

Review

SARS-CoV-2 Treatment: Current Therapeutic Options and the Pursuit of Tailored Therapy

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Abstract: One year on from the worldwide outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), medicine has made several steps towards increasing the therapeutic options against its treatment. Despite the lack of specific therapies, international societies have introduced new guidelines and launched several trials to test the efficacy of new protocols and drugs. Drug repurposing has been a fundamental strategy to find quick ways to fight the pathogen, even if it is new compounds that are drawing the attention of the scientific community. Tailored therapy should be considered to be a milestone in treatment in order to increase drug efficacy and to reduce drug toxicity. Therefore, both drug characteristics (i.e., pharmacokinetic, pharmacodynamic and safety) and the patient characteristics (i.e., stage of disease, comorbidity, concomitant treatments and the mutation of single nucleotides) could represent the key to achieving this objective. In the present study we performed a narrative review of the pharmacological treatment used to date in the management of coronavirus disease 2019 (COVID-19).

Keywords: COVID-19; drug treatment; indication; drug metabolism; drug interaction; adverse drug reactions



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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a RNA beta coronavirus, whose main mechanism of viral entry is the interaction between the spike (S) protein and the human angiotensin-converting enzyme 2 (ACE 2) receptor [1].

Coronavirus disease 2019 (COVID-19), which is caused by SARS-CoV-2, is characterized by a wide spectrum of symptom severity, from the absence of clinical manifestations, to mild or severe symptoms (e.g., cough, fever, fatigue, myalgia, dyspnea and ageusia) up to death [2]. Although COVID-19 commonly affects respiratory function, other systems can be affected (i.e., renal, cardiovascular, gastrointestinal, neurologic, ophthalmologic, endocrinologic and dermatologic systems) [3].

According to the illness severity, five categories of patients can be described (Table 1) [4].

The most important concern in COVID-19 management is related to ensuring appropriate treatment according to the stage of infection. In the first phase (lasting approximately a week, often with an asymptomatic patient), SARS-CoV-2 replicates quickly and therefore antivirals must be used to block the viral proliferation. In the following stages, which are characterized by several symptoms (due to the interindividual differences in immune responses), the increase in levels of cytokines can result in a multisystem inflammatory syndrome (MIS); therefore, corticosteroids as well as antimicrobial or monoclonal antibodies can be added to the antiviral drugs to reduce the immune response [5].

Table 1. Category of patients with SARS-CoV-2 infection. NPS: Naso-pharyngeal swab for SARS-CoV-2; SpO₂: oxygen saturation; PaO₂/FiO₂: arterial partial pressure of oxygen/fraction of inspired oxygen.

Category of Illness	Sign and Symptoms	Dyspnea	NPS	Chest Imaging	SpO ₂	PaO ₂ /FiO ₂
asymptomatic	No	No	Negative	Negative	>94%	>300 mmHg
Mild	cough, fever, fatigue, myalgia, and ageusia	No	Positive	Negative	>94%	>300 mmHg
Moderate	cough, fever, fatigue, myalgia, and ageusia	No	Positive	Positive, lung infiltrates <50%	>94%	>300 mmHg
Severe	respiratory rate >30 breaths/min	Yes	Positive	lung infiltrates >50%	<94%	<300 mmHg
Critical	septic shock, respiratory failure	Yes	Positive	lung infiltrates >50%	<94%	<300 mmHg

Historically, drug repurposing, which consists in finding new therapeutic indications for existing drugs, has represented the main instrument for discovering a cure, however science is now trying to develop new compounds that will be added to those which have already demonstrated their efficacy. Therefore, several clinical trials have been launched, and the scientific community is paying strong attention to their results [6].

Even if we are facing the same syndrome, the same virus and its variants, tailored therapies must be considered to be an imperative in modern medicine (especially as tailored therapies take into consideration the gender, comorbidity, polytherapy, genetic characteristics, and clinical presentation of the patient), because they can reduce costs, hospitalizations and can help to pursue patient healing.

The aim of this narrative review is to summarize current COVID-19 treatments, according to the different stages of the disease and focusing on the pharmacological features of these drugs, which can be helpful in clinical management in a tailored-patient approach.

2. Search Strategy

References were identified through a literature search on PubMed, Medscape and Google Scholar and a manual search of the reference lists of identified articles up to April 2021. The searches combined the terms (“COVID 19” OR “SARS-CoV-2” AND “therap *” OR “treatment *”). Only papers in English were assessed. National and international treatment guidelines were also evaluated.

The final reference list included high-quality evidence-based international guidelines and search results were reviewed, assessing novelty, importance and relevance to the scope of this review.

3. Symptomatic Treatment

Symptomatic management and supportive care are recommended in unhospitalized patients [4].

Non-steroidal anti-inflammatory drugs (NSAIDs) are used frequently in clinical practice, but they are associated with serious adverse events (gastrointestinal, nephrotoxicity, cardiovascular and bleedings) [7–9].

Paracetamol should be considered as the first-line antipyretic agent, while ibuprofen was indicated for patients who do not tolerate paracetamol [10,11].

Hospitalized non-pregnant adults with COVID-19 should receive prophylactic dose anticoagulation. Preventive anticoagulants and antiplatelet therapy should not be initiated for unhospitalized patients unless the patient has other indications for the therapy or is participating in a clinical trial. If antithrombotic therapy is prescribed in pregnancy before COVID-19, this therapy should be continued. Pregnant women hospitalized for severe COVID-19 should receive a prophylactic dose of anticoagulation if not contraindicated [4]. This treatment is aimed to reduce the thromboembolic risk associated with COVID-19 [12].

4. Antiviral Therapy

Remdesivir

Remdesivir is an adenosine analogue, a prodrug, that is administered intravenously and binds the RNA dependent-RNA polymerase and blocks the protein activity (Tables 2 and 3) [4,13,14].

Table 2. Rationale, current clinical indications and dosages of COVID-19 drugs.

	Mechanism(s) of Action	Current Clinical Indications	Dosage Suggested	Route of Administration	References
Bamlanivimab/etesevimab	Monoclonal antibodies against different epitopes of the SARS-CoV-2 spike protein	Outpatient with mild to moderate disease and high progression risk	Bamlanivimab 700 mg/ etesevimab 1400 mg	Intravenous	[4,15]
Baricitinib	Inhibition of JAK 1 and JAK 2 activity	Hospitalized patients, in co-administration with remdesivir when CCs cannot be used	4 mg daily up to 14 days	OS	[4,16,17]
Casirivimab/imdevimab	Monoclonal antibodies against different epitopes of the SARS-CoV-2 spike protein	Outpatient with mild to moderate disease and high progression risk	Casirivimab 1200 mg/ imdevimab 1200 mg	Intravenous	[4,18]
Chloroquine or hydroxychloroquine	Inhibition of the fusion mechanism(s) of SARS-CoV-2; immunomodulatory activity	None. In clinical trial only.	Different dosages depending on clinical trial	OS	[4,19,20]
Dexamethasone	Suppression of inflammatory response mainly inhibiting the activation of NF- κ B	Hospitalized patients receiving either IV or oxygen alone	6 mg daily dose up to 10 days	OS or intravenous	[4,21,22]
Favipiravir	RNA polymerase inhibition	None. In clinical trial only	2 doses of 2400 mg to 3000 mg TD followed by 1200 mg to 1800 mg TD	OS or intravenous	[23,24]
Ivermectin	It docks to the SARS-CoV-2 Spike Receptor binding domain	None. In clinical trial only	One 200 μ g/kg dose in addition to usual clinical care; a second dose at day 7 could be administered	OS	[4,25–27]
Lopinavir/ritonavir	HIV type 1 aspartate protease inhibitors	None. In clinical trial only	Lopinavir 400 mg/ ritonavir 100 mg TD up to 14 days	OS	[4,28–31]
Remdesivir	RNA polymerase inhibition	Hospitalized adult and pediatric patients aged \geq 12 years and weighing \geq 40 kg *	Single loading dose of 200 mg followed by 100 mg OD up to 10 days	Intravenous	[4,13,14,32–34]
Tocilizumab	Monoclonal antibody against the IL-6 receptor	In combination with dexamethasone in hospitalized patients with rapid respiratory decompensation	Single dose of 8 mg/kg, up to 800 mg	Intravenous	[4,35–37]

* Emergency Use Authorization for other categories. CCs, corticosteroids; IL, interleukin; IV, invasive mechanical ventilation; JAK, Janus kinases; NF- κ B, nuclear factor κ B; OD, once daily; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TD, twice daily.

Table 3. Pharmacokinetic characteristics of COVID-19 drugs.

	Oral Bioavailability	Time to Peak Concentration	Serum Half-Life (t _{1/2})	Protein Binding	Transporter Proteins	Metabolism	Metabolites
Baricitinib	79%	0.5–3.0 h	12.5–12.9 h	~50%	OAT3, P-gp, BCRP and MATE2-K	<10% through oxidation (CYP3A4)	4 minor oxidative metabolites (3 in urine; 1 in feces)
Chloroquine/hydroxychloroquine	79% (HCQ)	3–4 h (HCQ, OS)	30–50 days	~50%	-	CYP 2D6, 3A4, 3A5 and 2C8	Desethylhydroxychloroquine, desethylchloroquine and bidesethylchloroquine
Dexamethasone	61–86%	3 h (OS) 5 min (IV)	3.5–4.5 h (biological half-life 36–54 h)	77–80%	P-gp	CYP3A4	Hydroxy-6-dexamethasone and dihydro-20-dexamethasone
Favipiravir	97.6%	2 h	2–5.5 h	54%	-	Mainly aldehyde oxidase; partially xanthine oxidase	T-705M1 (urine, inactive) T-705-RTP (activated)
Ivermectin	Moderately well absorbed. Improved absorption with high fat meal.	4.4 h	~18 h	93.2%	P-gp	CYP3A4	3'-O-demethyl ivermectin and 4a-hydroxy ivermectin (main metabolites)
Lopinavir/ritonavir	Not been established	4 h	5–6 h	98–99%	-	Lopinavir: CYP3A4; ritonavir: both CYP3A and CYP2D6	Lopinavir (main metabolites): 4-oxo and 4-hydroxymetabolite epimeric pair
Remdesivir	-	At end of infusion	1 h	88%	OATP1B1 and P-gp	Plasma esterases, CYP2C8, 2D6 and 3A4	GS-443902 (active), GS-704277 and GS-441524
Tocilizumab	-	At end of infusion	151 ± 59 h (6.3 days) §	95%	-	-	None
	Enzymes Inductor/Inhibitor	Elimination	Dose Changes in Hepatic Disease	Dose Changes in Renal Disease	References		
Baricitinib	OCT1 inhibitor (no clinically significant interactions)	75% urine 20% feces	Mild or moderate hepatic impairment: no dose adjustment Severe hepatic impairment: not recommended.	Creatinine clearance 30–60 mL/min: 2 mg OD Creatinine clearance < 30 mL/min: not recommended	[16]		
Chloroquine/hydroxychloroquine	CYP 2D6 and P-gp inhibitor	20–25% urine	Advanced liver disease (CPT C): a loading dose with a reduction of 50% for maintenance dosing and no more than 400 mg per day	AIFA: dosage adjustment is needed FDA: no dosage adjustment	[4,38–41]		
Dexamethasone	CYP3A4 and P-gp moderate inducer	65% urine	Use with caution	Use with caution *	[4,38,39,42]		
Favipiravir	None described, partial data	Urine	Caution needed Dose reduction in CPT C patients	Caution needed Lack of studies in patients with eGFR <30 mL/min	[23,24,43]		
Ivermectin	None described, lack of studies	Mainly in feces (<1% urine)	Caution in severe hepatic disease	No dose adjustment	[4,44–46]		
Lopinavir/ritonavir	CYP2C9 and CYP2C19 inducer ^o CYP3A4 and 2D6, P-gp, BCRP and OATP1B1 inhibition	10.4 ± 2.3% urine 82.6 ± 2.5% feces	Mild to moderate hepatic impairment: no dosage adjustments are needed Severe hepatic impairment: not recommended (no data available)	No dose adjustment	[28,47]		
Remdesivir	CYP3A4 inhibitor. Temporary inhibition of CYP2B6, 2C8, 2C9 and 2D6 in the first day of administration. In vitro, CYP1A2 and CYP3A induction, OATP1B1 and OATP1B3 inhibition	74% urine 18% feces	NIH/FDA: discontinue if ALT levels increase to >10 times or if there is any increase in ALT levels associated with liver symptoms or alteration of biomarkers EMA: discontinue (and not initiate) if ALT is ≥5 times the upper limit of normal levels and there are signs of liver inflammation or other hepatic biomarkers alterations	Not approved in patients with eGFR <30 mL/min **	[4,13,14]		
Tocilizumab	Normalize the IL-6 mediated reduction in the expression CYP1A2, 2C9, 2C19 and 3A4	Mainly urine	Not been studied in patients with hepatic impairment (no dose recommendations can be made)	Mild or moderate renal impairment: no dose adjustment is required Severe renal impairment: monitor closely	[48]		

§ After a 10 mg/kg single dose, up to 16 days at week 12 administering 8–12 mg/kg every 4 weeks. BCRP, breast cancer resistance protein; CYP, cytochromes P450; HCQ, hydroxychloroquine; IV, intravenous; MATE, multidrug and toxic extrusion protein; NA, not available; OS, oral; OAT, organic anion transporters; OATP, organic anion transporting polypeptide; P-gp, p-glycoprotein. * Even if Sanders and colleagues suggested no dose adjustment [23]. ** Even if two studies showed no significant differences in patients with impaired renal function [49,50]. ^o It has also the potential to decrease exposure of drugs metabolized by CYP1A2, CYP2B6 and glucuronidation [51]. AIFA, Agenzia Italiana del Farmaco; ALT, Alanine Aminotransferase; BCRP, breast cancer resistance protein; CPT (Child-Pugh-Turcotte score); CYP, cytochromes P450; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; NIH, National Institutes of Health; NA, not available; OATP, organic anion-transporting polypeptide; OCT, Organic Cation Transporter; OD, once daily P-gp, P-glycoprotein.

According to the National Institutes of Health (NIH) guidelines, remdesivir is the only antiviral drug approved for COVID-19 and it is recommended for patients ≥12 years and weighing ≥40 kg or in Emergency Use Authorization (EUA) for other categories. Early evidences about its use in pregnancy seem to be positive [34].

It can be used: alone (or optionally adding dexamethasone) in hospitalized patients who need supplemental oxygen, without the need of other devices; in exclusive combination with dexamethasone in patients requiring a high flow nasal cannula (HFNC) or non-invasive ventilation (NIV). It is not used in people who need invasive ventilation (IV) or extracorporeal membrane oxygenation (ECMO) [4].

Remdesivir can be also administered with baricitinib in patients who need supplemental oxygen, HFNC or NIV, but not in patients who need IV or ECMO. In unhospitalized

patients with mild to moderate COVID-19, there are insufficient data to recommend these drugs [4].

In a compassionate study of 53 patients hospitalized for severe COVID-19, Grein et al. [32] after an 18-day follow-up, documented that 36 patients (68%) had an improvement in oxygen-support class, including 17 of 30 patients (57%) receiving mechanical ventilation who were extubated. A total of 25 patients (47%) were discharged, and seven patients (13%) died, suggesting that remdesivir could be used in hospitalized patients with severe disease.

In a double-blind, randomized controlled trial Beigel et al. [16] reported a reduced time to recovery in hospitalized COVID-19 patients treated with remdesivir for ten days compared with the placebo (median time to recovery 10 days (95% confidence interval [CI] of 9–11 days) vs. 15 days (95% CI, 13–18 days)). Moreover, in a 14-day follow-up during an interim analysis of patients with severe COVID-19, Olender et al., documented a clinical recovery (based on improvement on a 7-point ordinal scale) in 74.4% of patients enrolled in remdesivir group vs. 59.0% in non-remdesivir group (adjusted odds ratio (OR), 2.03; 95% CI, 1.34–3.08; $p < 0.001$).

However more recently, the same authors [52] performed a final day-28 comparative analysis of the data that were previously analyzed [53], and documented that remdesivir vs. the standard of care improves clinical recovery and lowers mortality from severe COVID-19 (12.0% in remdesivir group vs. 16.2% in non-remdesivir group; OR, 0.67; 95% CI, 0.47–0.95; $p = 0.03$).

Moreover, these data suggest that remdesivir reduces the burden on hospitals during surges in SARS-CoV-2 infections.

Adverse drug reactions (ADRs) include diarrhea or gastrointestinal symptoms, rash, renal impairment, increased hepatic enzymes and hypotension, up to multiple organ-dysfunction syndrome and septic shock. These effects were more common in patients receiving invasive ventilation [32]. Headache, phlebitis, constipation, ecchymosis, nausea, and extremity pain were also observed [14].

In agreement with FDA and NIH guidelines, the compound must be discontinued when alanine transaminase (ALT) levels increases >10 times (with respect to the basal values) or when the increase in ALT levels is associated with liver symptoms or the alteration of biomarkers (e.g., increases of: prothrombin time without international normalized ratio [INR] modifications, conjugated bilirubin, or alkaline phosphatase) [4]. In such cases, the European Medicines Agency (EMA) suggests that remdesivir should be discontinued (and not initiated) if the ALT is ≥ 5 times the upper limit of normal levels and if the patient shows signs of liver inflammation or other hepatic biomarkers alterations [13].

Remdesivir is not approved in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min, even though two studies showed no significant differences in patients with impaired renal function [4,13].

5. Chloroquine and Hydroxychloroquine

Historically an antimalarial drug, chloroquine (CQ) has been used to synthesize hydroxychloroquine (HCQ), which is commonly used in the treatment of rheumatic disease, such as rheumatoid arthritis and lupus [54–56].

The antiviral effects of CQ have been well known since 2003 [55], when its capacity to raise endosomal pH and to contrast viral fusion was described, alongside its immunomodulatory activity (Tables 2 and 3).

Even if this drug is well-tolerated, concomitant use with drugs prolonging QTc (some antidepressants, macrolides, quinolones, antipsychotics), or oral hypoglycemic agents can increase the risk of cardiological symptoms or hypoglycemia. Older adults with COVID-19 may suffer from electrolyte disturbance and dehydration, and these conditions may favor the occurrence of arrhythmias if HCQ is co-administered [57]. Co-administration with azithromycin is not indicated [4]. HCQ can also increase the risk of seizures, reducing the activity of antiepileptic drugs [56].

In vitro studies have demonstrated that CQ is effective against SARS-CoV-2 [58].

Even if a minor number of studies reported a certain efficacy of HCQ [19], there is no indication that it improves clinical symptoms [20].

A recent meta-analysis [59] evaluating Eight RCTs (with 6592 unique participants; mean age = 59.4 years; 42% women) documented that CQ/HCQ did not show any mortality benefit when compared with standard supportive therapy (Pooled Relative Risk [RR] 1.07; 95% CI = 0.97–1.18; I2 statistic = 0.00%). ADRs were significantly higher in patients randomized to CQ/HCQ (RR = 2.51; 95% CI = 1.53–4.12; n = 1818 patients), suggesting that the use of CQ or HCQ does not demonstrate any benefit in the treatment of COVID-19 patients.

6. Lopinavir/Ritonavir

Lopinavir is a human immunodeficiency virus (HIV) type 1 aspartate protease inhibitor (Tables 2 and 3), while ritonavir (a protease inhibitor, also) is administered with lopinavir to increase its plasma half-life through the inhibition of CYP450. Lopinavir showed in vitro activity against SARS-CoV-2 and, in a clinical trial, the administration of lopinavir/ritonavir did not improve clinical symptoms more than the standard of care (SOC) [29].

Both RECOVERY and The Solidarity Trial, confirmed that lopinavir/ritonavir is not useful in hospitalized patients with COVID-19 [30,31].

A previous study performed with eight COVID-19 patients, Schoergenhofer et al. [60] documented that the median LPV steady state plasma concentration (13.6 $\mu\text{g/mL}$) was below the concentration required for SARS-CoV-2 (16.4 $\mu\text{g/mL}$) [61].

Therefore, supposing that the lack of any clinical benefit of LPV/RTV was the low dosage, Karolyi et al. [62], recently randomized 51 COVID-19 patients (30% female; median age of 59 years) to receive a high dosing scheme (LPV/RTV 200/50 mg: four tablets bid as loading dose, then three tablets bid for up to 10 days) or a standard dosing scheme. The authors recorded that the post-loading dose was significantly higher ($p < 0.01$) in patients enrolled in the high dosage scheme (LPV 24.9 $\mu\text{g/mL}$; RTV 1.2 $\mu\text{g/mL}$) vs. those in the standard dosing scheme. In contrast, during the maintenance therapy (after day two), the authors failed to document higher plasma LPV levels in patients enrolled in the high dosing scheme vs. the normal dose scheme (12.9 $\mu\text{g/mL}$ vs. 13.6 $\mu\text{g/mL}$, respectively). Moreover, the authors documented a gender difference in plasma concentration of both LPV and RTV. In particular, they documented a trend towards a higher LPV concentration in females, while RTV plasma levels were significantly higher in females. These differences could be related to body weight, volume of distribution, drug–drug interactions or differences in transporter or enzyme expression. The analysis of the above reported data indicates that it is possible to evaluate that LPV/RTV do not have an antiviral effect in COVID-19 patients at both standard and high dosages. This is particularly important if the patient receives a concomitant treatment with dexamethasone, which is a known CYP3A4 inducer which contributes to the metabolism of LPV (Table 4) [47] and can also increase the ADRs (liver toxicity).

Table 4. COVID-19 drugs as perpetrators of drug–drug interactions.

	Effect of the Combination	Mechanism of Interaction	Selection of Drugs Affected	Clinical Comment
CYP3A4 substrates	Serum level↓by dexamethasone [§] [42] Serum level↑by remdesivir [4,13,14] and lopinavir/ritonavir [28,47] *	CYP3A4 induction CYP3A4 inhibition	Alfuzosin, bisoprolol, some statins *, gliptins, ranolazine, antiarrhythmic drugs (amiodarone, dronedarone), clarithromycin, rivaroxaban, azoles, some antihistamines, some opioids [63] some antipsychotics, antidepressants, carbamazepine, lopinavir/ritonavir, ivermectin, calcineurin inhibitors, mTOR inhibitors	Risk for reduced efficacy Risk for adverse events, potential risk of serotonin syndrome Possible interactions in transplant recipients with COVID-19 [64].

Table 4. Cont.

	Effect of the Combination	Mechanism of Interaction	Selection of Drugs Affected	Clinical Comment
CYP2D6 substrates	Serum level↑by chloroquine and hydroxychloroquine [4,40,57]	CYP2D6 inhibition	Beta-blockers (i.e., metoprolol, bisoprolol, carvedilol), calcium antagonists, antidepressants, antipsychotics, codeine, antiarrhythmic drugs (often class I)	Risk for adverse events, potential risk of serotonin syndrome; co-administered cautiously. The coadministration of protease inhibitors and class IC antiarrhythmics is not recommended, whereas in the other cases caution is needed [12,65]
CYP2C9 and CYP2C19 substrates	Serum level↓by lopinavir/ritonavir [28,47]	CYP2C9 and CYP2C19 induction	Phenytoin, sulphonylureas	Risk for reduced efficacy.
CYP1A2, 2C9, 2C19 and 3A4 substrates	Serum level↓ by tocilizumab [48,66]	Normalization of the IL-6 mediated reduction in the enzymes' expression	methylprednisolone, dexamethasone, (with possible oral glucocorticoid withdrawal syndrome), atorvastatin, calcium channel blockers, theophylline, warfarin, phenprocoumon, phenytoin, ciclosporin, benzodiazepines, some anticancer drug (i.e., vincristine), antipsychotics	Dosage increases may be needed accordingly
P-gp substrates	Serum level↑by chloroquine, hydroxychloroquine [4,39] and lopinavir/ritonavir [28,47]	P-gp inhibition	Protease inhibitors, digoxin, antitumor drugs, calcineurin inhibitors, mTOR inhibitors	Risk for adverse events.
	Serum level↓by dexamethasone [42]	P-gp induction		Risk for reduced efficacy
UGT substrates	Serum level↓by ritonavir	UGT induction [65,67]	Canagliflozin	Risk for reduced efficacy

Data reported can be found in SmPC.; ↑, increased; ↓, decreased. § Interactions with remdesivir seem not to be significant, whereas the combination with lopinavir/ritonavir could be affected by interactions [28,47]. * Among statins, pravastatin has less interactions. Lopinavir can worsen myalgia [65].

However, some phase 3 clinical trials are still ongoing and focusing on use of a combination of these drugs (NCT04403100, NCT04321174).

7. Other Antivirals

Several compounds have been examined and new trials have been launched to improve COVID-19 treatment.

Favipiravir (FPV), the prodrug of a purine nucleotide, inhibits the RNA polymerase (Tables 2 and 3). On April 2020 there was lack of empirical evidence about favipiravir effectiveness against SARS-CoV-2, although it was described as having clinical efficacy for moderate COVID-19, compared with arbidol [23].

A clinical study—albeit one that was not randomized, not double blinded and not placebo controlled—documented that FVP improves chest imaging, inducing a shorter viral clearance time [24].

In a multicenter, randomized controlled study performed in COVID-19 patients randomized into CQ and FPV groups, Dabbous et al. [68] documented a lower duration of hospitalization in FVP-group vs. CQ-group.

In contrast, a recent single center observational study comparing IFN-based therapy (interferon β -1b, ribavirin, and lopinavir/ritonavir) vs. FPV in 222 non-critical hospitalized COVID-19 patients documented that IFN-based therapy was associated with a lower 28-day mortality vs. FPV (6 (9%) vs. 18 (12%)), without a difference in hospitalization duration [69].

Other phase 3 clinical trials, which are ongoing, are evaluating the effect of FVP in COVID-19 (e.g., NCT04336904, NCT04558463, NCT04349241, NCT04600895).

Common ADRs include gastrointestinal symptoms, decrease of neutrophil count, increase of transaminases, psychiatric symptom reactions, increase in blood triglycerides and uric acid elevations.

Umifenovir, ribavirin, oseltamivir, darunavir, camostat mesylate, nitazoxamide are being tested and need further analysis in order to determine their real efficacy [23,70].

8. Immunomodulants

Immunomodulants (i.e., corticosteroids, Janus kinases [JAK] inhibitors and monoclonal antibodies) could mitigate and prevent the dysregulated and excessive immune/inflammatory response to the infection, which has a central role in the later stages of COVID-19 and can lead to multiple organ dysfunction syndrome. Therefore, these treatment options could be of benefit in severe forms of the disease and in critically ill patients.

9. Corticosteroids

Corticosteroids modulate immune responses (both innate and adaptive) through pleiotropic mechanisms [71]. They suppress inflammatory responses mainly by inhibiting the activation of nuclear factor (NF)- κ B, genes, encoding pro-inflammatory cytokines IL-4, IL-10, IL-13, and TGF β (Tables 2 and 3) [21,72,73].

Preliminary data from the RECOVERY trial showed an improved survival in hospitalized COVID-19 patients receiving either invasive mechanical ventilation or oxygen alone and who were treated with dexamethasone (6 mg once daily, administered orally or intravenously) [22]. Compared with usual care or a placebo, 28-day all-cause mortality resulted lower in patients with severe and critical COVID-19 when treated with systemic corticosteroids (i.e., dexamethasone or equivalent doses of other corticosteroids if not available) [74]. However, theoretical concerns that corticosteroids might slow viral clearance have been raised, thus co-administration with remdesivir is recommended.

A phase 4 clinical trial (NCT04663555) is ongoing in order to evaluate the effect of dexamethasone in patients with ARDS and COVID-19 [75].

Pooled data from epidemiological studies showed a low prevalence of asthma and chronic obstructive pulmonary disease (COPD) in hospitalized COVID-19 patients, despite the high burden of these diseases [76]. Therefore, it has been suggested that inhaled corticosteroids (i.e., budesonide) might reduce the infection risk and the development of COVID-19 symptoms, inhibiting coronavirus replication and cytokine production. Indeed, *in vitro* studies showed a reduction of SARS-CoV-2 replication and a downregulated expression of both ACE2 and transmembrane protease serine 2 (TMPRSS2) genes, involved in viral entry into the host cells [77,78].

Recently, an open-label, parallel-group, phase 2, randomized controlled trial compared the early administration of inhaled budesonide (total daily dose 1600 μ g, until symptom resolution) with symptomatic treatment of cough and fever in 146 patients with mild COVID-19, stratified for age, sex, and number of comorbidities. Budesonide induced a 91% decrease of clinical impairment, reducing both the likelihood of requiring urgent care and time to recovery. Therefore, inhaled budesonide seems to be an effective treatment for early COVID-19 infection, likely unaffected by the emergence of new SARS-CoV-2 variants [79].

Nonetheless, the safety and efficacy of corticosteroids for the treatment of COVID-19 warrant more thorough investigations, particularly in patients with diabetes, obesity, hypertension, and cardiovascular disease. Indeed, many side effects related to a supraphysiological exposure to glucocorticoids (i.e., hyperglycemia, hypertension, weight gain and

increased risk of cardiovascular events) are associated with severe outcomes in COVID-19. Bearing in mind that adverse effects related to glucocorticoid administration depend on the dose and duration of therapy, potential risks associated with the relatively short exposure to corticosteroids (~7–10 days) in treating COVID-19 should be further clarified [4,71]. Additionally, as corticosteroids are substrates and moderate CYP3A4 inducers, potential pharmacokinetic interactions (Tables 4 and 5) should be assessed.

Table 5. COVID-19 drugs as victims of drug-drug interactions.

Selection of Drugs	Mechanism of Interaction	Effect of the Combination	Clinical Comment
Analgesics			
Ibuprofen or diclofenac	OAT3 inhibition [16]	↑of baricitinib	No clinically significant
Antibiotics			
Macrolides [80] (e.g., clarithromycin, erythromycin)	CYP3A4 inhibition	Potential ↑of lopinavir/ritonavir [28,47], remdesivir [13,14], hydroxychloroquine [40], ivermectin [46], corticosteroids	Risk for adverse events. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects
Anticancer drugs *			
Crizotinib, lapatinib [65] and others	CYP3A4 inhibition	↑of lopinavir/ritonavir, remdesivir, hydroxychloroquine, ivermectin, corticosteroids	Risk for adverse events Observe the patient In general, remdesivir interactions need further analysis [13]. Cytotoxic therapies should be stopped, even for outpatients, and they are contraindicated for patients in intensive care unit. The combination of the immunosuppression mediated by anticancer and COVID-19 treatment can be also another important issue [4]
Dabrafenib, enzalutamide, vemurafenib [65] and others	CYP3A4 induction	↓ of lopinavir/ritonavir, remdesivir, hydroxychloroquine, ivermectin, corticosteroids	Risk for reduced efficacy Observe the patient
Antidepressants [81,82]			
Fluoxetine, fluvoxamine	CYP3A4 inhibitors	↑of lopinavir/ritonavir, hydroxychloroquine remdesivir, ivermectin, corticosteroids	Risk for adverse events
Fluoxetine, paroxetine, citalopram, escitalopram, fluvoxamine, sertraline, duloxetine, bupropion	CYP2D6 inhibitors	↑ritonavir, hydroxychloroquine [40], remdesivir	Risk for adverse events
Antidiabetics			
Glitazones	CYP3A4 inhibitors	Potential ↑of lopinavir/ritonavir, hydroxychloroquine remdesivir, ivermectin, corticosteroids	Rosiglitazone has a stronger effect than pioglitazone [83]

Table 5. Cont.

Selection of Drugs	Mechanism of Interaction	Effect of the Combination	Clinical Comment
Antifungals (azoles)			
Ketoconazole, itraconazole, fluconazole [83]	CYP3A4 inhibition	Potential ↑ of lopinavir/ritonavir, hydroxychloroquine, remdesivir, ivermectin, corticosteroids	Risk for adverse events
	P-gp Inhibition [84,85]	Potential ↑ of remdesivir, baricitinib	Risk for adverse events
Antipsychotics [81,82]			
Chlorpromazine, thioridazine, perphenazine	CYP2D6 inhibitors	Potential ↑ of ritonavir, hydroxychloroquine, remdesivir	Risk for adverse events
Phenotiazin	P-gp inhibition	Potential ↑ of remdesivir, baricitinib	Risk for adverse events
Anti-seizure medications			
Carbamazepine and phenytoin	CYP3A4 induction	Potential ↓ of lopinavir/ritonavir, ivermectin, hydroxychloroquine, remdesivir, corticosteroids	Risk for reduced efficacy Remdesivir interactions need further analysis
Anti-tuberculosis drugs			
Rifampicin	CYP3A4 induction	Potential ↓ of lopinavir/ritonavir levels, ivermectin levels, hydroxychloroquine, remdesivir, corticosteroids	Risk for reduced efficacy
	P-gp induction	Potential ↓ of remdesivir, baricitinib	Risk for reduced efficacy
Cardiovascular drugs			
Amiodarone, clopidogrel, calcium channel blockers (diltiazem, verapamil), ticlopidine [86]	CYP3A4 inhibition	Potential ↑ of remdesivir, lopinavir/ritonavir, hydroxychloroquine, ivermectin, corticosteroids	Risk for adverse events. Remdesivir interactions need further analysis
Propafenone	CYP2D6 inhibition	Potential ↑ of ritonavir, hydroxychloroquine, remdesivir	Risk for adverse events
HIV protease inhibitors	CYP3A4 inhibition	Potential ↑ of remdesivir, lopinavir/ritonavir, hydroxychloroquine, ivermectin, corticosteroids	Risk for adverse events
Lopinavir/ritonavir	P-gp inhibition	Potential ↑ of remdesivir, baricitinib	Risk for adverse events
Immunosuppressants			
Dexamethasone [42]	CYP3A4 induction	Potential ↓ of remdesivir, lopinavir/ritonavir, hydroxychloroquine, ivermectin	Interaction between remdesivir and dexamethasone seems not clinically relevant [13]
	P-gp induction	Potential ↓ of remdesivir, baricitinib	Risk for reduced efficacy

Table 5. Cont.

Selection of Drugs	Mechanism of Interaction	Effect of the Combination	Clinical Comment
Hydroxychloroquine	CYP2D6 inhibition	Potential ↑ of ritonavir, hydroxychloroquine, remdesivir	Risk for adverse events. CQ and HCQ seem to interfere with remdesivir activity
Tacrolimus, everolimus, ciclosporin, sirolimus [83,87–89]	CYP3A4 inhibition	Potential ↑ of remdesivir, lopinavir/ritonavir, hydroxychloroquine ivermectin, corticosteroids	Risk for adverse events
Ciclosporin [90]	P-gp inhibition	Potential ↑ of remdesivir, baricitinib	Risk for adverse events

If not different specified, data reported can be found in SmPC. * other anticancer drugs inhibit or induce UGTs, or certain drug transporters and could change the pharmacokinetics of favipiravir, lopinavir/ritonavir, hydroxychloroquine, or remdesivir [65]. HCQ, hydroxychloroquine; CQ, chloroquine; CYP, cytochromes P450; OAT, organic anion-transporting polypeptide; P-gp, P-glycoprotein; ↑, increased levels; ↓, decreased levels.

10. Tocilizumab

Tocilizumab is a monoclonal antibody directed against the interleukin (IL)-6 receptor (Table 2), administered intravenously (single dose of 8 mg/kg, up to 800 mg) [91]

Early treatment with tocilizumab has not provided benefits on COVID-19 progression in hospitalized adult patients compared with standard care in a prospective, open-label, randomized clinical trial [92]. Likewise, in the EPACTA study (a randomized, double-blind, placebo-controlled, phase 3 trial), tocilizumab has not improved survival in hospitalized patients who were not receiving mechanical ventilation, although a reduction in the likelihood of COVID-19 progression has been observed [35].

On the other hand, a modest mortality benefit has been reported with the coadministration of tocilizumab and corticosteroids (with or without remdesivir) in severely ill patients [36,37], suggesting that tocilizumab could be used as add-on therapy in hospitalized patients with rapid respiratory decompensation and increased markers of inflammation (CRP \geq 75 mg/L). In order to effectively evaluate the effect of tocilizumab on COVID-19, some phase 3 clinical trials are currently in the recruiting stage (NCT04412772).

Tocilizumab should be avoided in immunosuppressed patients (absolute neutrophil count [ANC] $< 0.5 \times 10^9$ /L) or when there is a platelet count $< 50 \times 10^3$ / μ L or uncontrolled, severe, non-SARS-CoV-2 infections. Furthermore, an increased risk of opportunistic infections or reactivation may be associated with the coadministration of tocilizumab and corticosteroids [93,94].

Since a dose-dependent increase in liver enzyme levels is frequently reported, tocilizumab should be carefully administered in patients with active hepatic disease or hepatic impairment and is contraindicated in patients with an ALT that is five times above the upper limit of normal [95]. Dose adjustments are not required in elderly patients and in patients with mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 mL/min and ≥ 50 mL/min) [95]. In vitro studies showed an IL-6 mediated reduction in the expression of CYP450 enzymes (i.e., CYP1A2, 2C9, 2C19 and 3A4) which can be normalized by tocilizumab [66]. Therefore, a decrease in plasma concentrations of concomitant drugs which are substrates of these isozymes may occur and dosage increases may be needed accordingly, even for several weeks after tocilizumab discontinuation due to its long elimination half-life (up to 16 days) (Tables 3–5).

11. Baricitinib

Baricitinib modulates cytokine signaling through a selective and reversible inhibition of JAK1 and JAK2 enzymatic activity (Table 2), resulting in reduced phosphorylation and the activation of signal transducers and activators of transcription (STATs). It also shows a dose-dependent inhibition of IL-6-induced STAT3 phosphorylation. Furthermore, it has been postulated to have an antiviral effect involving SARS-CoV-2 endocytosis, reducing, as a consequence, the virus' ability to infect lung cells [96] (Tables 3–5).

In a double-blind, randomized, placebo-controlled trial, baricitinib (4 mg daily for 14 days, os) combined with remdesivir (200-mg loading dose administered intravenously on day one, followed by a 100-mg maintenance daily dose for up to 10 days) reduced recovery time and accelerated clinical improvements in hospitalized patients with moderate to severe COVID-19, more than remdesivir alone [17]. In subgroup analyses, the greatest benefits have been reported in patients who needed high-flow oxygen or noninvasive ventilation [17].

In order to clarify the effects of baricitinib in COVID-19, some phase 2 (NCT04321993) and phase 3 clinical trials have been performed (NCT04640168, NCT04421027). Baricitinib should be avoided in patients with ANC $< 1 \times 10^9$ cells/L, and it is not recommended when creatinine clearance is < 30 mL/min and in severe hepatic impairment [16].

12. Other Immunomodulant Drugs

To date, there are no sufficient data to recommend IL-6 and JAK inhibitors other than tocilizumab and baricitinib, respectively, but ongoing trials will better define their potential role.

In preclinical and in vitro studies, the selective serotonin reuptake inhibitor (SSRIs) fluvoxamine showed anti-inflammatory effects [97,98]. These findings need to be confirmed in clinical studies and further investigations are mandatory to clarify whether fluvoxamine can be an effective COVID-19 treatment. The same considerations can be made about colchicine. Among its pleiotropic mechanisms, this microtubule inhibitor shows an encouraging potential anti-inflammatory effect, particularly through the inhibition of NLRP3 inflammasome [99], which may represent a valid target to treat SARS-CoV-2 infection. However, only a modest benefit in non-hospitalized patients has been reported in the COLCORONA trial [4].

13. Monoclonal Antibodies

Bamlanivimab/Etesevimab

Bamlanivimab and etesevimab are two monoclonal antibodies which act towards two different epitopes of the SARS-CoV-2 spike protein.

Bamlanivimab monotherapy is associated with the advent of SARS-CoV-2 variants, so its role was resized.

Guidelines suggest the use of bamlanivimab/etesevimab combination in outpatient with mild to moderate COVID-19 with high progression risk (EUA criteria) (Table 2).

In a randomized, double-blind, placebo controlled trial, in patients with mild to moderate COVID-19, Gottlieb et al. [15] documented that the combination of bamlanivimab plus etesevimab (700/1400 mg) is better than bamlanivimab alone (700 mg, 2800 mg, 7000 mg).

ADRs include urinary tract infections, nausea, diarrhea, hypersensitivity, dizziness, headache, pruritus, vomiting, pyrexia, and rashes. Metabolic interactions with other drugs are not described, and seem to be improbable.

Another important statement is that the COVID-19 vaccine should be deferred for at least 90 days if the patient has received monoclonal antibody treatment because the treatment could interfere with the immune response generated by vaccines [4].

14. Casirivimab/Imdevimab

Casirivimab plus imdevimab is approved in outpatients with mild to moderate COVID-19 (EUA criteria). Casirivimab (1200 mg) and imdevimab (1200 mg) are recombinant human monoclonal antibodies that bind to different segments of the spike protein RBD (Table 2) [4].

Weinreich et al. [18] showed that casirivimab (REGN10933) and imdevimab (REGN10987) reduce the viral load of patients without immune responses or with a high viral load at baseline. Of note, patients with antibodies at baseline (serum positive) had minor benefits from the administration of casirivimab/imdevimab.

ADRs were represented by infusion related reactions and hypersensitivity, even if similar effects to those cited for bamlanivimab/etesevimab were documented. No described interactions with CYP450 and other drugs have been described, but further studies on pharmacokinetics and pharmacodynamics are required [4,100]. The criteria of administration are like those for bamlanivimab/etesevimab. It should be kept in mind that IgG antibodies could cross placenta, although they are not available data. Similarly, to the case of bamlanivimab/etesevimab, the anti SARS-CoV-2 vaccination should be deferred for at least 90 days. Finally, casirivimab/imdevimab seems to be more effective than bamlanivimab/etesevimab against the majority of the variants [101].

15. Discussion

The management of COVID-19 is based on some key points.

Clinicians should remember that the symptomatic infection history of a patient can be pathogenetically divided in two phases: viral replication and inflammation [5]. This is the first step in pursuing the proper therapy, considering the infection stage.

Another key item is related to the patient's clinical condition, which can dramatically change the medical choices in the scale from symptomatic therapy to intensive care unit admission [4].

Besides these two important issues, the peculiar characteristics of the patient should be taken into account [102]. A gender-based approach has been theorized in some studies, which described some differences between men and women [103].

Males had higher plasma levels of innate immune cytokines such as IL-8 and IL-18 and showed a more consistent role of non-classical monocytes. Females had more important T cell activation than male patients during SARS-CoV-2 infection, which was sustained in old age.

T cell activity had an inverse relation with age and poor activity was characterized by worse outcome in males, but not in females. Higher innate immune cytokines in female patients were associated with worse disease progression, but not in male patients. CCL5 and CXCL10 were more elevated in men. Being male seems to be a risk factor for severe disease. All of these differences are probably related to the gender variance in immune responses. Elevated BMI was described as a risk factor for a worse outcome, especially in men. Despite this, there were no significant differences in viral load and serum antibodies between men and women [103].

Black patients and white patients were compared in another study. Black patients had higher prevalence of other comorbidities than white patients. Being black, of increased age, having a higher score on the Charlson Comorbidity Index (which describes illness burden), residing in a poor area and having obesity were risk factors associated with higher chances of hospitalization [104]. Of the 326 patients in this study who died, 70.6% were black. However, further analysis demonstrated that being black is not independently associated with an increased risk of death, so it has been hypothesized that sociodemographic factors affected the results [105]. Biochemical and laboratory differences were seen between the two groups: a higher percentage of black people than white people presented with elevated levels of creatinine, AST, or inflammatory markers; while white people showed lower white-cell, lymphocyte, or platelet counts, more elevated levels of brain-type natriuretic peptide, lower sodium levels [104]. Other data can reflect differences that are determined by other chronic conditions, as exemplified by the finding that chronic renal insufficiency at baseline and acute renal failure during hospitalization were more common among black patients. Procalcitonin, C-reactive protein were more likely to be elevated in black patients and fever was more common. These results may suggest a race-related immune response to COVID-19 [104]. In fact, African ancestry was associated with a stronger inflammatory response to pathogens than European ancestry [106]. Interestingly, the multiinflammatory syndrome in children (MIS-C) is more common in non-white children, with obesity the most common comorbidity [107].

These findings opened up a debate on personalized treatment, which should also consider biochemical and immunological differences related to gender and ethnicity.

Furthermore, polytherapy and consequent potential drug-interactions should be carefully evaluated. Deprescribing in COVID-19 is a tough task because of the lack of therapeutic alternatives and the presence of a great number of interactions.

Elderly and frail patients often need someone that can help them to manage a large number of medications that involve multiple different branches of medicine.

CQ/HCQ, lopinavir/ritonavir and azithromycin are associated with QTc prolongation and torsade de pointes (TdP) risk, alongside other cardiotoxic substances. Risk factors are represented by congenital long-QT syndromes, advanced age, female sex, structural heart disease, electrolyte disturbances (e.g., concomitant use of diuretics), hepatic/renal failure, concomitant QTc-prolonging medications, fever, sepsis, baseline QTc prolongation, and inflammatory state [12,108]. Antiarrhythmics, calcineurin inhibitors, antidepressants, antipsychotics (exception aripiprazole and lurasidone), antiretroviral drugs, some anti-tuberculosis drugs, antineoplastic agents, calcineurin inhibitors, M-TOR inhibitors, and salmeterol can all increase this effect, whereas bradycardizing drugs like β -blockers can aggravate clinical status [12,65].

Corticosteroids are metabolized by CYP3A4 and are also able to induce it, leading to other potential interactions [42] (Tables 4 and 5).

Notably, ARDS can increase pulmonary capillary permeability, increasing the volume of distribution of water-soluble drugs, reducing their systemic action and concentration [109,110].

Pregnancy is an unexplored special condition: guidelines recommend to not withhold the treatment of COVID-19 in pregnancy even if there are not data about it. Children have some different indications compared to adults. Mild or moderate disease can be treated with supportive care alone, whereas remdesivir is approved in hospitalized children aged ≥ 12 years with COVID-19 who have risk factors for severe disease and have an emergent or increasing need for supplemental oxygen, or in hospitalized children aged ≥ 16 years with COVID-19 who have an emergent or increasing need for supplemental oxygen, regardless of whether they have risks factors for severe disease, even though it may be considered in all the cases where oxygen is needed by the patient [4]. Dexamethasone can be used for patients who need HFNC, NIV, IV, and ECMO. There are insufficient data to recommend baricitinib, tocilizumab or monoclonal antibodies, whereas convalescent plasma and sarilumab are contraindicated outside clinical trials. In a MIS-C setting, intravenous immunoglobulin, corticosteroids and anti-IL-1 antibodies are the main therapeutic option [4]. A low number of clinical trials have been reported, so these scenarios need further analysis in order to assess the safety of the newer drugs [111].

Treating immunocompromised patients is a challenging task, especially because many of the COVID-19 medications could aggravate the vulnerability related to basal and chronic conditions like HIV, transplants, and the assumption of other immunosuppressant drugs. These patients often suffer from opportunistic infections and reductions in immunosuppression are often advocated by many clinicians [4,64,112].

Hepatotoxicity is another key point in the therapeutic management: favipiravir, remdesivir, tocilizumab and lopinavir can induce it [23], and the clinician should be careful in cases where the patient has impaired liver function, in liver transplant settings or where concomitant treatments like paracetamol have been administered. Paracetamol is commonly used in COVID-19 symptomatic treatment, but clinicians should always avoid the coadministration with hepatotoxic compounds. Favipiravir produce a modest increase in paracetamol levels [65].

Lopinavir/ritonavir and remdesivir can damage renal function [79], and other drugs should be administered evaluating eGFR like HCQ or CQ (excreted in urine or in bile) [23].

Even in a cardiovascular setting, some difficulties may arise: antiplatelets can interact with COVID-19 therapy; P2Y12 inhibitor levels can be boosted by protease inhibitors; ticagrelor levels can be increased, whereas clopidogrel antiplatelet activity seems strangely

to diminish. Prasugrel is considered to be the best option when the coadministration with lopinavir/ritonavir is needed [12,65].

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin-Receptor Blockers (ARBs) can variously interact with COVID-19 therapies. Ritonavir can block the transformation of losartan and irbesartan in their active forms. Somewhat differently, valsartan levels may increase because of the inhibition of the hepatic efflux transporter, MRP2 and OATP1B. Ivabradine levels can increase after CYP450 inhibition [12,65].

Spironolactone is preferred to eplerenone because its interactions are weaker. Other diuretics have not produced significant interactions. Antiarrhythmic drugs may also have several interactions: class I is often a CYP2D6 substrate, while in class III amiodarone is metabolized by CYP3A4.

Some COVID-19 treatments can produce hyperglycemia (lopinavir/ritonavir, corticosteroids, remdesivir) or hypoglycemia (HCQ and CQ) [80].

Concomitant treatment in cancer is also a difficult situation to be managed. In cancer patients, the risk of neutropenia is very high and may be treated with a granulocyte colony stimulating factor (G-CSF). It is important to avoid treatment delays, because some cancer therapies must be administered in a narrow temporal interval [4]. Regimens that do not aggravate COVID-19 outcomes may not be altered. Despite the risk of neutropenia, G-CSF can increase the inflammation level and so must be stopped if not essential [4].

Hormone therapy, immunotherapy or radiotherapy, one month before the SARS-CoV-2 infection, was not associated with an increased risk of mortality among cancer patients with COVID-19 [65].

Another particular setting is related to immune-depressed people, whose status can worsen as a result of some of the COVID medications which reduce the immune response [78].

Besides these everyday clinical possibilities, every substrate, inducer, or inhibitor of CYPs involved in COVID-19 treatment should be under the attention of the medical team.

More than a year after SARS-CoV-2 pandemic started, treatment is changing substantially. In the first months of the pandemic, scientists tried to study virus' biology and to repurpose old drugs, which may have been fit for this specific situation [54]. Monotherapy and the discovery of a specific bullet, at first, was theorized and hoped for by pharmaceutical industry and scientific societies. Unfortunately, the virus' characteristics seemed to present obstacles to this kind of management, because of its tendency to produce variants relatively quickly [113].

Similarities between SARS-CoV-2 and HCV, another RNA virus with an important mutation rate, have been analyzed in order to pursue drug repurposing. Both are RNA viruses, with a similar effect on immune response, comparable structure of the protease, and ion channels (protein E for SARS-CoV-2 and protein p7 for HCV) that they use to survive and replicate. Some HCV drugs showed a certain degree of effectiveness against the virus, glycyrrhizin above all. The immune response is dominant in HCV action, whereas it has an important role only in the early phase of SARS-CoV-2 infection [114,115]. Therapeutic schemes of HCV involve more than one drug, and, recently, guidelines around COVID-19 have described a major incidence of mutations in patients treated with bamlanivimab alone, rather than bamlanivimab plus etesevimab [15]. A progressively reduced efficacy of bamlanivimab plus etesevimab has been described, while casirivimab plus imdevimab seems to have a better effect [4]. In each case, combination therapy seems to reduce the incidence of variants, with a similar concept to HCV therapy and Highly Active Antiretroviral Therapy (HAART) for HIV.

16. Conclusions and Future Directions

COVID-19 treatment is far from achieving a definitive shape, or permanent indications. One year after the advent of the pandemic, steps have been taken, but the scientific community must face a lot of important challenges and questions.

Firstly, the management of multiple drugs in elderly and frail patients' needs an expert level of care. New professional figures are called to fulfil this role. Medical professionals with an elite knowledge of drug interactions, pharmacokinetics, pharmacodynamics, and adverse events can be crucial in this sense. This can lead to the key achievement of tailored therapy.

Another important debate involves the choice between repurposing [116] or creating new molecules [117] in the treatment of SARS-CoV-2. If repurposing can be quick and less expensive, drug discovery would ensure a specific therapeutic action towards the virus' unique structures or mechanisms of action. States, the pharmaceutical industry and medical professionals should apply high formation and professional notions of economy to pursue the right management of the public health.

Further challenges include the recognition and the treatment of asymptomatic and mild to moderate COVID-19 patients who are not at high risk of progression. No therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression [4]. If clinical management of the asymptomatic and mild to moderate patients is not a problem, since only symptomatic therapy and follow-up are required, if necessary, this category is considered to be a silent treatment, because, if not diagnosed, they can infect a significant number of people, especially non-vaccinated people. SARS-CoV-2 vaccines are certainly an important part of the solution (to reduce virus diffusion), but their efficacy is not 100% [118] and emerging variants [113] may constitute a major issue in this setting, if not thwarted soon.

As such, several clinical trials are ongoing in order to evaluate the role of new monoclonal antibodies in the management of COVID-19 infections in both hospitalized (NCT04770467; NCT04441918) and non-hospitalized settings (NCT04840459; NCT04952805)

Moreover, old drugs have been proposed as add-in therapy in COVID-19. Recently we suggested that escin treatment could be useful in patients with severe diseases [119]. Some clinical trials are currently ongoing in order to test its efficacy (NCT04322344).

Finally, new therapies are being tested in trials and theorized by scientists. Stem cells [120], ion channel targeted therapy [114], new antibodies [121,122], TMPRSS2 targeting drugs [123], TMEM16 inhibitors (like niclosamide) [124], high mobility group box-1 (HMGB1) targeting [125], complement inhibitors and fostamatinib (an inhibitor of spleen tyrosine kinase) [2], TLR7 activation [126], photodynamic therapy [127], are examples of trials or discussions, with many other drugs or compounds [6], similarly to repurposed drugs, also currently under clinical trial [4,116].

Therefore, our hope is that specific treatments will be added to current therapeutic options and prevention strategies and that the management of interactions, deprescribing, prescriptive appropriateness and costs will be planned with solid rationality.

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