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Current Opinion in Pharmacology

Treatments for COVID-19: Lessons from 2020 and new therapeutic options

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Abstract

To face the COVID-19 pandemic, prophylactic vaccines have been developed in record time, but vaccine coverage is still limited, accessibility is not equitable worldwide, and the vaccines are not fully effective against emerging variants. Therefore, therapeutic treatments are urgently needed to control the pandemic and treat vulnerable populations, but despite all efforts made, options remain scarce. However, the knowledge gained during 2020 constitutes an invaluable platform from which to build future therapies. In this review, we highlight the main drug repurposing strategies and achievements made over the first 18 months of the pandemic, but also discuss the antivirals, immunomodulators and drug combinations that could be used in the near future to cure COVID-19.

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Current Opinion in Pharmacology 2022, **62**:43–59

This review comes from a themed issue on **Anti-infectives (2022)**

Edited by **Nora A. Fierro, Santiago Mirazo** and **Jesus Torres-Flores**

For complete overview about the section, refer Anti-infectives (2022)

Available online 18 November 2021

https://doi.org/10.1016/j.coph.2021.11.002

Introduction

Since its first description in December 2019, coronavirus disease 2019 (COVID-19) has spread throughout the world, causing more than 245 million confirmed cases and ~5 million deaths as of November 1st, 2021 (https://covid19.who.int/) [1]. COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense single-stranded RNA-enveloped virus from the *Coronaviridae* family [1,2]. Over the last 18 months, the scientific community has deciphered SARS-CoV-2 biology and COVID-19 physiopathology, and developed preventive and curative treatments [3,4]. Since December 2020, several prophylactic vaccines have been approved, others are under development, and a large vaccination campaign has begun [5–7]. However, to date, only a third of the world population is fully vaccinated, countries have unequal access to jabs, and we are far from the vaccine coverage that could effectively protect the population if vaccine effectiveness was 100% [7]. Thus, complementary therapeutic treatments are necessary to protect vulnerable populations from fatality or prolonged COVID-19 sequelae [8], face the emergence and dissemination of SARS-CoV-2 variants associated with potential resistance to treatments [9–11], and sustainably mitigate the impact of the pandemic. This review takes stock of the main therapeutic strategies evaluated in the past 18 months and discusses promising future strategies.

Physiopathology of COVID-19 disease

The natural history of SARS-CoV-2 in the host has been extensively described elsewhere [3,12]. Accumulating evidence shows that, although the respiratory tract is the primary target of the virus, COVID-19 is a systemic disease that in the worst cases can lead to multiorgan failure [13]. Despite most patients being clinically asymptomatic or having mild-to-moderate clinical manifestations, 10–20% will develop severe pathology that can evolve toward critical illness and eventually death, especially those with risk factors or comorbidities [14,15]. Recent studies have also shown that inborn genetic defects of type I interferon (IFN–I) responses [16] or the presence of neutralizing autoantibodies against IFN-I also contribute to disease severity [17,18]. The physiopathology can broadly be divided into three stages that may overlap: (I) the upper respiratory tract (URT) viral stage, (II) the pulmonary stage, and (III) the hyperinflammatory stage (Figure 1) [14]. Stage I begins at the time of infection and includes the incubation period and early establishment of the disease; patients whose immune

response successfully limits viral spread likely have a good recovery. Others may progress toward moderate illness (stage II), where the main symptoms are pneumonia, with fever, cough, and hypoxemia in some but not all cases. Some patients present with severe/critical forms of the disease (stage III), with symptoms including severe respiratory distress, shock, and organ failure. Although only a small number of patients reach this stage, the mortality rate is considerably increased in this population [14,15,19].

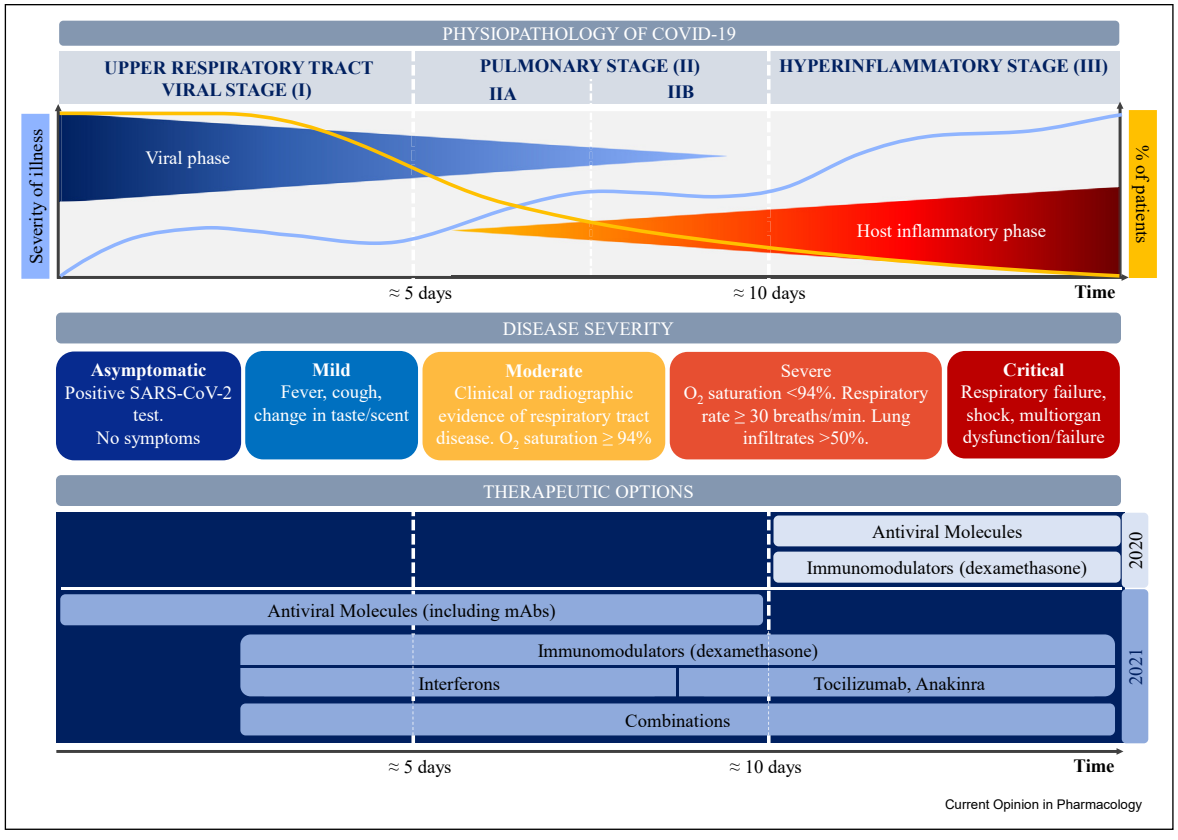
Mechanistically, COVID-19 can be defined as a two-phase disease. While the first phase is mostly driven by viral replication in the URT, the second is mainly due to a host-dependent deregulated inflammatory response, leading to cytokine storm, damage to different organs, and eventually systemic failure. This particular evolution of the clinical presentation is of upmost importance for patient management, for which the choice and timing of the appropriate treatment depends on the phase of the pathology [20].

Treatments for COVID-19: lessons from 2020

During 2020, considering the urgency for therapeutic solutions to fight COVID-19, drug repurposing strategies were favored. Among the hundreds of clinical trials completed or still in progress, many antiviral molecules and immunomodulators were administered to patients with severe COVID-19. This section focuses on those treatments evaluated in large and adaptive randomized clinical trials (RCTs) with robust statistical validation, which have proved to bear the highest predictive value (Table 1).

The SOLIDARITY and RECOVERY trials were the flagship international adaptive RCTs, designed to study the efficacy of several molecules in large cohorts of moderate/severe COVID-19 patients. Candidates included antiviral molecules such as experimental remdesivir (RDV), FDA-approved lopinavir/ritonavir (LPV/r), and hydroxychloroquine (HCQ), antibiotics such as azithromycin, and immunomodulators such as

Figure 1



Time course of COVID-19 progression and therapeutic options. Time course of COVID-19 progression (blue line), shows an increasing disease severity (asymptomatic to critical) through the three stages of the disease: upper respiratory tract viral stage (I), pulmonary stage (II) and hyperinflammatory stage (III). The average (non-adjusted by age, comorbidities, etc) percentage of patients in each stage (orange line) shows that only a small proportion of patients (up to 10–20%) develop a severe to critical disease. The "therapeutic options" section presents the evolution regarding the administration time point of therapeutic molecules in 2020 vs 2021.

dexamethasone, convalescent plasma, and interferon beta-1a (IFNb-1a). In October 2020, the WHO SOLIDARITY trial published interim results showing that RDV, HCQ, LPV/r, and IFNb-1a regimens had little or no effect on overall mortality, initiation of ventilation, or duration of hospital stay in hospitalized patients with COVID-19 [21]. Similar conclusions were obtained by the RECOVERY trial for HCQ [22], LPV/r [23], convalescent plasma [24], by RECOVERY and PRINCIPLE trials for azithromycin [25,26] and by the ACTT-1 trial and a Cochrane meta-analysis for RDV [27,28]. Only dexamethasone, a corticosteroid commonly used in the treatment of acute respiratory distress syndrome (ARDS), showed 30% and 12% reductions in 28-day mortality among oxygen-requiring patients respectively receiving or not invasive mechanical ventilation versus the usual care group [29,30]. Currently, WHO recommends corticosteroids (i.e., dexamethasone) as a standard of care for the treatment of patients with severe and critical COVID-19 (https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2).

New therapeutic options

This section discusses relevant preclinical studies and clinical trials evaluating promising new monotherapies and drug combinations (Tables 1–3).

Antivirals: target the virus at the early stage of infection

Antiviral therapies can target viral and/or host determinants that are crucial for viral replication (Table 1). SARS-CoV-2 entry relies on the angiotensin-converting enzyme-2 (ACE2) as a receptor and also transmembrane serine protease 2 (TMPRSS2) that cleaves and activates the viral spike (S) protein [31]. One strategy to inhibit S/ACE2 interaction is the use of neutralizing antibodies. Treatment of high-risk adult outpatients with mild/moderate COVID-19 with sotrovimab (STV), an anti-S monoclonal antibody (mAb), resulted in an 85% reduction in the risk of hospitalization or death [32]. According to GSK (https://www.gsk.com/en-gb/media/press-releases/gsk-and-vir-biotechnology-announce-sotrovimab-vir-7831-receives-emergency-use-authorization-from-the-us-fda/), STV maintains *in vitro* activity against all known variants of concern, including B.1.617.2, and it recently received an FDA Emergency Use Authorization (EUA). mAbs are at the frontline of currently developed COVID-19 treatments, but their use should be based on an accurate characterization and selection, since they might either inhibit or enhance S-mediated membrane fusion and formation of syncytia [33]. Moreover, mAb monotherapies have already shown their limits, as exemplified by the resistance of B.167.2 to bamlanivimab [11], therefore current directives suggest the use of mAb cocktails to target multiple and complementary epitopes [34,35]. Camostat mesilate, a TMPRSS2 inhibitor approved for treatment of pancreatitis in Japan [36,37], was repurposed as a potent inhibitor of SARS-CoV-2 entry *in vitro*. However, no improvement was observed in the first clinical trial including 137 hospitalized patients with mild/moderate pathology [38]; other clinical studies are ongoing.

Nucleoside analogs (NAs) have historically been primary options against emerging RNA viruses and this was no exception for SARS-CoV-2. Molnupiravir (MPV), a potent experimental NA and prodrug of the synthetic nucleoside derivative N4-hydroxycytidine, introduces copying errors during viral RNA replication [39,40]. Initially developed by Merck to inhibit influenza viruses [41], MPV has the advantage over RDV of being administered orally. Preclinical data showed that it efficiently inhibited SARS-CoV-2 replication *in vitro* and in *in vivo* models [42–44], and its therapeutic potential is currently being tested in patients with mild/moderate COVID-19. In patients with confirmed SARS-CoV-2 infection and symptom onset within 7 days, MPV cleared infectious viruses from nasopharyngeal swabs at day 5 and reduced by 50% the time to elimination of SARS-CoV-2 RNA (14 *vs* 27 days for placebo) [45]. However, some concerns have been raised regarding MPV due to its toxicity and potential teratogenic effects [40,46]; a phase 2 trial is currently evaluating its safety and efficacy on SARS-CoV-2 shedding in hospitalized patients. Other repurposed drugs potentially targeting multiple steps of the SARS-CoV-2 life cycle are currently being tested, such as ivermectin (IVM), a broad-spectrum antiparasitic agent with previously reported antiviral activity *in vitro* [47–49]. Although a small study on 57 patients with mild COVID-19 showed a reduction in symptom duration and viral detection in the URT of treated patients [50], no robust evidence to support its clinical use was provided by other studies [51,52] or by a recent Cochrane meta-analysis [53].

Preclinical evaluation of other molecules (Table 2), such as soluble ACE2 peptides that compete with human ACE2 for the interaction with S, or inhibitors of cathepsin L (SLV213), a cysteine protease that plays a key role in SARS-CoV-2 entry, is ongoing [54]. Both soluble ACE2 peptides and SLV213 blocked SARS-CoV-2 infection *in vitro* with a 50% inhibitory concentration (IC50) in the nanomolar range [55,56]. A phase 2 clinical trial in patients with mild/moderate COVID-19 is planned. Another approach evaluates virus neutralization with a new class of genetically engineered antibody mimetic drugs (DARPin®) [57]. Pre-treatment using ensovibep, a DARPin targeting three domains of S, reduced virus load in the URT and LRT *in vivo* by four and two log, respectively [58]. Ensovibep is currently under evaluation in a phase 2/3 clinical trial in patients with mild COVID-19 and it recently received FDA Fast Track Designation for use in both hospitalized and ambulatory settings. Plitidepsin, an inhibitor of eukaryotic translation elongation factor 1A, reduced

Table 1

Principal monotherapies evaluated for COVID-19.

	Class	Type	Name	ClinicalTrials id [Reference]	Disease stage	Country(ies)	Nb of patients treated[a]	Results	Adverse Events	Validation Degree[b]	Comments
2020	Antiviral Molecules	Nucleoside analogs	Remdesivir (RDV)	NCT04647669 (SOLIDARITY) [21]	Severe	International	2750	RDV had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay in hospitalized patients.	RDV was not associated with increased risk of adverse events.	Strong (severe COVID-19)	Antiviral therapy needs to be administrated at the right time. Indeed, the improvement observed in the ACTT-1 trial is probably linked to the enrollment of patients with moderate symptoms.
				NCT04280705 (ACTT-1) [28]	Moderate/severe	International	541	RDV was superior to placebo in shortening the time to recovery in hospitalized adults with COVID-19.		Medium (small sample size)	
		Protease inhibitors	Lopinavir/ritonavir (LPV/r)	NCT04381936 (RECOVERY) NCT04647669 (SOLIDARITY) [21,23]	Severe	International	1616 (RECOVERY) 1411(SOLIDARITY)	LPV/r was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death.	LPV/r was associated with gastrointestinal symptoms (anorexia, nausea, diarrhea).	Strong	The efficacy of LPV/r in patients with less severe COVID-19 was not evaluated.
		Antibiotic	Azithromycin (AZM)	NCT04381936 (RECOVERY) ISRCTN86534580 (PRINCIPLE) [25,26]	Severe Mild	International United Kingdom	2582 (RECOVERY) 526 (PRINCIPLE)	AZM did not substantially improve time to recovery and admissions to hospital.	One serious adverse event was reported: pseudomembranous colitis.	Strong	Widespread use of AZM is at risk. Indeed, it is classified within the WHO Watch Group of Antibiotics (i.e., antibiotics that have higher resistance potential).
		Antimalarial	Hydroxychloroquine (HCQ)	NCT04381936 (RECOVERY) NCT04647669 (SOLIDARITY) [21,22]	Severe	International	1561 (RECOVERY) 954 (SOLIDARITY)	Among patients hospitalized with COVID-19, those who received HCQ did not have a lower incidence of death at 28 days than those who received usual care.	HCQ was not associated with increased risk of adverse events.	Strong	The use of HCQ as prophylaxis or in patients with less severe COVID-19 was not evaluated.
	Immunomodulators	Antibodies	Convalescent plasma (CCP)	NCT04381936 (RECOVERY) [24]	Severe	International	5795	CCP was not associated with improved outcomes for patients with COVID-19.	13 reports submitted to the serious hazards of transfusion hemovigilence scheme.	Strong	The trial does not address whether CCP has any benefit if given early after SARS-CoV-2 infection and before the onset of significant disease.
		Interferon	IFNb-1a	NCT04647669 (SOLIDARITY) [21]	Severe	International	2063	Subcutaneous IFNb1a had little or no effect on overall mortality, initiation of ventilation, and duration of hospital stay in hospitalized patients.	Not reported.	Strong	Approximately half the patients who were assigned to IFNb1a (and half their controls) received glucocorticoids, but the rate ratio for death with IFNb1a as compared with its control seemed unaffected by glucocorticoid use.
		Corticosteroids	Dexamethasone (DXM)	NCT04381936 (RECOVERY),	Severe Moderate/ severe	International Brazil	2104 (RECOVERY) 151 (CODEX)	The use of DXM resulted in a 30% reduction 28-day mortality among patients	DXM was not associated with increased risk of adverse events.	Strong (for patient receiving	WHO strongly recommends corticosteroids (i.e.,

				NCT04327401 (CODEX) [29,30]				receiving invasive mechanical ventilation compared to usual care group. No benefit among patients not requiring respiratory support.		respiratory support)	DXM, hydrocortisone, or prednisone) for the treatment of patients with severe and critical COVID-19.
		Anticoagulants	Heparin or low molecular weight heparin (LMWH)	NCT04372589 (ATTACC), NCT04505774 (ACTIV-4), NCT02735707 (REMAP-CAP), NCT04359277 [74,75]	Moderate	International	1181	The study found a 98.6% probability that a therapeutic dose of heparin or LMWH increased survival until hospital discharge without organ support.	More major bleeding occurred with treatment than with thromboprophylaxis (1.9% vs 0.9%)	Medium	Those trials were open-labeled. Methods of prophylaxis were not standardized and resulted in a mix of doses within treatment groups.
					Severe	International	534	Therapeutic dose of heparin or LMVH did not improve days without organ support.	More major bleeding complication than usual-care prophylaxis (3.8% vs 2.3%)	Medium	
2021	Antiviral Molecules	Neutralizing antibodies	Sotrovimab (VIR-7831)	NCT04545060 [32]	Mild/moderate	United States	291	Treatment with sotrovimab resulted in an 85% reduction in the risk of hospitalization or death in high-risk adult outpatients compared to placebo.	Sotrovimab was not associated with increased risk of adverse events.	Low (small sample size)	Preprint publication. The U.S FDA granted an Emergency Use Authorization (EUA) for sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients who are at high risk for progression to severe COVID-19, including hospitalization or death. Results need to be validated in other trials (e.g.; NCT04913675, NCT04779879).
		Nucleoside analogs	Molnupiravir (MPV)	NCT04405570 [45]	Mild/moderate	United States	140	MPV treatment cleared infectious viruses from nasopharyngeal swabs at day 5 and reduced by 50% the time to elimination of SARS-CoV-2 RNA (14 vs 27 days for placebo) in outpatients with COVID-19.	MPV was not associated with increased risk of adverse events.	Low (small sample size)	Preprint publication. Results need to be validated in other trials (eg; NCT04575584; NCT04405739, NCT04575597).
		TMPRS22 inhibitor (host-targeting agent)	Camostat mesilate (CM)	NCT04321096 (CamoCO-19) [38]	Mild/moderate	Danemark, Sweden	137	CM treatment did not affect time to clinical improvement, progression to intensive care unit admission, or mortality.	CM treatment was not associated with increased adverse events.	Low (small sample size)	Publication of the CAMELOT trial results (NCT04583592) are expected to confirm or refute the ineffectiveness of CM.
		Anti-parasitic	Ivermectin (IVR)	NCT04529525 [51]	Mild	Argentina	250	IVR had no significant effect on preventing hospitalization of patients with COVID-19.	Patients who received IVR required invasive mechanical ventilatory support earlier in their treatment.	Low (small sample size)	There was a low percentage of hospitalization events, the dose of IVR given was low, and the population did not include only high-risk patients.
				NCT04405843 [52]	Mild	Colombia	238	Among adults with mild COVID-19, a 5-day course of IVR, compared with placebo, did not significantly improve the	IVR was not associated with increased risk of adverse events.	Low (small sample size)	In all the study population, the incidence of clinical deterioration was below 3%.

(*continued on next page*)

Table 1. (*continued*)

Class	Type	Name	ClinicalTrials id [Reference]	Disease stage	Country(ies)	Nb of patients treated[a]	Results	Adverse Events	Validation Degree[b]	Comments
							time to resolution of symptoms.			
			NCT04716569 [50]	Mild	Egypt	57	IVR significantly reduced durations of fever, cough, dyspnea, and anosmia, as well as the duration of detectable virus in the upper respiratory tract.		Low (small sample size)	Larger studies in patients with COVID-19 are needed to further investigate the therapeutic potential of IVR (eg, NCT04529525).
Immunomodulators	Antibodies	Tocilizumab (TCZ) anti-IL-6 receptor monoclonal antibody	NCT04381936 (RECOVERY), NCT02735707 (REMAP-CAP) [80,81]	Severe	International	2022 (RECOVERY), 353 (REMAP-CAP)	In hospitalized COVID-19 patients with hypoxia and systemic inflammation, TCZ improved survival, increased the chances of successful hospital discharge, and reduced the chances of requiring invasive mechanical ventilation.	Three reports of serious adverse reactions believed to be related to TCZ: one each of otitis externa, *Staphylococcus aureus* bacteraemia, and lung abscess.	Strong	In June 2021, the U.S. FDA issued an EUA for TCZ for the treatment of hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.
	IL1-receptor antagonist	Anakinra (ANA)	NCT04341584 (CORIMUNO-ANA-1) [82]	Mild/moderate	France	59	ANA did not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia.	ANA was associated with an increased risk of bacterial sepsis and hepatic cytolisis.	Low (small sample size)	Another trial (CORIMUNO-ANA-2) that aims to assess the effect of ANA in patients with more severe COVID-19 has been completed and is being analyzed.
			NCT04318366 [83]	Severe	Italy	62	IL-1 inhibition was associated with a 12% reduction in mortality compared to the placebo group in patients admitted to hospital with COVID-19, respiratory insufficiency, and hyperinflammation.	Not reported.		Observational study. Clinical differences between groups at baseline introduce the possibility of confounding. However, clinical differences were mixed and did not confer any study group a clear survival advantage.
	Interferon	Inhaled IFNb-1a (SNG001)	NCT04385095 [63]	Moderate/severe	United Kingdom	48	Patients who received SNG001 showed more than three-fold greater odds of improvement and recovery on day 28 compared to the placebo group.	The most common treatment-emergent adverse event in the SNG001 group was headache.	Low (small sample size)	Larger studies in patients with COVID-19 are needed to further investigate the therapeutic potential of Inhaled IFNb-1a (eg, NCT04732949).
		peg-IFNλ-1	NCT04354259 (ILIAD) [64]	Mild/moderate	Canada	30	By day 7, decline in SARS-CoV-2 RNA in nasal swabs was 2.42 log greater with peg-IFNλ-1 and viral	Peg-IFNλ-1a was not associated with increased adverse events.	Low (small sample size)	Larger studies in patients with COVID-19 are needed to further investigate the

						clearance was 2-fold greater for patients with baseline RNA of 10^6 copies per mL or greater compared to the placebo group.			therapeutic potential of peg-IFNλ-1 (e.g., NCT04344600 and NCT04354259).
Corticosteroids	Inhaled budesonide (BUD)	NCT04416399 (STOIC) [70]	Mild	United Kingdom	73	Early administration of inhaled BUD in patients with chronic respiratory disease reduced mortality by 12%, increased chances of successful hospital discharge by 14%, and reduced the chances of requiring invasive mechanical ventilation by 20%.	Adverse events reported in five participants (four had sore throat; one had dizziness).	Low (small sample size)	Larger studies in patients with COVID-19 are needed to further investigate the therapeutic potential of Inhaled BUD (e.g., NCT04355637 and NCT04331054).
		ISRCTN86534580 (PRINCIPLE) [71]	Mild/moderate (nonhospitalized patients)	United Kingdom	2530	Administration of inhaled BUD reduced the time of recovery (11.8 days vs 14.8 days for the control group), and hospital admissions and death (6.8% vs 8.8% for the control group).	Two serious adverse events in treated group and 4 in the control group (hospital admissions unrelated to COVID-19).	Medium	Open-label trial.
Angiotensin receptor blocker	Telmisartan	NCT04355936 [85]	Mild/moderate	Argentina	78	Telmisartan-treated patient had a reduced median discharge time by 6 days, ICU admission by 2.4 fold and up to 80% mortality at day 30 was observed compared with the placebo group.	No adverse events reported. Well tolerated even at high dose.	Low (small sample size)	Exclusion of intensive care unit patients on randomization. Restriction to patients with a relatively short time from symptom onset to randomization. Further studies are needed to confirm the therapeutic potential of telmistran in COVID-19 (eg, NCT04394117 and NCT04920838).
Selective serotonin reuptake inhibitor and a σ-1 receptor agonist	Fluvoxamine	NCT04727424 [78]	Mild	Brazil	741	Treatment with fluvoxamine (100 mg twice daily for 10 days) among high-risk outpatients with early diagnosed COVID-19 reduced the need for hospitalisation defined as retention in a COVID-19 emergency setting or transfer to a tertiary hospital.	No significant differences in number of treatment emergent adverse events among patients in the fluvoxamine and placebo groups.	Medium	The population had a higher rate of hospitalisation events than observed in most clinical trials, thus permitting inferences on treatment effects in this higher-risk population.

[a] Number of patients treated with the indicated molecule.

[b] Subjective assessment of the robustness of currently available data.

Table 2

COVID-19 treatments under preclinical development.

	Class	Type	Name [Reference]	Model(s)	Results	Validation Degree[a]	Ongoing/Future ClinicalTrial Id
Monotherapies	Antiviral molecules	DARPin (Antibody mimetic proteins)	Ensovibep [58]	Vero E6 cells and Syrian golden hamsters	Neutralization capacity in the low picomolar range. Ensovibep pretreatment reduced virus load in the lower and upper respiratory tract by 4 and 2 log respectively.	Medium	NCT04828161 Inclusion in NCT04501978
		Soluble angiotensin-converting enzyme-2 (ACE2)	hACE2 peptide mimics [55]	Vero E6 and Calu-3 cells	Best peptide mimics are able to block SARS-CoV-2 infection with an inhibitory concentration (IC50) in the nanomolar range upon binding to the virus spike protein with high affinity.	Low	
		Cathepsin L inhibitor (host-targeting agent)	SLV213 (K177) [56]	Vero E6, Caco-2, A549/ACE2 cells	SLV213 blocks primary infection of SARS-CoV-2 in several cell lines with nanomolar potency.	Low	NCT04843787
		eEF1A inhibitor (host-targeting agent)	Plitidepsin [59]	Vero E6 cells and HACE2-transgenic mice	Plitidepsin treatment reduced viral replication in the lung by 2-fold *in vivo* in two different mouse models.	Medium	NCT04784559
		Anti-parasitic (host-targeting agent)	Inhaled niclosamide (NIC) human lysozyme (hLYS) [60]	Vero E6 cells and HACE2-transgenic mice	Intranasal administration of NIC-hLYS improved survival and reduced viral tissue loads *in vivo* at a level that was comparable to remdesivir (RDV).	Medium	NCT04932915; NCT04399356
	Immunomodulator	Inducer of IFN antiviral response	Diltiazem [66,67]	A549/ACE2 cells, reconstitued human airway epithelia (HAE) and non-human primate (NHP)	High stimulation of endogenous type-III interferon response in the A549/ACE2 cell line, HAE, and upper airway samples and lung tissue from NHP. Inhibition of SARS-CoV-2 infection with an *in vitro* IC50 in the micromolar range and viral clearance up to 3 log in nasal and tracheal swabs at day 3 post-exposure in NHP.	High	DICOV

Combinations	Antiviral molecules	Monoclonal antibodies	C135-LS + C144-LS (combination of antispike neutralizing monoclonal antibodies) [88]	Rhesus macaque	Administration one day after SARS-CoV-2 infection improved clinical outcome, reduced virus replication in upper and lower respiratory tracts, and reduced lung inflammation.	Strong	NCT04700163: safety and pharmacokinetics of the cocktail
		Nucleoside analog + antifungal or antidepressant	RDV + itraconazole RDV + fluoxetine [91]	Calu-3 cells	Both combinations display synergic effects. Inhibition of production of viral particles >90%.	Low	
		Nucleoside analog + drug with cellular broad spectrum activities	RDV + diltiazem [66,67]	Vero E6 cells and HAE	High levels of synergy between RDV and diltiazem. Diltiazem potentiates effect of RDV in Vero E6 cells and HAE.	Medium	
		Nucleotide anolog + protease inhibitor	GS441524 (RDV parent nucleotide analog) + GC376 (feline coronavirus prodrug) [92]	Vero E6 cells and mouse-adapted SARS-CoV-2 infected mouse model	GS441524 blocked SARS-CoV-2 proliferation in the mouse upper and lower respiratory tracts. Combined application of both drugs has a synergistic effect.	Medium	
	Antiviral molecules + immunomodulators	Nucleoside analog + glucocorticoid (anti-inflammatory)	Methylprednisolone (MP) monotherapy or combined with RDV [99]	Human monocyte-derived macrophages and Syrian hamster model of SARS-CoV-2 infection	MP monotherapy increased SARS-CoV-2 replication. In hamster, MP + RDV had antiviral and anti-inflammatory effects leading to suppression of viral replication, inflammation, and tissue damage.	Medium	

[a] Subjective assessment of the robustness of currently available data.

lung SARS-CoV-2 viral load by two-fold *in vivo* in hACE2-transgenic mice [59], and its safety and efficacy is currently being evaluated in a phase 3 trial in patients with moderate COVID-19. Niclosamide, an anthelminthic and antibacterial drug, was formulated with human lysozyme for its delivery to the URT and LRT. Its intranasal administration improved survival and reduced lung SARS-CoV-2 viral load by three log in hACE2-transgenic mice [60]; its safety and efficacy is being currently evaluated in mild/moderate COVID-19 patients. In March 2021, Pfizer initiated a phase 1 study of PF-07321332, a novel antiviral targeting the SARS-CoV-2 3CL protease and concluded that it has a potent *in vitro* antiviral activity against SARS-CoV-2 and other coronaviruses.

Immunomodulators: restoration of the antiviral immunity and control of cytokine storm

The use of immunomodulators has proved to be an efficient strategy to dampen hypercytokinemia and improve patients' clinical outcomes (Table 1). IFN-I and type III interferons (IFN-III) are central players of the early immune response, rapidly induced during viral infection to restrict virus propagation [61]. Even if SARS-CoV-2 has evolved mechanisms to evade IFN-I and IFN-III responses [62], restoring potent IFN responses at early stages of infection could be beneficial. In 2020, subcutaneous administration of type I IFNb-1a in 2063 hospitalized patients with severe COVID-19 was not associated with improved clinical outcomes [21]. However, in 2021, treatment with an inhaled formulation of IFNb-1a showed more than three-fold greater odds of improvement and recovery on day 28 versus the placebo group in 48 hospitalized patients with moderate/severe disease [63]. Another trial evaluated a subcutaneous administration of type III peg-IFNλ-1 in 30 outpatients with moderate and mild disease. By day 7, decline in SARS-CoV-2 RNA in nasal swabs was 2.42 log greater with peg-IFNλ-1 and viral clearance was two-fold greater for patients with baseline RNA of 10^6 copies/ml or greater versus the placebo group [64]. Finally, our group has shown that diltiazem, an old antihypertensive drug (calcium channel blocker) has *in vitro* and *in vivo* host-directed anti-influenza properties, mainly due to its capacity of inducing the IFN-III antiviral response within reconstituted human airway epithelium (HAE) [65]. Diltiazem also displays antiviral effects against SARS-CoV-2 in *in vitro* and non-human primate (cynomolgus) models ([66,67] and unpublished data). A double-blind randomized phase 2 clinical study in patients with mild/moderate COVID-19 is planned at the end of 2021.

Given the positive results obtained with dexamethasone, the COVIDICUS trial is currently testing low versus high doses of this drug in severe COVID-19 patients. Other corticosteroids are also being evaluated for their control of immune and inflammatory responses. Inhaled glucocorticoids are commonly used to treat patients with asthma or chronic obstructive pulmonary disease and, interestingly, some studies have shown that these pathologies were underrepresented among hospitalized COVID-19 patients [68,69]. To assess whether the widespread use of inhaled glucocorticoids in these patients might account for this observation, inhaled anti-inflammatory budesonide was administered to 73 outpatients with mild COVID-19 and chronic respiratory disease. Results showed a 91% reduction in the likelihood of needing urgent medical care and a clinical recovery 1 day shorter versus the usual care group [70]. More recently, inhaled budesonide was tested in 2530 mild/moderate COVID-19 non-hospitalized patients and showed an improved time of recovery (11.8 *vs* 14.7 days) and reduced hospital admissions and deaths (6.8% *vs* 8.8%) versus the usual care group [71]. In addition to an uncontrolled inflammatory response, COVID-19 is often associated with coagulopathy and thromboembolic events in severe patients [72]. The use of anticoagulants has been considered to treat patients, but there are contradictory meta-analysis data [72,73]. Recently, two studies from combined clinical trial programs showed that therapeutic-dose heparin increased the probability of survival and reduced need for organ support in moderate but not severe hospitalized patients versus usual-care thromboprophylaxis [74,75]. However, more major bleeding events were observed in therapeutic versus thromboprophylaxis treatment, raising caution regarding the use of such molecules, with the WHO advising low doses to be used in hospitalized patients. Alternatively, fluvoxamine, an antidepressant with potential immunomodulatory effect and putative antiviral properties, has been recently evaluated in a phase 3 clinical trial among 1497 high-risk symptomatic patients [76—78]. Preliminary results suggest a potential positive effect of the drug on COVID-19 patients but further investigations are needed.

Interleukin-1 and -6 (IL-1 and IL-6) are two of the main pro-inflammatory cytokines produced during infection and are also drivers of cytokine storms [79]. Tocilizumab, an anti-IL-6 receptor mAb, was evaluated in 2375 hospitalized patients with severe COVID-19 with both hypoxia and systemic inflammation. Compared with placebo, it reduced mortality by 12%, increased chances of successful hospital discharge by 14%, and reduced the chances of requiring invasive mechanical ventilation by 20% [80,81]. Tocilizumab recently received an EUA for the treatment of hospitalized adults and pediatric patients who are receiving systemic corticosteroids and require supplemental oxygen. Anakinra, an IL-1 receptor antagonist, was also evaluated in 59 hospitalized patients with mild-to-moderate COVID-19 pneumonia but showed no benefit and resulted in an increased risk of bacterial sepsis and hepatic cytolysis [82]. Nonetheless,

Table 3

Combined COVID-19 treatments under clinical evaluation.

Class	Type	Name	ClinicalTrials id [Reference]	Country (ies)	Disease stage	Nb of patients treated[a]	Results	Adverse Events	Validation Degree[b]	Comments
Antiviral molecules	Combination of anti-spike neutralizing monoclonal antibodies	Casirivimab + imdevimab	NCT04425629 (REGN-CoV-2/REGEN-CoV) [34,35]	United States	Mild or moderate	182	Reduction of viral load, in particular in patients with no previous endogenous immune response (−0.56 log10 viral copies/ml SARS-CoV-2 in treatment group compared to control) or with a high viral load at baseline (difference vs placebo: −0.36, −0.59, −0.81, and −1.03 log10 copies/ml for 104, 105, 106, or 107 copies/ml baseline serum antibody status, respectively).	Infusion-related reaction in few cases.	Medium	Emergency use authorization for casirivimab + imdevimab published by U.S Food & Drug administration in Nov 2020. In vitro study shows efficacy against P.1 and B.1.351. Ongoing additional trials: NCT04666441, NCT04426695, and NCT04452318.
		Bamlanivimab (BAM) + etesevimab (ETE)	NCT04427501 (BLAZE-1) [86,87]	United States, Puerto Rico	Mild or moderate, nonhospitalized (≥18)	114 combination 317 BAM	Treatment with combination associated with a reduction in SARS-CoV-2 viral load at day 11 (−0.57 log10 viral load compared to placebo). COVID-19-related hospitalization significantly lower in combination group.	Nausea and diarrhea. Immediate hypersensitivity reactions that could have been infusion related.	Medium	Small sample size. The primary end point at day 11 may have been too late in the immune response to optimally detect treatment effects. An earlier time point, such as day 3 or day 7, might have been more appropriate to measure viral load.
					Mild/moderate, nonhospitalized patients at high risk for severe disease (adolescent ≥12 and adults)	518	Early administration of drug combination reduced incidence of hospitalization (2.1% vs 7% in treated vs placebo). 0 vs 10 deaths in placebo group and faster resolution of symptoms. −1.2log viral load in treated patient compared to placebo group at day 7.	Similar in both group and low (around 1%).	High	Emergency use authorization for BAM + ETE published by U.S Food & Drug administration in Feb 2021. Withdrawn in June 2021 due to lack of activity against P.1 and B.1.251.
Antivirals molecules + immunomodulators	Proteases inhibitors + nucleoside analog + interferon	Lopinavir-ritonavir (LPV/r) + ribavirin + IFNb-1b	NCT04276688 [95]	Hong Kong	Mild/moderate	86 combination 41 LPV/r	Combination relieved symptoms within 4 days vs 8 days for LPV/r alone.Virus clearance was observed in 7 vs 12 days for control group, and hospital stay was reduced to 9 days against 14.5 days in control.	Self-limited nausea and diarrhea (no difference between the two groups).	Low	Small sample size. Triple combination was not used for patients who started treatment 7 days or more after symptoms (concerns about the proinflammatory side effects of IFNb-1b).
	Nucleoside analog + Janus kinase inhibitor	Remdesivir (RDV) + baricitinib (BAR) or RDV alone	NCT04401579 (ACTT-2) [98]	International	Moderate/severe	515 combination 518 RDV	Combination was superior to RDV alone in reducing recovery time and accelerating improvement of clinical status (among those receiving high-flow oxygen or noninvasive ventilation).	Fewer adverse events in the combination group than in the control group.	Medium	A trial (NCT04421027) that aims to assess the effect of BAR alone is ongoing. Larger studies are needed to validate the results.

[a] Number of patients treated with the indicated molecule or combination.

[b] Subjective assessment of the robustness of currently available data.

an observational study in 62 patients admitted to hospital for severe COVID-19 with respiratory insufficiency and hyperinflammation showed a 12% reduction in mortality versus the placebo group without adverse events [83].

Internalization of ACE2 receptors, while in complex with S, induces a loss of its enzymatic function, and eventually increases angiotensin II plasma levels, promoting inflammation and leading to ARDS [84]. Treatment with the angiotensin receptor blocker telmisartan resulted in a reduction in the median discharge time by 6 days, in ICU admission by 2.4 fold, and of up to 80% in mortality at day 30 versus placebo in 78 hospitalized COVID-19 patients [85].

Altogether, further large and adaptive RCTs are still needed to assess the therapeutic potential of IFNs, inhaled glucocorticoids, IL-1/IL-6 blockers, and angiotensin receptor blockers in COVID-19.

Drug combinations

Although the complexity of COVID-19 makes unlikely the discovery of a unique drug suitable to treat all patients, combining virus- and host-targeting agents could be an alternative to monotherapy approaches, which, up to now, have mostly failed (Tables 2 and 3).

Cocktails of neutralizing mAbs targeting S are currently used to block viral attachment and entry. Casivimab and imdevimab, two non-competing antibodies, are being evaluated in mild/moderate nonhospitalized COVID-19 patients [34]. Interim results show a reduction of 0.56 log10 viral copies/ml in the serum of primary infected patients, with the largest benefit observed in patients with higher viral loads at baseline (reduction of up to 1.03 log10 copies/ml vs placebo). These promising results prompted an EUA for this cocktail. Copin et al. also showed that this cocktail is effective against all current variants *in vitro*, *in vivo*, and in SARS-CoV-2 isolates of 1000 COVID-19 non-hospitalized patients, while an additional third mAb further increased protection against viral escape [35]. Administration of bamlanivimab and etesevimab in 577 nonhospitalized patients with mild/moderate disease resulted in a reduction of 0.57 log10 viral load in treated patients [86]. Early administration of this treatment in nonhospitalized patients with mild and moderate symptoms and at high risk for severe disease reduced both hospitalization rate (2.1% vs 7% in treated vs placebo) and viral load (−1.2 log) [87]. This cocktail received an EUA in February 2021; however, a recent update now advises against its use due to reduced or lack of activity against the B.1.351, P.1, and B.1.617 variants [11]. A preclinical study in macaques evaluating C135-LS and C144-LS, mAbs with extended half-life and targeting complementary epitopes of S, showed a significant reduction in virus replication in the URT and LRT, coupled with reduced lung inflammation and improved clinical scores [88]. Safety, pharmacokinetics and efficacy of this cocktail in COVID-19 patients are currently under investigation in phase 1 and as part of the ACTIV-2 trial, respectively. Preclinical experiments on tixagevimab and cilgavimab, two synergistic long-acting anti-S mAbs, showed that this cocktail is able to protect animal models from infection and demonstrated potent neutralizing activity including against B.1.1.7, B.1.351, B.1.1.28, B.1.617.1, and B.1.617.2 [89,90]. This cocktail is currently being evaluated for postexposure prophylaxis, but also as a treatment for outpatients and inpatients.

Preclinical evaluation of the antifungal itraconazole and the antidepressant fluoxetine, both proposed to have antiviral activity against SARS-CoV-2 most likely through modulation of the endosomal cholesterol pathways, have shown synergistic activity in combination with RDV when compared with monotherapy [91]. Our group has shown that diltiazem displays synergistic effects against SARS-CoV-2 in HAE when combined with RDV [66]. Moreover, a suboptimal low-dose combination of a coronavirus RNA-dependent RNA polymerase enzyme inhibitor (GS441524) and an inhibitor of the M^{pro} protease (GC376) synergistically blocked SARS-CoV-2 infection in the mouse respiratory tract [92]. Of note, GS441524 is the parent nucleoside of RDV. It has a 1000-fold higher concentration in serum than RDV when the latter is administered by IV injection and a better safety profile than the prodrug *in vitro* and in animal models; it also has antiviral activity comparable with RDV and is well-suited for pneumocyte-targeted delivery [93,94].

The dual viral-immunologic nature of COVID-19 sets a strong case for combining antiviral and immunomodulatory molecules. In 2020, a clinical trial tested the triple association of LPV/r, ribavirin, and IFNb-1b versus LPV/r alone in 127 patients with mild/moderate COVID-19 [95]. The combination shortened the time to negative nasopharyngeal swab (7 vs 12 days), alleviated symptoms in 4 days (8 in control), and reduced hospital stays to 9 days (14.5 in control). Treatment with RDV and baricitinib, a selective inhibitor of Janus kinase 1 and 2 that inhibits production of cytokines [96,97], in 1033 hospitalized patients with moderate/severe disease resulted in faster recovery, particularly in patients under ventilation (10 *vs* 18 days with placebo) [98]. A preclinical study evaluated the efficacy of RDV associated with the glucocorticoid methylprednisolone against SARS-CoV-2 infection in hamsters. Early treatment with methylprednisolone significantly reduced pulmonary inflammation and alleviated tissue damage, although it increased tissue viral RNA loads and titers and suppressed the development of anti-S antibodies [99]. The combination inhibited viral replication and reduced

tissue inflammation. This dichotomy highlights the need of adapting treatment regimens to the disease stage and patient conditions.

Conclusions

Over the last 18 months, knowledge of COVID-19 has dramatically increased, vaccines have become available, but curative treatments are still lacking [4,14,15]. The holy grail will probably not be found, but taking account of patients' clinical picture, comorbidities, and disease stage will maximize the chances of success. As such, the combination therapy approach, already used to treat other viral diseases [100–102], is promising. From onset of symptoms, a combination of antiviral molecules, such as FDA-approved mAbs combinations [34,35] or new combinations including NAs plus mAbs (e.g., MPV + casirivimab) and mAbs or NAs plus host-targeting agents with antiviral activity (e.g., MPV + diltiazem), could be interesting. For patients with comorbidities and for those with moderate/severe COVID-19, combining antiviral molecules with immunomodulators should be considered. Combining NAs with Janus kinase inhibitors (e.g., MPV + baricitinib) or mAbs plus corticosteroids (e.g., casirivimab + imdevimab + dexamethasone) are possible options. Combination therapies have the potential to prevent disease progression in vulnerable populations, and notably in the context of the potential emergence of virus variants with increased pathogenicity and/or reduced susceptibility to preventive/therapeutic treatments. However, strong validation in relevant preclinical models is mandatory before clinical evaluation. Eventually, identification of early prognostic biomarkers such as IL-6 and autoantibodies against IFN-I, reported to predict poor evolution of the disease and whose levels seem to correlate with disease severity, could also be helpful [17,18,103,104].

Author contributions

FS, TL, EL, AP, and MR-C conceived and discussed the content of the manuscript. FS, TL, and EL drafted the manuscript. FS and TL made the tables and figures. AP and MR-C revised the manuscript. All authors revised the final version of the manuscript.

Conflict of interest statement

AP and MR-C are co-founders of Signia Therapeutics SAS, co-inventors of a patent application filed by INSERM, CNRS, Université Claude Bernard Lyon 1, and Signia Therapeutics for the repurposing of diltiazem for the treatment of SARS-CoV-2 infections (FR 20/02351). All of the other authors declare no competing interests.

Acknowledgments

The authors want to thank Dominique Deplanque (Université de Lille) for his critical review of the manuscript. While this research did not receive any specific funding, the VirPath Team received INSERM, CNRS, and Mérieux COVID-19 research grants. The sponsors had no role in the study, or in the decision to submit the article for publication.

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