chan KL, Mok CC. Glucocorticoid-induced avascular bone necrosis: diagnosis and management. *Open Orthop J*. 2012;6:449–457. doi:10.2174/1874325001206010449

131. Dequin P-F, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically Ill patients with COVID-19: a randomized clinical trial. *JAMA*. 2020;324(13):1298–1306. doi:10.1001/jama.2020.16761

132. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet*. 2020;395(10223):473–475. doi:10.1016/s0140-6736(20)30317-2

133. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: a potential strategy to avoid steroid-related strongyloides hyperinfection. *JAMA*. 2020;324(7):623–624. doi:10.1001/jama.2020.13170

134. Martel N, Cotte L, Trabaud M-A, et al. Probable corticosteroid-induced reactivation of latent hepatitis B virus infection in an HIV-positive patient involving immune escape. *J Infect Dis*. 2012;205(11):1757–1761. doi:10.1093/infdis/jis268

135. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc*. 2006;81(10):1361–1367. doi:10.4065/81.10.1361

136. Lewis DA, Smith RE. Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. *J Affect Disord*. 1983;5(4):319-332. doi:10.1016/0165-0327(83)90022-8

137. Silva RG, Tolstunov L. Steroid-induced psychosis: report of case. *J Oral Maxillofac Surg*. 1995;53(2):183–186. doi:10.1016/0278-2391(95)90398-4

138. Zhang H, Zhou P, Wei Y, et al. Histopathologic changes and SARS-CoV-2 immunostaining in the lung of a patient with COVID-19. *Ann Intern Med*. 2020;172(9):629–632. doi:10.7326/m20-0533

139. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med*. 2020;8(4):420–422. doi:10.1016/s2213-2600(20)30076-x

140. Brotman DJ, Girod JP, Posch A, et al. Effects of short-term glucocorticoids on hemostatic factors in healthy volunteers. *Thromb Res*. 2006;118(2):247–252. doi:10.1016/j.thromres.2005.06.006

141. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med*. 2006;354(16):1671–1684. doi:10.1056/NEJMoa051693

142. Czock D, Keller F, Rasche FM, Haussler U. Pharmacokinetics and pharmacodynamics of systemically administered glucocorticoids. *Clin Pharmacokinet*. 2005;44(1):61–98. doi:10.2165/00003088-200544010-00003

143. Morris AG. Interferons. *Immunol Suppl*. 1988;1(Suppl 1):43–45.

144. Davoudi-Monfared E, Rahmani H, Khalili H, et al. A randomized clinical trial of the efficacy and safety of interferon beta-1a in treatment of severe COVID-19. *Antimicrob Agents Chemother*. 2020;64(9):e01061-20. doi:10.1128/AAC.01061-20

145. Rahmani H, Davoudi-Monfared E, Nourian A, et al. Interferon beta-1b in treatment of severe COVID-19: a randomized clinical trial. *Int Immunopharmacol*. 2020;88:106903. doi:10.1016/j.intimp.2020.106903

146. Gaines AR, Varricchio F. Interferon beta-1b injection site reactions and necroses. *Mult Scler*. 1998;4(2):70–73. doi:10.1177/135245859800400205

147. Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir Med*. 2021;9(2):196–206. doi:10.1016/S2213-2600(20)30511-7

148. Sleijfer S, Bannink M, Van Gool AR, Kruit WH, Stoter G. Side effects of interferon-alpha therapy. *Pharm World Sci*. 2005;27(6):423–431. doi:10.1007/s11096-005-1319-7

149. Di Domizio J, Cao W. Fueling autoimmunity: type I interferon in autoimmune diseases. *Expert Rev Clin Immunol*. 2013;9(3):201–210. doi:10.1586/eci.12.106

150. Choubey D, Moudgil KD. Interferons in autoimmune and inflammatory diseases: regulation and roles. *J Interferon Cytokine Res*. 2011;31(12):857–865. doi:10.1089/jir.2011.0101

151. Raison CL, Demetrashvili M, Capuron L, Miller AH. Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs*. 2005;19(2):105–123. doi:10.2165/00023210-200519020-00002

152. Savale L, Sattler C, Günther S, et al. Pulmonary arterial hypertension in patients treated with interferon. *Eur Respir J*. 2014;44(6):1627–1634. doi:10.1183/09031936.00057914

153. Papani R, Duarte AG, Lin YL, Kuo YF, Sharma G. Pulmonary arterial hypertension associated with interferon therapy: a population-based study. *Multidiscip Respir Med*. 2017;12:1. doi:10.1186/s40248-016-0082-z

154. Dhillon S, Kaker A, Dosanjh A, Japra D, Vanthiel DH. Irreversible pulmonary hypertension associated with the use of interferon alpha for chronic hepatitis C. *Dig Dis Sci*. 2010;55(6):1785–1790. doi:10.1007/s10620-010-1220-7

155. Food and Drug Administration US. Interferon beta-1a (Rebif) [package insert]. Accessed December 2, 2020. https://www.

accessdata.fda.gov/drugsatfda_docs/label/2019/103780s5204lbl.pdf

156. Food and Drug Administration US. Interferon alpha-2b (Intron A) [package insert]. Accessed December 2, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103132Orig1s5199lbl.pdf

157. Hellwig K, Duarte Caron F, Wicklein EM, Bhatti A, Adamo A. Pregnancy outcomes from the global pharmacovigilance database on interferon beta-1b exposure. *Ther Adv Neurol Disord*. 2020;13:1756286420910310. doi:10.1177/1756286420910310

158. Burkill S, Vattulainen P, Geissbuehler Y, et al. The association between exposure to interferon-beta during pregnancy and birth measurements in offspring of women with multiple sclerosis. *PLoS One*. 2019;14(12):e0227120. doi:10.1371/journal.pone.0227120

159. Food and Drug Administration US. Anakinra (Kineret) Prescribing Information. Accessed March 2, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103950s5136lbl.pdf

160. Agency EM. EMA recommends approval for use of Kineret in adults with COVID-19. Accessed January 13, 2022. https://www.ema.europa.eu/en/news/ema-recommends-approval-use-kineret-adults-covid-19

161. Tharaux P-L, Pialoux G, Pavot A, et al. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. *Lancet Respir Med*. 2021;9(3):295–304. doi:10.1016/s2213-2600(20)30556-7

162. Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med*. 2021;27(10):1752–1760. doi:10.1038/s41591-021-01499-z

163. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol*. 2020;2(7):e393–e400. doi:10.1016/S2665-9913(20)30164-8

164. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(6):e325–e331. doi:10.1016/S2665-9913(20)30127-2

165. Aouba A, Baldolli A, Geffray L, et al. Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 pneumonia: case series. *Ann Rheum Dis*. 2020;79(10):1381–1382. doi:10.1136/annrheumdis-2020-217706

166. Kooistra EJ, Waalders NJB, Grondman I, et al. Anakinra treatment in critically ill COVID-19 patients: a prospective cohort study. *Crit Care*. 2020;24(1):688. doi:10.1186/s13054-020-03364-w

167. Yoshikawa T, Hill T, Li K, Peters CJ, Tseng CT. Severe acute respiratory syndrome (SARS) coronavirus-induced lung epithelial cytokines exacerbate SARS pathogenesis by modulating intrinsic functions of monocyte-derived macrophages and dendritic cells. *J Virol*. 2009;83(7):3039–3048. doi:10.1128/JVI.01792-08

168. Moreno-Pérez O, Andres M, Leon-Ramirez J-M, et al. Experience with tocilizumab in severe COVID-19 pneumonia after 80 days of follow-up: a retrospective cohort study. *J Autoimmun*. 2020;114:102523. doi:10.1016/j.jaut.2020.102523

169. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. *Eur J Intern Med*. 2020;76:36–42. doi:10.1016/j.ejim.2020.05.011

170. Toniati P, Piva S, Cattalini M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev*. 2020;19(7):102568. doi:10.1016/j.autrev.2020.102568

171. Perrone F, Piccirillo MC, Ascierto PA, et al. Tocilizumab for patients with COVID-19 pneumonia. The single-arm TOCIVID-19 prospective trial. *J Transl Med*. 2020;18(1):405. doi:10.1186/s12967-020-02573-9

172. Podlasin RB, Kowalska JD, Pihowicz A, et al. How to follow-up a patient who received tocilizumab in severe COVID-19: a case report. *Eur J Med Res*. 2020;25(1):37. doi:10.1186/s40001-020-00438-x

173. Lian N, Xie H, Lin S, Huang J, Zhao J, Lin Q. Umifenovir treatment is not associated with improved outcomes in patients with coronavirus disease 2019: a retrospective study. *Clin Microbiol Infect*. 2020;26(7):917-921. doi:10.1016/j.cmi.2020.04.026

174. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117(20):10970–10975. doi:10.1073/pnas.2005615117

175. Alattar R, Ibrahim TBH, Shaar SH, et al. Tocilizumab for the treatment of severe coronavirus disease 2019. *J Med Virol*. 2020;92(10):2042–2049. doi:10.1002/jmv.25964

176. Muhovic D, Bojovic J, Bulatovic A, et al. First case of drug-induced liver injury associated with the use of tocilizumab in a patient with COVID-19. *Liver Int*. 2020;40(8):1901-1905. doi:10.1111/liv.14516

177. Pettit NN, Nguyen CT, Mutlu GM, et al. Late onset infectious complications and safety of tocilizumab in the management of COVID-19. *J Med Virol*. 2021;93(3):1459–1464. doi:10.1002/jmv.26429

178. Gatti M, Fusaroli M, Caraceni P, Poluzzi E, De Ponti F, Raschi E. Serious adverse events with tocilizumab: pharmacovigilance as an aid to prioritize monitoring in COVID-19. *Br J Clin Pharmacol*. 2021;87(3):1533–1540. doi:10.1111/bcp.14459

179. Roche. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. Accessed December 9, 2020. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm

180. Sanofi and Regeneron Pharmaceuticals I. Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. Accessed March 2, 2021. https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00

181. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. *medRxiv*. 2020. doi:10.1101/2020.04.01.20048561

182. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20(4):400–402. doi:10.1016/S1473-3099(20)30132-8

183. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med*. 2021;384(9):795–807. doi:10.1056/NEJMoa2031994

184. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol*. 2020;146(1):137-146 e3. doi:10.1016/j.jaci.2020.05.019

185. Yang EJ, Yoon JH, Chung KC. Bruton's tyrosine kinase phosphorylates cAMP-responsive element-binding protein at serine

133 during neuronal differentiation in immortalized hippocampal progenitor cells. *J Biol Chem*. 2004;279(3):1827–1837. doi:10.1074/jbc.M308722200

186. Rada M, Qusairy Z, Massip-Salcedo M, Macip S. Relevance of the bruton tyrosine kinase as a target for COVID-19 therapy. *Mol Cancer Res*. 2021;19(4):549–554. doi:10.1158/1541-7786.MCR-20-0814

187. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol*. 2020;5(48):abd0110. doi:10.1126/sciimmunol.abd0110

188. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood*. 2020;135(21):1912–1915. doi:10.1182/blood.2020006288

189. Feinbloom D. Periprocedural management of antithrombotic therapy in hospitalized patients. *J Hosp Med*. 2014;9(5):337–346. doi:10.1002/jhm.2166

190. Nopp S, Moik F, Jilma B, Pabinger I, Ay C. Risk of venous thromboembolism in patients with COVID-19: a systematic review and meta-analysis. *Res Pract Thromb Haemost*. 2020;4(7):1178–1191. doi:10.1002/rth2.12439.

191. Health NIf. COVID-19 Treatment Guidelines: Antithrombotic Therapy. Accessed March 4, 2021. https://www.covid19treatmentguidelines.nih.gov/antithrombotic-therapy/

192. Han H, Yang L, Liu R, et al. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med*. 2020;58(7):1116–1120. doi:10.1515/cclm-2020-0188

193. Roberts LN, Whyte MB, Georgiou L, et al. Postdischarge venous thromboembolism following hospital admission with COVID-19. *Blood*. 2020;136(11):1347–1350. doi:10.1182/blood.2020008086

194. Lemos ACB, do Espirito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: a randomized phase II clinical trial (HESACOVID). *Thromb Res*. 2020;196:359-366. doi:10.1016/j.thromres.2020.09.026

195. Liverpool Uo. COVID-19 Drug interactions - Interaction Checker. Accessed 2021. https://covid19-druginteractions.org/