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Drug repurposing clinical trials in the search for life-saving COVID-19 therapies; research targets and methodological and ethical issues

Ensaios clínicos para reposicionamento de medicamentos para COVID-19 na busca de terapias para salvar vidas; alvos de pesquisa, e questões metodológicas e éticas

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ABSTRACT

Introduction: So far, there is no vaccine, nor are there effective drugs to treat COVID-19, an emerging viral respiratory infection deadlier than influenza. **Objective:** To take a snapshot picture of planned and ongoing clinical research addressing drugs potentially useful for treating SAR-CoV-2 infections. **Method:** A search was conducted (20 April 2020) in an international registry of clinical studies (https://ClinicalTrials.gov, US NIH). After excluding observational studies and other interventions that fell outside the scope of this study, 294 research protocols (out of 516 retrieved protocols) were selected for analysis. **Results:** Of 294 included trials, 249 were Randomized Controlled Trials (RCT), 118 of which were double-, triple- or quadruple-blinded studies. The interventions (drug therapies) were compared with "standard-of-care" (SOC) or with the placebo plus SOC, or yet with presumed "active" comparators. RCT focused on the primary treatment of the disease (inhibitors of viral replication) or on the therapy for resolution of hyperinflammation in pneumonia/Acute Respiratory Distress Syndrome (ARDS) and thromboembolism associated with SARS-CoV-2. The trials found in the database involve existing antiviral compounds and drugs with multiple modes of antiviral action. Antiparasitic drugs, which inhibited viral replication in cell-culture assays, are being tested as well. Regarding the adjunctive immunomodulatory, anti-inflammatory and antithrombotic therapies, a number of drugs with distinct pharmacological targets are under investigation in trials enrolling patients with severe COVID-19. **Conclusions:** Although many clinical studies of drugs for COVID-19 are planned or in progress, only a minority of them are sufficiently large, randomized and placebo-controlled trials with masking and concealment of allocation. Owing to methodological limitations, only a few clinical trials found in the registry are likely to yield robust evidence of effectiveness and safety of drugs repurposable for COVID-19.

KEYWORDS: COVID-19; Clinical Trials; Antiviral Drugs; Pneumonia; Acute Respiratory Distress Syndrome

RESUMO

Introdução: Até agora, não há vacinas ou medicamentos eficazes para tratar COVID-19, uma infecção viral respiratória emergente mais letal do que a gripe. **Objetivo:** Desenhar um quadro das pesquisas planejadas e em curso sobre medicamentos potencialmente úteis para tratar infecções por SARS-CoV-2. **Método:** Um levantamento foi realizado (20 de abril de 2020) em um registro internacional de estudos clínicos (https://ClinicalTrials.gov, US NIH). Após excluir estudos observacionais e outras interveções fora do escopo deste estudo, 294 protocolos (de 516 identificados na busca) foram selecionados para análise. **Resultados:** De 294 ensaios incluídos, 249 eram Ensaios Controlados Randomizados (ECR), dos quais 118 eram estudos duplo-, triplo- ou quadruplo-cego. As intervenções (medicamentos testados) foram comparadas com o "tratamento padrão" (TP) ou com

placebo mais TP, ou ainda com comparadores supostamente ativos. ECR abordaram o tratamento primário da doença (inibidores da replicação viral) ou a resolução da super-inflamação na pneumonia e Síndrome do Desconforto Respiratório Agudo (SDRA), e do tromboembolismo associados ao SARS-CoV-2. Os ensaios localizados no registro envolviam fármacos antivirais com múltiplos modos de ação e medicamentos anti-parasitários que inibem a replicação viral em cultura de células. Em relação às terapias imunomodulatória, antiinflamatória e antitrombótica adjuvantes, inúmeros medicamentos com alvos farmacológicos distintos também estão sendo investigados em ensaios envolvendo pacientes graves com COVID-19. **Conclusões:** Embora muitos ensaios clínicos de medicamentos para COVID-19 tenham sido planejados e estejam em andamento, apenas uma minoria deles são estudos suficientemente grandes, randomizados, controlados com placebo e com mascaramento, e ocultação da alocação. Em virtude das limitações metodológicas apontadas, provavelmente apenas uns poucos ensaios clínicos fornecerão evidências robustas da eficácia e segurança de medicamentos potencialmente redirecionáveis para COVID-19.

PALAVRAS-CHAVE: COVID-19; Estudos Clínicos; Drogas Antivirais; Pneumonia; Síndrome Respiratória Aguda Grave

INTRODUCTION

The COVID-19 pandemic might be anything but unforeseeable. Throughout history, mankind has faced many devastating pandemics, such as the Middle Age bubonic plague (´Black death`), the 20th century Spanish flu (H1N1 first pandemic) and AIDS (HIV), and the swine flu (H1N1 second pandemic) in the past decade. Notwithstanding a similar deadly viral infection (SARS-CoV-1) had lit a warning light in 2002-4, no vaccine was created, nor were drugs against coronaviruses developed[1].

If vaccines are not available, strategies to curb the spread of contagious illnesses rely on quarentine, a traditional health practice dating back to 1377[2], disease-specific preventive actions and medications.

When swine flu (H1N1) emerged in 2009, there existed neuraminidase-inhibiting antiviral drugs (oseltamivir, zanamivir) for treatment and prophylaxis of influenza infections[3]. Neuraminidase blockage prevents virion release from the surface of infected cells thereby halting their replication[3]. Although expectations on oseltamivir for prophylaxis and treatment of swine flu were largely unmet[4,5,6,7], a vaccine was developed and H1N1 was finally tamed.

Contrasting to the poor performance of antiviral medicines in H1N1 pandemic, the extensive use of effective antiretroviral therapies (ART) was a notable public health triumph. ART combines three or more drugs (new molecular entities, NME) acting on distinct molecular targets, and by doing so it maximally suppresses HIV replication. The combination of antiretroviral drugs not only stopped disease progression in HIV-infected patients, but it also prevented onward transmission of the virus[8]. It took decades, however, to develop such a set of antiretrovirals with complementary and synergistic modes of action, including inhibition of virus reverse-transcriptidase, protease, integrase and cell entry/fusion. This lenght of time is not available under the current scenario of COVID-19 pandemic progression.

Development of NME drugs from the bench to the bedside is a long and costly endeavor the success of which can not be taken for granted. Certainly, it is not on the table when we are facing COVID-19, a fast-spreading viral infection that, within a few days, may progress from relatively mild symptoms to a life-threatening Acute Respiratory Distress Syndrome (ARDS).

Tackling such a challenging contagious disease, drug repurposing or repositioning (DR) seems to be the most viable approach to find effective therapies in a timely manner. DR implies in identifying new medical uses for existing (in use, discontinued, shelved or experimental) drugs. It requires conducting clinical trials of drug effectiveness and safety for new and still unapproved therapeutic indications[9].

The advantage of DR over NME drug development is a reduction of development time, costs and uncertainty. Since data on manufacturing process, quality control and analytical methods, as well as nonclinical safety, pharmacokinetics, pharmaceutical formulation and first-use in humans are available for existing medications, these time-consuming steps of drug development are circumvented[9].

In the quest for life-saving COVID-19 therapies, time is certainly the most valuable commodity. Those researchers and managers who are committed to developing COVID-19 drugs hear the clock ticking constantly while pandemic death toll steadily rises. It is not surprising that the pandemic had broken the emergency glass on all possible options and many drugs are rushing into compassionate use and clinical investigation even when enough preliminary evidence of safety and efficacy for COVID-19 is missing.

This study was performed to identify and analyze drug clinical trials (on April 20th, 2020) addressing the treatment of COVID-19 and infection-related Acute Respiratory Distress Syndrome (ARDS). A special focus was placed on identifying which drugs are being considered for repurposing and their pharmacological targets as well as the drawbacks and strengths of ongoing DR studies. Moreover, this report addresses prospects and perils ahead in the desperate race to find a drug useful to attenuate COVID-19 (and ARDS) morbidity and death toll.

METHOD

On April 20th, 2020, a clinical trials database (https://clinicaltrials.gov) was searched for identifying which drug treatments (DR, drug repurposing or repositioning) for COVID-19 are under investigation. The foregoing clinical trials registry is run by the United

States National Library of Medicine at the US National Institutes of Health. It is the largest international registry of clinical trials and holds registrations from over two hundred countries. The searching terms used to identify studies of pharmacological therapies for COVID-19 were as follows: Status ("All"); Condition or Disease ("Covid"); Other terms ("Treatment"); Countries (no selection). All retrieved trials that investigated therapeutic options other than drugs (e.g., hyperbaric O_2, mesenchymal stem cells, plasma of convalescent patients and others) were excluded and so were non-interventional trials (i.e., observational, cohort or case-control designs). Information extracted from all potentially relevant studies (records) found in the searched database were: Registry ID number, status (recruiting, not yet recruiting, active, complete, terminated, suspended), drug treatment, clinical indication, study design features (arms, randomization, masking, type of comparator, i.e., placebo or active treatment comparator, number of patients enrolled), estimated date of completion, and, if available, study results. Extracted data were consolidated in spreadsheets for further analysis and qualitative synthesis.

All authors screened the retrieved records for trials which were relevant for the study and took part in data extraction. Data were extracted independently by each investigator and cross-checked by the others.

RESULTS AND DISCUSSION

Unsurprisingly, the emergence of COVID-19, a fast-spreading respiratory infection much deadlier than influenza, has unleashed a worldwide race for finding effective pharmacological therapies. This survey (on 20 April 2020) identified 516 studies addressing therapeutic interventions for COVID-19 (Table 1). About 57.0% of these studies were trials of potentially repurposable drugs while the remaining ones were of hyperbaric O_2, mesenchymal stem cells, plasma of convalescent patients, heat-killed *Mycobacterium*, medical devices and observational (prospective cohorts or case-control) designs (n = 37, 17.0% of excluded studies). It was amazing to find such an expressive number of observational studies in ClinicalTrials.gov database because it supposedly should contain only trials, i.e., interventional clinical studies (Figure).

The majority of drugs under clinical investigation for COVID-19 are antiviral agents developed for and used to treat other viruses. Two structurally related old antimalarial compounds (chloroquine and hydroxychloroquine) with mild immunossupressive properties and putative antiviral activity, and a diversity of drugs belonging to other therapeutic classes are being tested as well (Tables 2 and 3).

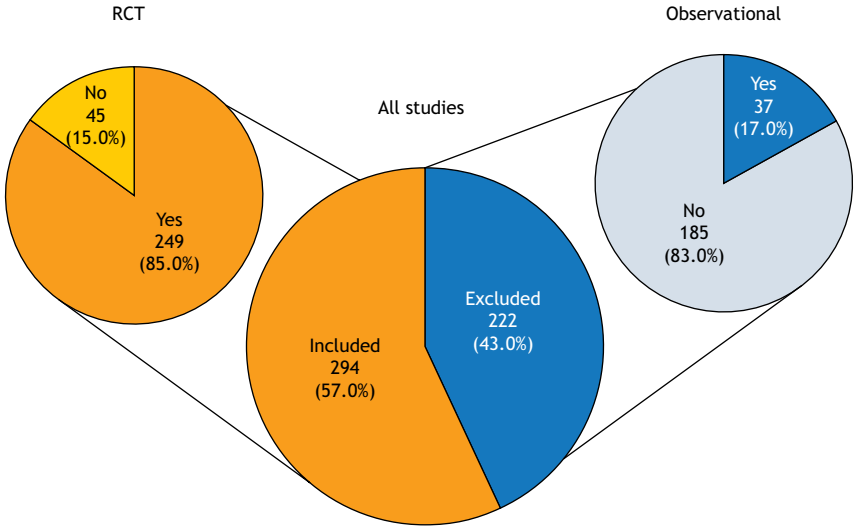
Table 1. Results of the search for planned and ongoing clinical research on drugs potentially repurposable for COVID-19.

All search findings N = 516	Included studies N = 294 (57.0%)		Excluded studies N = 222 (43.0%)	
	Randomized 259 (85.0%)	Not randomized 45 (15.0%)	Observational 37 (17.0%)	Interventional 185 (83.0%)
Sample size of trials included in the analysis				
≤ 25	15		5.1%	
30 ≤ N ≤ 100	82		27.9%	
102 ≤ N ≤ 200	52		17.7%	
202 ≤ N ≤ 300	30		10.2%	
304 ≤ N ≤ 400	30		10.2%	
405 ≤ N ≤ 500	17		5.8%	
510 ≤ N ≤ 600	13		4.4%	
630 ≤ N ≤ 900	12		4.1%	
804 ≤ N ≤ 1,300	14		4.8%	
1,450 ≤ N ≤ 2,414	10		3.4%	
2,486 ≤ N ≤ 4,140	13		4.4%	
≥ 6,000	6		2.0%	
Total	294		100.0%	

Number of arms and type of masking in randomized controlled trials (RCT)

Arms	Trials	Masking				
		No	Single	Double	Triple	Quadruple
2	197	83	18	28	15	53
3	31	15	5	5	2	4
4	19	11	1	3	1	3
≥ 5	12	7	1	1	1	2
Total	259	116	25	37	19	62

Source: https://ClinicalTrials.gov at the US NIH on 20 April 2020.



Source: https://ClinicalTrials.gov at the US NIH on 20 April 2020.

Figure. Clinical studies and randomized controlled trials (RCT) on drugs potentially repurposable for COVID-19 identified in an international registry of clinical trials.

Survey results revealed that pharmacological interventions against COVID-19 generally pursue one of two distinct therapeutic goals: 1) to accelerate resolution and/or to prevent worsening of oligosymptomatic or mild COVID-19 infections (i.e., proactive prophylaxis) or 2) to relieve symptoms and to reduce mortality in severe infections and ARDS.

Drugs that effectively inhibit SARS-CoV-2 replication in humans are likely to be of benefit to patients with mild symptoms as well as to those with severe manifestations of COVID-19. Based on the pathophysiology of COVID-19 pneumonia and ARDS[10], it is plausible to think that drugs other than typically antiviral compounds, such as immunosuppressive and anti-inflammatory agents, might also be useful to alleviate the respiratory symptoms and to reduce disease fatality rate. Immunosuppression, on the other hand, is likely to facilitate viral proliferation thereby aggravating mild, oligo and asymptomatic infections. Physicians should be aware that risks of drug adverse events (AE) that might be tolerable for critically ill patients are not necessarily acceptable for those who exhibit only mild symptoms of COVID-19.

A recent report by the World Health Organization (WHO) estimated that approximately 80.1% of patients with laboratory confirmed COVID-19 infection had only mild to moderate symptoms and showed spontaneous resolution of the disease, while 13.8% developed ARDS and 6.1% had infections that progressed to a critical clinical condition (respiratory failure, septic shock and multiple organ dysfunctions)[11].

Obviously, patients showing only mild symptoms of COVID-19 should not receive drugs that are capable of causing moderate to severe AE. In mild COVID-19 infections, depending on the drug toxicity profile, AE might eventually be worse than the disease. A different picture emerges when drugs are prescribed to treat severe and life-threatening manifestations of COVID-19. In severely ill patients, one might presume that expected (but still undemonstrated) clinical benefits of a repurposable drug are likely to outweigh risks of AE. So far, there exists no approved treatment for COVID-19, nor are there sufficient data to recommend for or against the use of drugs outside of clinical trials[12]. In other words, there are no proven beneficial effects to support COVID-19-specific pharmacological interventions. Along this line, compassionate (or expanded) use of repositionable medicines for COVID-19 must be cautious and based on robust scientific evidence. Narrow margin-of-safety (MOS) medicines, for instance, must be avoided in oligosymptomatic or mild clinical presentations of the infection.

Antiviral agents

Clinical trials on drug repurposing for COVID-19 address a diversity of existing and experimental (new) antiviral drugs with distinct mechanisms of action, such as inhibition of viral protease – Lopinavir+Ritonavir (LOP+RIT), Darunavir, DRV, ASC09[13,14]; RNA replicase – Favipiravir (FAV), Remdesivir (RDV)[15,16,17]; neuraminidase (OSV)[3]; RNA synthesis and mRNA capping (Ribavirin, RBV)[18]; and membrane fusion, a key step for enveloped viruses entry into cells (Umifenovir, UMV)[19,20] (Table 2). The boosted protease inhibitors form an integral part of the current ART for HIV infections. Guanosine analog inhibitors of RNA synthesis (RBV) are used in the treatment of respiratory syncytial virus (RSV) and hepatitis C virus (HCV), and a few other infections[18,21]. The remaining antiviral agents under investigation for COVID-19 (UMV and OSV) are predominantly used to treat influenza infections. It is of note that OSV and RBV had been used experimentally in 2003's outbreak of SARS. Poutanen et al.[22] reported that five of seven SARS Canadian patients treated with RBV improved with the therapy. However, since RBV-treated patients also received an array of other drugs, it is unclear whether RBV did in fact affect the clinical outcome[22].

Table 2. Antiviral, antibiotic and antiparasitic drugs under clinical investigation (RCT trials) for the treatment of COVID-19. Information retrieved from *ClinicalTrials.gov* database (National Library of Medicine at the US NIH) on 20 April 2020.

Drug	Mode of action	Clinical target in COVID-19 trials	RCT masking/blinding [$#]
		Antiviral agents	
Favipiravir (FAV)	Inhibitor of viral RNA-dependent RNA polymerase (or RNA replicase). FAV was originally developed to treat influenza infections[17].	Interventions targeted to unspecified (any) clinical manifestations, mild to moderate, or moderate to severe infections.	Open (n = 40, n = 100, n = 120, n = 150, n = 210, n = 320); S (n = 120); D (n = 100)
FAV + (LOP+RIT)		COVID-19	Open (n = 320)
Remdesivir (RDV)	Inhibitor of viral replicase. Development focused treatment of Ebola virus infections. Further laboratory tests showed promising activity against SARS and MERS[16].	Interventions targeting mild, moderate or severe COVID-19 infections.	Open (n = 700, n = 1600, n = 3100, n = 6,000); D (n = 800); Q (n = 237, n = 308)
Umifenovir (UMV)	Broad-spectrum antiviral activity. UMV (or Arbidol) blocks membrane fusion, an essential step when enveloped viruses enter cells. Used to treat influenza in Russia and China[20].	Interventions focusing on COVID-19 with clinical manifestations of pneumonia (confirmed by CT imaging). Prophylaxis/prevention of progression from mild to severe infections.	Open (n = 18, n = 380, n = 520); T (n = 40)
Darunavir (DRV)	Inhibitor of viral protease. DRV is generally combined with other drugs in HIV antirretroviral therapies (ART)[13].	Interventions to treat COVID-19 patients with pneumonia.	Open (n = 30)
Lopinavir+Ritonavir (LOP+RIT)	Although both drugs are inhibitors of viral protease, RIT is a potent inhibitor of CYP3A4 and combined to lopinavir and other protease inhibitors as pharmacokinetic enhancer. This combination is part of antiretroviral (HIV) therapies (ART)[8].	Interventions to treat COVID-19 hospitalized patients with mild and moderate to severe symptoms and/or pneumonia.	Open (n = 60, n = 80, n = 127, n = 150, n = 150, n = 160, n = 165, n = 440, n = 500, n = 520, n = 3,100); S (n = 400); T (n = 40, n = 40, n = 1,200); Q (n = 4,000)
Oseltamivir (OST)	OST inhibits viral neuraminidases that cleave sialic acid in cell glycoproteins. Since glycoproteins help new virions to exit the cells, neuraminidase inhibition prevents the release of new viral particles. Some influenza strains became resistant to it[4].	Interventions to treat Covi-19 patients with pneumonia.	Open (n = 320); S (n = 60, n = 400); D (n = 500)
ASC09	New HIV protease inhibiting compound (developed by Ascletis pharma) under clinical testing in HIV patients. The experimental drug ASC09F is a combination of ASC09 and ritonavir[14].	Tested in COVID-19 patients with mild to moderate respiratory symptoms. Patients with severe respiratory symptoms were excluded.	Open (n = 160); S (n = 60)
Ribavirin (RBV)	Guanosine analog and nucleoside inhibitor that stops viral RNA synthesis and mRNA capping, thereby inhibiting viral replication. RBV is used to treat infections by Respiratory Syncytial Virus (RSV), hepatitis C and some hemorrhagic fever viruses. Activity against filoviruses (Ebola, Marburg) and flaviviruses (dengue, yellow fever) was shown to be poor[18].	Hospitalized COVID-19 patients (moderate to severe infections). COVID-19 and ARDS.	Open (n = 127); D placebo-controlled (n = 340)
		Antibiotics	
Carrimycin (CRM)	Macrolide antibiotic effective against gram-negative bacteria. CRM was effective in vitro against Mycobacterium tuberculosis. It is predominantly used to treat upper respiratory tract infections caused by bacteria.	Interventions to treat patients with any clinical stratification of COVID-19, including mild as well as severe cases with ARDS.	Open (n = 520)
Azithromycin (AZM)	AZM binds to 50S subunit of bacterial ribosome thereby inhibiting translation of mRNA into protein and thus protein synthesis. It is widely used to treat a variety of bacterial infections and COPD (chronic obstructive pulmonary disease).	Intervention to treat hospitalized COVID-19 with moderate to severe symptoms including the ARDS.	Open (n = 160, n = 276, n = 405, n = 440, n = 500, n = 500, n = 600, n = 630); S (n = 75); D (n = 150, n = 900); T (n = 240); Q (n = 456, n = 2,271)
		Antiparasitic agents	
Chloroquine (CQ)	CQ and its derivative HCQ are 4-aminoquinoline antimalarials. Both inhibit formation of hemozoin in the protozoa digestive vacuole leading to increased levels of free heme and parasite death. CQ and HCQ also present mild immunosuppressive action and are clinically used to treat rheumathic and auto-immune diseases. Both 4-aminoquinolines inhibited the replication of a variety of enveloped viruses (including coronaviruses) in cell culture assays[24,34,35,36].	COVID-19 patients with any (unspecified) clinical presentation of the illness. Prevention: health care workers HIV+COVID-19; COVID-19 with comorbidities Mild COVID-19 Moderate to severe COVID-19	Open (n = 40, n = 210, n = 250, n = 400, n = 500); S (particip.) (n = 120); D (n = 55000) ♣; Q (n = 210, n = 440); CQ or HCQ for HIV+COVID-19, Open (n = 560); CQ or HCQ Open (n = 950)
Hydroxychloroquine (HCQ)		Interventions to treat mild, moderate and severe COVID-19, including pneumonia and ARDS. HCQ was also tested for proactive prophylaxis and prevention of progression from mild to severe clinical symptoms. COVID-19 outpatients; Prevention: exposed health care workers; exposed people. COVID-19 patients from a group at risk of complications;	Open (n = 30, n = 80, n = 150, n = 202, n = 300, n= 350, n = 400, n = 500, n = 700, n = 1,116, n = 1,200, n = 1,500, n = 1,550); S (n = 75, n = 530, n = 1,250, n = 2,486); D (n = 86, n = 400, n = 800, n = 850, n = 900, n = 1,300, n = 2,000); T (n = 100, n = 400, n = 440, n = 1,200, n = 1,660, n = 3,000, n = 15,000); Q (n = 58, n = 210 n = 334, n = 350, n = 400, n = 400, n = 440, n = 456, n = 500, n = 1,600, n = 2,700, n = 3,000, n = 3,500, n= 4,000).

continue

continuation

Nitazoxanide (NTZ)	Thiazolide compound with broad spectrum anthelmintic and anti-protozoal activities. NTZ is used to treat infections by helminths and protozoa. In vitro studies indicated that NTZ inhibits replication of a variety of viruses. It blocks the maturation of influenza virus hemagglutinin at the post-translational stage. Repositioning clinical trials suggest that NTZ is useful to treat influenza infections[41].	Interventions targeting COVID-19 (symptoms and illness severity unspecified). Uncomplicated COVID-19.	S (partic.) (n = 120) T (n = 600); Q (n = 50); NTZ vs HCQ: S (particip.) (n = 86)
Ivermectin (IVM)	Broad spectrum anti-parasitic drug used in veterinary and human medicine (onchocerciasis and other worms)). In in vitro assays, IVM inhibited interaction between HIV virus integrase and importin and integrase nuclear import. In laboratory tests ivermectin inhibited the replication of several viruses including SARS-CoV-2[42].	Interventions targeting COVID-19 (symptoms and infection severity unspecified). COVID-19	Open (n = 60); S (particip.) (n = 120); D (n = 50)
Niclosamide (NCL)	NCL is widely used against tapeworm (Cestoda) infestations. In tapeworms, NCL inhibits glucose uptake, oxidative phosphorylation and anaerobic metabolism. In vitro testing suggests that NCL inhibits replication of several viruses including coronaviruses[43,44].	Interventions targeting treatment of COVID-19 (symptoms and illness severity unspecified).	S (partic.) (n = 120); Ditiazem+NCL: S (invest.) (n = 480)
Levamisole (LVM)	LVM is an anthelmintic drug. It was shown to possess immuoenhancing properties. LVM use as immuno stimulant has been discouraged by serious adverse events such as neutropenia and agranulocytosis[45,49].	Interventions focusing on patients with mild COVID-19. Exposed health care workers (prevention).	LVM: Open (n = 100) ♣; LVM vs HCQ/RIT+LOP: D (n = 30)

Source: https://ClinicalTrials.gov at the US NIH on 20 April 2020.
Diltiazem: Ca^{2+} channel blocker used to treat high blood pressure, angina, and certain heart arrhythmias; ♣: preventive intervention (exposed health care workers); RCT: randomized controlled; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; ART: antirretroviral therapies; HIV: Human Immunodeficiency Virus; ARDS: Acute Respiratory Distress Syndrome; FAV: Favipiravir; LOP: Lopinavir; RIT: Ritonavir; RDV: Remdesivir; UMV: Umifenovir; DRV: Darunavir; OST: Oseltamivir; RBV: Ribavirin; CRM: Carrimycin; AZM: Azithromycin; CQ: Chloroquine; HCQ: Hydroxychloroquine; NTZ: Nitazoxamide; IVM: Ivermectin; NCL: Niclosamide; LVM: Levamisole.
[§] Number of trial participants shown in brackets (n=); open: no masking; single blinded (participant or outcomes assessor); D: double blinded (participant and investigator or investigator and assessor); T: triple blinded (participant, care provider and investigator); Q: quadruple blinded (participant, care provider, investigator and outcomes assessor). [#] These examples of RCT studies are illustrative but not necessarily exhaustive. Sometimes the tested pharmacological intervention is a combination therapy (2 or more drugs) rather than a monotherapy.

Among the tested antivirals, RDV is perhaps researchers' best guess in an effective anti-COVID-19 drug, and, therefore, there is a great deal of expectation regarding the results of ongoing clinical trials. In *in vitro* assays, RDV strongly inhibited replication of SARS-CoV-1 and MERS-CoV viruses in several cell lines[23,24]. Furthermore, data from a cohort of patients hospitalized for severe COVID-19 who had received RDV in a compassionate-use basis, indicated that 36 (68%) drug-treated patients showed a clear-cut clinical improvement[25]. Early results (29 April 2020) of an ongoing US NIH-sponsored large (> 1,000 participants) placebo-controlled randomized controlled trial (RCT) suggested that RDV cut recovery time for hospitalized COVID-19 patients by four days, or 31% (i.e., about 11 days in RDV-treated against 15 days in the placebo group)[26]. A nonsignificant reduction in death rate (8% in RDV-treated patients against 11% in the placebo group) was also noted. Although these preliminary figures suggest a relatively modest clinical benefit, they were enthusiastically celebrated as a first reliable clinical indication of efficacy of a COVID-19 drug and a "proof-of-concept"[26] regarding this antiviral mode of action for SARS-CoV-2.

Antibiotics

It is hard to see the rationale behind the clinical trials on the potential benefits of macrolide antibiotics such as carrimycin (CRM) and azithromycin (AZM) in COVID-19 pneumonia. Antibiotics are known to be ineffective against viruses and their use for treatment or prevention of acute viral infections of the (lower and/or upper) respiratory tract is not only unnecessary but also inapropriate[27,28,29]. The most recently issued UK National Institute for Health and Care Excellence (NICE) guidelines recommend "not to offer an antibiotic for treatment or prevention of pneumonia if COVID-19 is likely to be the cause and symptoms are mild"[30]. In theory, use of antibiotics in patients with a diagnosis of COVID-19 pneumonia might have one of three explanations: physicians' uncertainty about the viral etiology of the pneumonia, to prevent a bacterial secondary infection if immunosupressive agents are employed as adjunct therapies, or a difficulty in ruling out the co-existence of viral and bacterial infections what considerably worsens the prognosis of critically ill patients[31,32,33].

Antiparasitic agents

Antimalarials

An array of antiparasitic drugs with putative antiviral activity (found in *in vitro* assays) are under investigation in COVID-19 clinical trials. The most well-known potentially repurposable drugs are the old antimalarials chloroquine (CQ) and hydroxychloroquine (HCQ) (Table 2). The hypothesis that CQ and HCQ might be useful to treat SARS-CoV infections can be traced back to 2003[34]. Based on the reports that CQ inhibited replication of enveloped RNA virus, Savarino et al.[35] proposed that it could be useful to treat the disease caused by SARS-CoV, a positive-stranded RNA virus. Further *in vitro* studies in African green

Table 3. Immumodulators, anti-inflammatory and miscellaneous drugs under evaluation (RCT trials) for the treatment of COVID-19 and the Acute Respiratory Distress Syndrome (ARDS). From *ClinicalTrials.gov* (US NIH) accessed on 20 April 2020.

Drug	Mode of action	Clinical target in COVID-19 trials	RCT masking status [§]
Immunomodulators and Anti-inflammatory agents			
Siltuximab	Anti-IL-6 chimeric monoclonal antibody.	COVID-19 Acute Respiratory Failure, cytokine release syndrome Hospitalized with Pneumonia - ICU	Open (n = 200, n = 342)
Tocilizumab	Anti IL-6 receptor human monoclonal antibody.	COVID-19 Acute Respiratory Failure, cytokine release syndrome.	Open (n = 24, n = 150, n = 228, n = 273, n = 276, n = 310, n = 342, n = 398); D (n = 330)
Leronlimab (PRO 140)	Antibody against chemokine CCR5 receptor on T lymphocytes. Used to treat HIV infections[52].	Severe or critical COVID-19 patients	Q (n = 75, n = 390)
Piclidenoson	Anti-inflammatory A3 adenosine receptor agonist (A3AR)[58].	Confirmed COVID-19 admitted to hospital	Open (n = 40)
Thymosin ß4	Hormone from the thymus. It stimulates T cells production - Thymosin Beta 4 possibly decreases mortality in sepsis via the regulation of actin and other anti-inflammatory properties[62].	COVID-19 severe pneumonia associated with lymphocytopenia	S (particip.) (n = 120)
PD-1 antibody	PD-1 is expressed on activated T cells and PD-1-related blockage is believed to decrease mortality in sepsis[63,64].		
Naproxen	Nonsteroidal anti-inflammatory drugs (NSAID), non-selective Cox1 and Cox2 inhibitors.	Critically-ill COVID-19 patients	Open (n = 584)
Ibuprofen		Severe COVID-19 patients with ARDS	D (n = 230)
Methylprednisolone	Agonist of glucocorticoid receptor (GR) with immunosuppressant and anti-inflammatory action.	COVID-19 admitted to hospital	Open (n = 80, n = 200, n = 310); S (n = 84, n = 100, n = 500); Q (n = 420)
Sirolimus	Rapamycin. Macrolide, inhibitor of cytokines transcription and synthesis.	COVID-19 patients with pneumonia admitted to hospital	D (n = 30)
Thalidomide	Mode of Action not entirely clear, reduction of TNFα and anti-inflammatory immunomodulating actions[54,55].	Moderate COVID-19	Q (n = 40, n = 100)
IFN-ß1a or IFN-ß1b	INF-ß regulates the expression of genes through the classical JAK/STAT and other pathways. Antiviral, antiproliferative and immunomodulatory activities on numerous cell types[65].	COVID-19 with $SpO_2 \leq 88\%$ Respiratory Rate ≥ 24 COVID-19 with $SPO_2 \leq 93\%$ OR respiratory rate ≥24 COVID-19 with ARDS	Open (n = 60, n = 80, n = 125, n = 3,100); T (n = 40, n = 40)
Pegylated INF-λ	Compared to IFN-ß, IFN-λ has a restricted cell response pattern and causes less adverse effects[66].	COVID-19	Open (n = 20); S (particip.) (n = 164)
Colchicine	Tubulin disruption, inhibition of neutrophil chemotaxis, adhesion and mobilization, inhibition of inflammasomes and IL-1ß processing and release[56].	COVID-19	Open (n = 102, n = 180, n = 310, n = 2,500); S (n = 600)
Tetrandrine	Ca^{2+} channel blocker, anti-inflammatory[59].	Mild and severe COVID-19 pneumonia	Open (n = 60)
Budesonide	Budesonide is an agonist of glucocorticoid receptors used in COPD and asthma.	COVID-19	S (particip.) (n = 120); D (n = 30)
Dexamethasone	Agonist of glucocorticoid receptor (GR) with immunosuppressant and anti-inflammatory action.	COVID-19 with ARDS	Open (n = 200, n = 290); S (n = 122); Q (n = 550)
Fingolimod	Fingolimod is a sphingosine-1-phosphate receptor modulator, which sequesters lymphocytes in lymph nodes. Used to treat Multiple Sclerosis[60].	Severe COVID-19 pneumonia	Open (n = 30)*
CD24Fc	Antibody-Cytokine Fusion Protein. It represses inflammation caused by tissue damage while preserving innate immune response to pathogens.	Severe hospitalized COVID-19 patients	Q (n = 230)
Ruxolitinib	Janus kinase (JAK) inhibitor selective for JAK1 and JAK2 thereby blocking cytokine signalling[53].	COVID-19 patients with respiratory symptoms and/or hypoxia ($Sp\ O_2 < 93\%$)	Open (n = 94)
Miscellaneous agentes			
Verapamil	Ion channel blockers; Amiodarone blocks voltage gated potassium (KCNH2) and voltage gated calcium channels (CACNA2D2). Verapamil blocks Ca^{2+} channel. Both drugs inhibited (cell culture) Filoviridae viruses (Ebola, Marburg) cell entry[77].	Hospitalized symptomatic COVID-19 patients with oxygenation index (PaO2 in mmHg / FiO2) > 200	S (outcome assess.) (n = 804)
Amiodarone			
Tranexamic acid (TXA)	Antifibrinolytic drug used to prevent/control post surgical or traumatic bleeding[71].	COVID-19 in patients recently admitted to the hospital	Q (n = 60, n = 100)

continue

continuation

Defibrotide	Mixture of single-stranded oligonucleotides Antithrombotic/ fibrinolytic. It protects the cells lining blood vessels and prevents blood clotting[69,70].	Hospital in patients with SARS-CoV-2 infection with clinical status grade 4, 5 or 6 according to the WHO classification	D (n = 120)
Losartan	Selective, competitive angiotensin II receptor type 1 (AT_1) antagonist, antihypertension drug.	COVID-19 patients admitted to hospital.	Open (n = 200, n = 10,000); S (n = 500); Q (n = 200, n = 580, n = 4,000)
Stopping ACEI / ARB	Testing a hypothesis that discontinuation of ACEI or ARB therapy would be of benefit in COVID-19.	COVID-19 symptomatic patients	Open (n = 554, n = 2,414); S (n = 152, n = 208, n = 215)
RhACE2 Ab	Antibody Recombinant human angotensin-converting enzyme 2.	COVID-19 patients admitted to hospitals	D (n = 200)

Source: https://ClinicalTrials.gov at the US NIH on 20 April 2020.
§ Number of trial participants shown in brackets (n =); open: no masking; S: single blinded (participant or outcomes assessor); D: double blinded (participant and investigator or investigator and assessor); T: triple blinded (participant, care provider and investigator); Q: quadruple blinded (participant, care provider, investigator and outcomes assessor).
# These examples of RCT studies are illustrative but not necessarily exhaustive. Sometimes the tested pharmacological intervention is a combination therapy (2 or more drugs) rather than a monotherapy. * non randomized allotation

monkey kidney (Vero) cells showed that CQ and HCQ changed terminal glycosylation of the cellular receptor Angiotensin Converting Enzyme 2 (ACE2) and spike proteins thereby blocking SARS-CoV cell infection at entry and post-entry stages[24,36]. Moreover, both antimalarials also have (mild) immunosuppressive properties and had been successfully repurposed for treatment of rheumatic and auto-immune diseases. Therefore, CQ and its derivative HCQ may have a dual therapeutic effect because one of the distinctive features of the pathophysiology of COVID-19 pneumonia (and ARDS) involves a massive release of cytokines (cytokine storm) leading to lung hyperinflammation[10]. The combined action on two disease-related targets, i.e., inhibition of virus replication (demonstrated *in vitro*) and immunosuppressive/anti-inflammatory action (shown in humans), could potentially make CQ and HCQ unique drugs for severe COVID-19. The severe and life-threatening adverse effects of CQ and HCQ (e.g., retinopathy and irreversible vision lost, cardiac arrhythmias, cardiomiopathy, hearing deficits and tinnitus, shortness of breath, mental disturbances and others) and the narrow margin of safety, however, are a hurdle for their widespread use, particularly to treat the less severe cases of COVID-19[34].

Results from a recently completed small study (pilot open-label RCT) involving 30 patients with confirmed COVID-19 showed no discernible difference in clinical improvement between patients treated with HCQ and those who received conventional therapy only[37]. This study has a number of methodological shortcomings and it is definitely underpowered to evaluate the effectiveness and safety of HCQ for COVID-19.

An observational study (published on 7 May 2020) compared the clinical outcomes in 811 COVID-19 patients who received HCQ with those in COVID-19 (unmatched) patients who did not. A Cox proportional-hazards regression model analysis showed that HCQ was not associated with a significantly higher or lower risk of intubation or death (hazard ratio: 1.04, 95% CI: 0.82 to 1.32)[38]. Results from this observational investigation do not support the use of CQ/HCQ in COVID-19 patients. Nonetheless, owing to the inherent limitations of studies with an observational design (e.g., unmeasured/uncontrolled confoundings and bias) this investigation is not sufficient to ascertain whether or not HCQ is in fact of benefit for COVID-19 patients. Patients treated with HCQ, for instance, might have been those with the most severe manifestations of COVID-19 and poorest prognosis.

The antiviral activities of CQ and HCQ in humans, and their effectiveness in the treatment of COVID-19 and ARDS remain to be proven by large, randomized and placebo-controled studies with masking and concealment of allocation.

Facing a widespread prescription of HCQ and CQ for COVID-19 patients, on April 24th 2020, the US Food and Drug Administration (FDA) issued a warning that it had received reports of serious heart-related adverse events and death in patients with COVID-19 receiving hydroxychloroquine and chloroquine, either alone or combined with azithromycin or other QT prolonging medicines. These adverse events included QT interval prolongation, ventricular tachycardia and ventricular fibrillation, and in some cases, death.

FDA authorized (*Emergency Use Authorization*) CQ-HCQ temporary use only in hospitalized patients with COVID-19 when clinical trials are not available or participation is not feasible[39]. Along the same line, the Brazilian Ministry of Health and National Agency of Sanitary Surveillance (Anvisa) had authorized (on March 27th, 2020) use of CQ and HCQ (strictly under medical prescription) for patients with the most severe manifestations of COVID-19[40,41].

Anthelmintics

Clinical trials on the repurposing of some anthelmintics (Nitazoxanide, NTZ; Ivermectin, IVT; Niclosamide, NCL) for COVID-19 seem to be based on *in vitro* data showing that these compounds inhibit replication of a variety of viruses in cell culture assays. NTZ, for instance, was active in cell culture assays against a broad range of influenza A and B, as well as other RNA and DNA viruses, such as RSV, parainfluenza, coronavirus, rotavirus, norovirus, hepatitis B and C viruses, dengue, yellow fever, Japanese encephalitis and HIV[42]. Likewise, in *in vitro* tests, IVM inhibited the replication of a broad range of viruses (dengue, West Nile virus, HIV, simian SV-40, influenza and others) and strongly repressed SARS-CoV-2 virus replication in Vero-hSLAM

cells[43]. Also in *in vitro* assays, NCL proved to be a potent inhibitor (nanomolar to micromolar range) of replication of SARS-CoV, MERS-CoV, zika virus, hepatitis C virus and human adenovirus[44]. NCL had been reported to be active (*in vitro*) against SARS-CoV at concentrations as low as 1.56 μM in 2003[45].

Contrasting to a direct inhibition of viral replication by NTZ, IVM and NCL, the hypothesis that Levamisole (LVM) could be useful in the prophylaxis and therapy of viral infections is based on its putative immuno-stimulant properties[46]. Several clinical trials (as to 1980) showed no benefit from LVM as compared to placebo in the treatment of herpes simplex virus recurrent infections[46,47,48]. A recent study in piglets, however, indicated that LVM could be useful to prevent intestinal damage in porcine rotavirus diarrhea[49]. At any rate, the scientific evidence supporting the conduction of clinical trials of LVM for COVID-19 is poor. Moreover, the use of LVM as anthelmintic and/or immunomodulator has been discouraged by their immunotoxic side effects and induction of agranulocytosis and neutropenia[50]. A number of cases of agranulocytosis have been reported in users of LVM-tainted cocaine[51].

Immunomodulators and anti-inflammatory agents

Since COVID-19 may elicit massive release of cytokines and pulmonary hyperinflammation, the use of immunosuppressive and anti-inflammatory drugs as adjuvant therapies could be expected[10,52]. Immunosuppression, however, might be a double-edged sword in these cases. Although it is likely to suppress the massive cytokine release syndrome and to mitigate lung inflammation, it may also facilitate viral proliferation, if it is not combined with effective antiviral therapy. Along this line, the open research questions are: how effective the tested anti-inflammatory interventions (with or without concomitant antiviral therapy) are in COVID-19 pneumonia, which is the most effective and safe immunosuppressive and/or anti-inflammatory compound and at which dosage regimen does it produce the best overall clinical response?

As shown in Table 3, a multiplicity of immunosuppressive drugs or therapies have been used to reverse the cytokine release syndrome in COVID-19 trials. The tested immunomodulating and/or anti-inflammatory drugs cover a broad range of compounds and modes of action such as classical glucocorticoids or agonists of glucocorticoid receptor (dexamethasone, methylprednisolone, budesonide), biologicals including some of the newest ones (anti-IL-6 monoclonal antibodies tocilizumab and siltuximab, the antibody against CCR5 receptors on T-lymphocytes leronlimab[53], and an antibody against cytokine fusion protein CD24Fc), ruxolitinib (Janus kinase JAK1 and JAK2 selective inhibitor and blocker of cytokine signalling)[54], thalidomide (inhibitor of production of TNF-α and activation of NF-κB)[55,56], colchicine (tubulin disruption, inhibition of neutrophil chemotaxis, adhesion and mobilization, inhibition of inflammasomes and IL-1β processing and release)[57], sirolimus (a macrolide inhibitor of cytokines transcription and synthesis)[58], piclidenoson (A3 adenosine receptor agonist)[59], tetrandrine (Ca^{2+} channel blocker anti-inflammatory)[60] and non-steroidal antinflammatory agents which are nonselective inhibitors of Cox1 and Cox2 (naproxen, ibuprofen, aspirin). Another immunosuppresive drug tested for COVID-19 is fingolimod, a sphingosine-1-phosphate receptor modulator, which sequesters lymphocytes in lymph nodes, preventing them from contributing to autoimmune reactions. It is mostly used to treat the relapsing form of muliple sclerosis[61]. It is of note that fingolimod-mediated immunodepression has been reported to enhance risks of viral, fungal and bacterial infections, and concerns have been raised regarding influenza infections, reactivation of herpes and varicela-zoster as well as John Cunningham virus, a polyomavirus related to the Progressive Multifocal Leukoencephalopathy[62].

A RCT study (NCT04268537) was designed to investigate whether treatment with thymosin or with PD-1 antibody would attenuate lung injury and improve prognosis of COVID-19 patients with respiratory failure and lymphocytopenia. Thymosin ß4 (a hormone from thymus) stimulates T-lymphocyte production and it is thought to possibly decrease mortality in sepsis via regulation of actin expression and anti-inflammatory actions[63]. Programmed Cell Death Ligand 1 protein (PD-1) is expressed on activated T-cells and PD-1-related blockage (PD-1 antibody) is believed to potentially decrease mortality in sepsis as well[64,65]. This research on the possible beneficial effects of thymosin or PD-1 antibody on critically ill COVID-19 patients seems to be based on the notion that sepsis is often secondary to excessive inflammatory response syndrome and that PD-1 and PDL-1 are key mediators of T-cell depletion in sepsis[64,65].

Moreover, two cytokines (interferons) playing a key role in innate immunity and control of viral infections, i.e., Interferon-lambda (IFN-λ) and Interferon beta (INF-ß), were tested in COVID-19 patients as well. INF-ß regulates the expression of a plethora of genes through the classical JAK/STAT and other pathways thereby eliciting antiviral, antiproliferative and immunomodulatory activities on numerous cell types. It is used to treat hepatitis C infection, multiple sclerosis and other conditions[66]. While acting on the control of viral infections (e.g., chronic hepatitis C) and also establishing a robust innate immunity against cancer, IFN-λ has a restricted cell response pattern and thus it was associated with fewer AE[67]. It has been proposed that administration of pegylated IFN-λ in influenza infections improves respiratory function and survival by reducing overabundance of neutrophils in the lungs. A recent study[68], however, called attention on the fact that IFN-λ, by decreasing neutrophyl motility, may impair bacterial clearance during influenza superinfection and by doing this it might increase the likelihood of a secondary bacterial pneumonia.

Miscellaneous drugs

The use of drugs from a variety of other pharmacological classes are also being tested in COVID-19 clinical trials.

Antifibrinolytics and antithrombotic agents

There have been several reports of strong associations between elevated levels of D-dimer (being a degradation product of

cross-linked fibrina, D-dimer reflects blood clot formation and its subsequent fibrinolysis) and poor prognosis in COVID-19 and, therefore, thrombotic complications (e.g., venous thromboembolism, disseminated intravascular coagulation, thrombosis) are a cause for deep concern[69]. Within this context, use of antithrombotic and fibrinolytic drugs (e.g., defibrotide) or heparin-like anticoagulants (e.g., enoxparin, a low molecular heparin) may be necessary to prevent thromboembolism, particularly, if levels of D-dimer are high[69,70,71]. The rationale for COVID-19 trials investigating the benefits of tranexamic acid (TXA), an antifibrinolytic agent used to prevent or control post-surgical or posttraumatic bleeding[72], however, is not so obvious. One trial of TXA in COVID-19 is based on a hypothesis that an endogenous protease plasmin acts on SARS-CoV-2 cleaving a newly inserted furin site in the virus S protein portion, what could (theoretically) increase its infectivity and virulence (see trial NCT04338126 in www.ClinicalTrials.gov). If so, the suppression of conversion of plasminogen to plasmin by TAX could blunt this process thereby decreasing the infectivity and virulence of SARS-CoV-2 in infected patients. Even though this hypothesis sounds plausible, nonclinical empiric evidence to adequately support it is missing.

Inhibitors of angiotensin-converting enzyme and angiotensin receptor blockers

Two apparently conflicting pharmacological interventions on the renin-angiotensin system are under investigation in distinct COVID-19 trials. A quadruple-blinded RCT trial evaluates whether administration of losartan, a selective competitive angiotensin II receptor (AT_1) blocker (a drug widely used for hypertension), might be beneficial for patients infected by COVID-19. A second RCT (single-blinded) study investigates whether discontinuation of chronic treatment with inhibitors of angiotensin-converting enzyme 2 (ACEI), or with angiotensin-2 receptor blockers (ARB), could improve outcomes in symptomatic SARS-CoV-2-infected patients. Both experimental interventions are ultimately based on the observation that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as the receptor binding domain for its spike protein[73,74]. Thus, it is believed that angiotensin-converting enzyme 2 (ACE2) is likely to be a functional receptor for SARS-CoV-2 to enter host target cells.

Experimental studies showed that continued treatments with ARB, as losartan, or ACEI, as captopril and enalapril, upregulate the expression of ACE2 receptors and theoretically might increase the morbidity and mortality of COVID-19[75]. However, studies in mice also indicated that, paradoxically, ARB could also have a protective effect against COVID-19 pneumonia and ARDS because ARB prevented aggravation of lung injury in mice infected with a similar virus (SARS-CoV-1 involved in 2002-2003 outbreak)[75,76,77]. It should be pointed out that, to date, there is no clinical or experimental indication that ARB or ACEI either increase the susceptibility to SARS-CoV-2 or aggravate the severity of clinical outcomes of COVID-19.

Also, based on this notion, another trial investigates the effectiveness of a recombinant antibody against human angiotensin-converting enzyme 2 (rhACE2) to block SARS-CoV-2 entry into cells and to inhibit viral replication in COVID-19 patients.

Antiarrhythmics

The antiarrhythmic drugs (ion channel blockers) verapamil and amiodarone were reported to block Filoviridae (e.g., Ebola and Marburg viruses) cell entry in cell culture tests[78]. Based on the foregoing non-clinical evidence, a clinical trial is in progress to investigate whether they are effective against SARS-CoV-2 as well (Table 3).

Mucolytics and bronchodilators

Mucolytics as bromhexine and compounds that decrease the resistance in the respiratory airway, thereby increasing airflow to the lungs (e.g., long-acting selective β_2-adrenergic agonists, as formeterol), are commonly used to treat pulmonary obstructive conditions such as asthma, chronic obstructive pulmonary disease (COPD) and others[79,80]. The therapeutic potential of bromhexine and formeterol as well as that of inhaled nitric oxide (NO), a reported selective pulmonary vasodilator[81], were tested in COVID-19 patients.

Traditional Chinese Medicine and other interventions

A few RCT COVID-19 trials investigate the effectiveness of traditional chinese medicine (TCM) remedies as adjunct therapies to the standard of care. A variety of other modern medicine drugs are under investigation for COVID-19 as well. Serine protease inhibitors (camostat mesylate and nafamostat mesylate) are under clinical testing for COVID-19. Serine protease inhibitors exhibit anti-inflammatory activity (through blockage of NF-κB signalling pathways), anticoagulant, anticancer and potential antiviral (against Ebola virus) properties[82,83,84]. Diurectics (spironolactone), symvastatin (inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase, a cholesterol-lowering statin), nintedanid (intracelular tyrosine kinase inhibitor used to slow progression of idiopathic pulmonary fibrosis), thyroid hormone T3 (triiodothyronine), high doses of vitamins D and C, deferoxamine (medication that binds iron and aluminium in the blood and enhance their elimination via urine), cobicistat (potent inhibitor of CYP3A subfamily enzymes; although lacking antiviral activity, cobicistat is combined to anti-HIV compounds to slow down their clearance)[85] and vagezepant (a small molecule calcitonin gene-related peptide-CGRP-receptor antagonist used in the treatment of migraine)[86,87]. Manufacturers of vagezepant have claimed that their drug might mitigate lung hyperimmune response in COVID-19 and thus this hypothesis is under investigation in a study (by intranasal route) in hospitalized patients requiring supplemental oxygen.

Strengths and weaknesses of COVID-19 drug trials

As aforementioned, this analysis of clinical trials, addressing drugs potentially repurposable for COVID-19, covers only studies involving more than one arm and that are randomized and controlled. Information avaliable on the *ClinicalTrials.gov* registry

database is rather limited and does not allow in depth and meticulous evaluations of the design and methodological quality of the study. Nonetheless, in a first-round to separate the wheat from the chaff, to keep only the wheat, we examined some study-design key features such as masking, type of comparators and number of participants. Of 294 included trials, 150 (51.0%) were open label (no masking) studies and 26 (8.8%) were single-blinded (participant, investigator or assessor only), so that only 40.1% seemed to have been properly masked (i.e., double-, triple- or quadruple-blinded) (Table 1). Open label studies and those with insufficient or inadequate masking and concealment of randomization entail a high risk of bias. Since under these study conditions clinical outcomes are likely to be influenced by investigators' and or participants' expectations, these not adequately blinded approaches do not yield robust evidence on drug effectiveness and safety. Another drawback of most controlled clinical trials of drugs for COVID-19 is the type of comparator chosen by investigators. Whenever there is no proven effective treatment for the disease (i.e., there is no "active" comparator), trials are expected to be placebo-controlled. Many included studies, however, used standard of care (no intervention arm) with no placebo for the drug as the inactive comparator. Even worse is to compare the intervention under testing with another drug of undemonstrated effectiveness against COVID-19 (e.g., chloroquine/hydroxychloroquine). Therapies of unproven efficacy are by no means suitable "active" comparators for a drug monotherapy or a drug combination under testing. In the set of clinical trials examined in this study, the "standard of care" or no intervention arm at times included drugs of unproven or questionable efficacy for COVID-19.

Adequate sample size estimation in clinical trials is crucial for the robustness of the evidence on drug efficacy and safety for a given therapeutic indication. As shown in Tables 2 and 3, sample sizes of COVID-19 trials ranged from a couple of tenths to thousands. The *ClinicalTrials.gov* registry data did not provide study-design details needed for examining the adequacy of the estimated trial sample size. However, some of the studies enrolled so few participants that they are definitely underpowered to produce any robust evidence of drug effectiveness and safety in COVID-19 patients.

In summary, notwithstanding the multiplicity of clinical studies of medications for COVID-19, only a minority of them (RCT), which are sufficiently large, randomized, placebo-controlled and designed with masking and concealment of allocation, are likely to yield robust evidence on potential benefits for infected patients.

Ethical issues

Ethically, there is a great divide between conducting expeditiously clinical studies on drug effectiveness (and safety) and rushing into trials in COVID-19 patients without a plausible hypothesis and appropriate evidence of safety. The COVID-19 health emergency is by no means a carte blanche for neglecting the ethical standards for clinical research.

An article by Emanuel et al.[88] listed seven conditions that need to be met to make ethical a clinical trial. The analysis of registered study protocols led to the conclusion that at least two of these conditions (scientific validity and favourable risk-benefit ratio) are not fully met in most COVID-19 clinical trials. As explained in the previous section, many trials on drugs for COVID-19 suffer from methodological shortcomings that weaken their power to demonstrate that the drugs are effective and safe for this disease. For instance, trials not testing a clear and scientifically founded hypothesis that are poorly designed (e.g., single arm, nonramdomized, open label) and do not have enough power to definitely respond the research question, do not meet scientific validity requirements. Moreover, of particular concern is the apparently unfavorable drug risk-benefit ratio in several of planned and ongoing trials. This is illustrated by some trials of CQ and HCQ in COVID-19. Both are drugs with narrow MOS that may cause serious AE such as irreversible vision loss, cardiac arrhythmias and death. Since most COVID-19 patients (80.0%) are oligosymptomatic achieving spontaneous cure within two weeks and antiviral activity of these antimalarials in humans remains unproven, it is fair to think that risk-benefit ratio of CQ/HCQ in preventive (prophylatic) intervention trials is unfavorable. For mild COVID-19 patients, risks of severe adverse effects would certainly outweigh the potential health benefits of disease prevention or treatment, even if CQ/HCQ were in fact effective antiviral drugs.

CONCLUSIONS

Ongoing and planned clinical trials of drug repurposing for COVID-19 address the primary treatment of the disease (inhibitors of viral replication) as well as adjunct therapies for resolution of hyperinflammation in pneumonia and thromboembolism associated with SARS-CoV-2 infection.

So far, no antiviral pharmacological intervention has proved to be effective against SARS-CoV-2 in humans. Virtually all existing antiviral compounds, and a multiplicity of modes of action which work against other viruses are under investigation. Antiparasitic drugs which inhibited viral replication in cell culture assays and new SARS-CoV-2 specific modes of action (e.g., rhACE2, TXA) are being tested as well.

As far as adjunctive immunomodulatory, anti-inflammatory and antithrombotic therapies are concerned, a number of drugs with different pharmacological targets are being used and tested in clinical trials mostly in severe cases of COVID-19. Strictly speaking, most of these drugs are not being repurposed for COVID-19, because their therapeutic effectiveness (e.g., glucocorticoids and others) has already been demonstrated for inflammation and thromboembolism in a wide variety of diseases and medical conditions and it is fair to assume that they shall work in COVID-19 infection complications as well. Collectively, the outcomes of these trials are expected to contribute to find out the best timing for the intervention, the most effective and safe drugs and dose regimens to be used, and to evaluate the relevance of the intervention for resolution

of severe COVID-19. Certainly, they will yield empiric information of value to update evidence-based clinical guidelines for COVID-19.

Finally, although a large number of clinical studies of drugs for primary treatment of COVID-19 are planned or in progress, only a minority of them are large, randomized and placebo-controlled trials with masking and concealment of allocation. Therefore, only a few of these studies are likely to produce robust clinical evidence of antiviral drug efficacy and safety for dealing with COVID-19 pandemic. Five months or so after SARS-CoV-2 emergence as a deadly pandemic, antiviral drug therapy is more and more unlikely to "change the game" in a timely manner along this first wave of COVID-19. Effective and safe vaccines seem to be the best guess for the coming years. Currently, old and proven effective behavioral approaches such as social-distancing and quarantine continue to be public health scientists' most powerful weapons to fight against the pandemic.

REFERENCES

1. Knobler S, Mahamoud A, Lemon S, Mack A, Sivitz L, Oberholtzer K, editors. Learning from SARS: preparing for the next disease outbreak. Washington: National Academies; 2004.
2. Gensini GF, Yacoub MH, Conti AA. The concept of quarantine in history: from plague to SARS. J Infect. 2004;49(4):257-61. https://doi.org/10.1016/j.jinf.2004.03.002
3. Moscona A. Neuraminidase inhibitors for influenza. N Engl J Med. 2005;353(13):1363-73. https://doi.org/10.1056/NEJMra050740
4. McKimm-Breschkin JL. Influenza neuraminidase inhibitors: antiviral action and mechanisms of resistance. Influenza Other Respir Viruses. 2013;7(Suppl 1):25-36. https://doi.org/10.1111/irv.12047
5. Ebell MH. WHO downgrades status of oseltamivir. BMJ. 2017;358:j3266. https://doi.org/10.1136/bmj.j3266
6. Jefferson T, Jones M, Doshi P, Spencer EA, Onakpoya I, Heneghan CJ. Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments. BMJ. 2014;348:1-2. https://doi.org/10.1136/bmj.g2545
7. Heneghan CJ, Onakpoya I, Jones MA, Doshi P, Del Mar CB, Hama R et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. Health Technol Assess. 2016;20(42):1-242. https://doi.org/10.3310/hta20420
8. Saha M, Bhattacharya S. A brief overview on HIV infection, diagnosis and treatment. Curr Top Med Chem. 2019;19(30):2739-41. https://doi.org/10.2174/1568026619302001030913335
9. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019;18(1):41-58. https://doi.org/10.1038/nrd.2018.168
10. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clin Immunol. 2020;1-7. https://doi.org/10.1016/j.clim.2020.108427
11. World Health Organization – WHO. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). Brussels: World Health Organization; 2020[access 2020 Apr 25]. Available at: https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
12. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate COVID-19. N Engl J Med. 2020 Apr. 24. https://doi.org/10.1056/NEJMcp2009249
13. Lefebvre E, Schiffer CA. Resilience to resistance of HIV-1 protease inhibitors: profile of darunavir. AIDS Rev. 2008;10(3):131-42.
14. Pharmaceutical Business Review Staff Writer. Ascletis receives IND approval for its HIV drug ASC09F. Pharmaceutical Business Review News. Apr 14, 2020[access 2020 May 4]. Available at: http://www.prnewswire.com/news-releases/ascletis-receives-ind-approval-for-its-hivdrug-asc09f-301039297.html
15. Velkov T, Carbone V, Akter J, Sivanesan S, Li J, Beddoe T et al. The RNA-dependent-RNA polymerase, an emerging antiviral drug target for the hendra virus. Curr Drug Targets. 2014;15(1):103-13. https://doi.org/10.2174/1389450114888131204163210
16. Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem. 2020. https://doi.org/10.1074/jbc.RA120.013679
17. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL et al. T-705 (favipiravir) and related compounds: novel broad-spectrum inhibitors of RNA viral infections. Antiviral Res. 2009;82(3):95-102. https://doi.org/10.1016/j.antiviral.2009.02.198
18. Khalili JS, Zhu H, Mak NSA, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: groundwork for an evaluation concerning COVID-19. J Med Virol. 2020:1-7. https://doi.org/10.1002/jmv.25798
19. Wang X, Cao R, Zhang H, Liu J, Xu M, Hu H et al. The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro. Cell Discov. 2020;6:1-7. https://doi.org/10.1038/s41421-020-0169-8
20. Haviernik J, Štefánik M, Fojtíková M, Kali S, Tordo N, Rudolf I et al. Arbidol (umifenovir): a broad-spectrum antiviral drug that inhibits medically important arthropod-borne flaviviruses. Viruses. 2018;10(4):1-8. https://doi.org/10.3390/v10040184
21. Clercq E, Li G. Approved antiviral drugs over the past 50 years. Clin Microbiol Rev. 2016;29(3):695-747. https://doi.org/10.1128/CMR.00102-15

22. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K et al. Identification of severe acute respiratory syndrome in Canada. N Engl J Med. 2003;348(20):1995-2005. https://doi.org/10.1056/NEJMoa030634
23. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med. 2017;9(396):1-20. https://doi.org/10.1126/scitranslmed.aal3653
24. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020;30(3):269-71. https://doi.org/10.1038/s41422-020-0282-0
25. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med. 2020:1-10. https://doi.org/10.1056/NEJMoa2007016
26. Idrus AA. Gilead's remdesivir speeds COVID-19 recovery in first controlled trial readout, but it's no 'silver bullet'. Fierce Biotech. Apr 29, 2020[access 2020 Apr 20]. Available at: https://www.fiercebiotech.com/biotech/silver-bullet
27. Hirschmann JV. Antibiotics for common respiratory tract infections in adults. Arch Intern Med. 2002;162(3):256-64. https://doi.org/10.1056/NEJMoa2007016
28. Shiley KT, Lautenbach E, Lee I. The use of antimicrobial agents after diagnosis of viral respiratory tract infections in hospitalized adults: antibiotics or anxiolytics? Infect Control Hosp Epidemiol. 2010;31(11):1177-83. https://doi.org/10.1086/656596
29. Krantz EM, Zier J, Stohs E, Ogimi C, Sweet A, Marquis S et al. Antibiotic prescribing and respiratory viral testing for acute upper respiratory infections among adult patients at an ambulatory cancer center. Clin Infect Dis. 2020;70(7):1421-8. https://doi.org/10.1093/cid/ciz409
30. The National Institute for Health and Care Excellence - NICE. COVID-19 rapid guideline: managing suspected or confirrmed pneumonia in adults in the community. NICE Guideline. Apr 26, 2020[access 2020 Apr 30]. Available at: www.nice.org.uk/guidance/NG165
31. Boersma WG. Antibiotics in acute exacerbations of copd: the good, the bad and the ugly. Eur Respir J. 2012;40(1):1-3. https://doi.org/10.1183/09031936.00211911
32. Huckle AW, Fairclough LC, Todd I. Prophylactic antibiotic use in copd and the potential anti-inflammatory activities of antibiotics. Respir Care. 2018;63(5):609-19. https://doi.org/10.4187/respcare.05943
33. Cawcutt KA, Kalil AC. Viral and bacterial co-infection in pneumonia: do we know enough to improve clinical care? Crit Care. 2017;21(1):1-2. https://doi.org/10.1186/s13054-016-1592-y
34. Paumgartten FJR, Delgado IF, Pittta LR, Oliveira ACAX. Chloroquine and hydroxychloroquine repositioning in times of COVID-19 pandemics, all that glitters is not gold. Cad Saude Publica. 2020;36(5):1-3. https://doi.org/10.1590/0102-311X00088520
35. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003;3:722-7. https://doi.org/10.1016/s1473-3099(03)00806-5
36. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J. 2005;2:1-10. https://doi.org/10.1186/1743-422X-2-69
37. Chen J, Liu D, Liu L, Liu P, Xu Q, Xia L et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ (Med Sci). 2020;49(1):215-9. https://doi.org/10.3785/j.issn.1008-9292.2020.03.03
38. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, Hripcsak G et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. N Engl J Med. 2020:1-8. https://doi.org/10.1056/NEJMoa2012410
39. US Food and Drug Administration – FDA. Hydroxychloroquine or chloroquine for COVID-19: drug safety communication: FDA cautions against use outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Washington: US Food and Drug Administration; 2020[access 2020 May 1]. Available at: https://www.fda.gov/safety/medical-product-safety-information/hydroxychloroquine-or-chloroquine-covid-19-drug-safety-communication-fda-cautions-against-use
40. Ministério da Saúde (BR). Nota informativa Nº 5, de 26 de março de 2020. Uso da cloroquina como terapia adjuvante no tratamento de formas graves do COVID-19. Diário Oficial União. 2020 mar 27.
41. Agência Brasileira de Vigilância Sanitária - Anvisa. Entenda a liberação de cloroquina e hidroxicloroquina. Notícias Novo Coronavirus. Mar 31, 2020[access 2020 May 2]. Available at: http://portal.anvisa.gov.br/resultado-de-busca?x=0&y=0&_3_keywords=cloroquina&_3_formDate=1441824476958&p_p_id=3&p_p_lifecycle=0&p_p_state=normal&p_p_mode=view&_3_groupId=0&_3_struts_action=%2Fsearch%2Fsearch&_3_cur=1&_3_format=
42. Rossignol JF. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. Antiviral Res. 2014;110:94-103. https://doi.org/10.1016/j.antiviral.2014.07.014
43. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020;178:1-4. https://doi.org/10.1016/j.antiviral.2020.104787
44. Xu J, Shi PY, Li H, Zhou J. Broad spectrum antiviral agent niclosamide and its therapeutic potential. ACS Infect Dis. 2020;6(5):909-15. https://doi.org/10.1021/acsinfecdis.0c00052
45. Wu CJ, Jan JT, Chen CM, Hsieh HP, Hwang DR, Liu HW et al. Inhibition of severe acute respiratory syndrome coronavirus replication by niclosamide. Antimicrob Agents Chemother. 2004;48(7):2693-6. https://doi.org/10.1128/AAC.48.7.2693-2696.2004

46. Russell AS. Use of levamisole in viral infections. Drugs. 1980;20:117-21. https://doi.org/10.2165/00003495-198020020-00004
47. Spruance SL, Krueger GG, MacCalman J, Overall Jr JC, Klauber MR. Treatment of recurrent herpes simplex labialis with levamisole. Antimicrob Agents Chemother. 1979;15(5):662-5. https://doi.org/10.1128/aac.15.5.662
48. Chi CC, Wang SH, Delamere FM, Wojnarowska F, Peters MC, Kanjirath PP. Interventions for prevention of herpes simplex labialis (cold sores on the lips). Cochrane Database Syst Rev. 2015;(8):1-73. https://doi.org/10.1002/14651858.CD010095.pub2
49. Chethan GE, De UK, Garkhal J, Sircar S, Malik YPS, Sahoo NR et al. Immunomodulating dose of levamisole stimulates innate immune response and prevents intestinal damage in porcine rotavirus diarrhea: a restricted-randomized, single-blinded, and placebo-controlled clinical trial. Trop Anim Health Prod. 2019;51(6):1455-65. https://doi.org/10.1007/s11250-019-01833-1
50. Johnson AG, Regal J. Immunotoxicity of immunotherapeutic agents. Springer Semin Immunopathol. 1985;8(4):347-59. https://doi.org/10.1007/BF01857389
51. Czuchlewski DR, Brackney M, Ewers C, Manna J, Fekrazad MH, Martinez A et al. Clinicopathologic features of agranulocytosis in the setting of levamisole-tainted cocaine. Am J Clin Pathol. 2010;133(3):466-72. https://doi.org/10.1309/AJCPOPQNBP5THKP1
52. Lee DW, Gardner R, Porter DL, Louis CU, Ahmed N, Jensen M et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124(2):188-95. https://doi.org/10.1182/blood-2014-05-552729
53. Miao M, Clercq E, Li G. Clinical significance of chemokine receptor antagonists. Expert Opin Drug Metab Toxicol. 2020;16(1):11-30. https://doi.org/10.1080/17425255.2020.1711884
54. Wang A, Singh K, Ibrahim W, King B, Damsky W. The promise of JAK inhibitors for treatment of sarcoidosis and other inflammatory disorders with macrophage activation: a review of the literature. Yale J Biol Med. 2020;93(1):187-95.
55. Sampaio EP, Carvalho DS, Nery JAC, Lopes UG, Sarno EM. Thalidomide: an overview of its pharmacological mechanisms of action. Antiinflamm Antiallergy Agents Med Chem. 2006;5(1):71-7. https://doi.org/10.2174/187152306775537337
56. Yasui K, Kobayashi N, Yamazaki T, Agematsu K. Thalidomide as an immunotherapeutic agent: the effects on neutrophil-mediated inflammation. Curr Pharm Des. 2005;11(3):395-401. https://doi.org/10.2174/1381612053382179
57. Leung YY, Hui LLY, Kraus VB. Colchicine: update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45(3):341-50. https://doi.org/10.1016/j.semarthrit.2015.06.013
58. Kahan BD. Sirolimus: a comprehensive review. Expert Opin Pharmacother. 2001;2(11):1903-17. https://doi.org/10.1517/14656566.2.11.1903
59. Silverman MH, Strand V, Markovits D, Nahir M, Reitblat T, Molad Y et al. Clinical evidence for utilization of the A3 adenosine receptor as a target to treat rheumatoid arthritis: data from a phase II clinical trial. J Rheumatol. 2008;35(1):41-8.
60. Li DG, Wang ZR, Lu HM. Pharmacology of tetrandrine and its therapeutic use in digestive diseases. World J Gastroenterol. 2001;7(5):627-9. https://doi.org/10.3748/wjg.v7.i5.627
61. Epstein DJ, Dunn J, Deresinski S. Infectious complications of multiple sclerosis therapies: implications for screening, prophylaxis, and management. Open Forum Infect Dis. 2018;5(8):1-8. https://doi.org/10.1093/ofid/ofy174
62. D'Amico E, Zanghì A, Leone C, Tumani H, Patti F. Treatment-related progressive multifocal leukoencephalopathy in multiple sclerosis: a comprehensive review of current evidence and future needs. Drug Saf. 2016;39(12):1163-74. https://doi.org/10.1007/s40264-016-0461-6
63. Belsky JB, Rivers EP, Filbin MR, Lee PJ, Daniel C, Morris DC. Thymosin beta 4 regulation of actin in sepsis. Expert Opin Biol Ther. 2018;18(Suppl. 1):193-7. https://doi.org/10.1080/14712598.2018.1448381
64. Zhang Q, Qi Z, Liu B, Li CS. Programmed cell death-1: programmed death-ligand 1 blockade improves survival of animals with sepsis: a systematic review and meta-analysis. Biomed Res Int. 2018:1-8. https://doi.org/10.1155/2018/1969474
65. Chang K, Svabek C, Vazquez-Guillamet C, Sato B, Rasche D, Wilson S et al. Targeting the programmed cell death 1: programmed cell death ligand 1 pathway reverses T cell exhaustion in patients with sepsis. Crit Care. 2014;18(1):1-8. https://doi.org/10.1186/cc13176
66. Hosseini-Moghaddam SM, Mousavi A, Alavian SM. Is ß-interferon a promising therapeutic option for the management of hepatitis C? *J Antimicrob Chemother.* 2009;63(6):1097-103. https://doi.org/10.1093/jac/dkp092
67. Lasfar A, Zloza A, Cohen-Solal KA. IFN- λ therapy: current status and future perspectives. Drug Discov Today. 2016;21(1):167-71. https://doi.org/10.1016/j.drudis.2015.10.021
68. Rich HE, McCourt CC, Zheng WQ, McHugh KJ, Robinson KM, Wang J et al. Interferon λ inhibits bacterial uptake during influenza superinfection. Infect Immun. 2019;87(5):1-12. https://doi.org/10.1128/IAI.00114-19
69. Oudkerk M, Büller HR, Kuijpers D, Es N, Oudkerk SF, McLoud TC et al. Diagnosis, prevention, and treatment of thromboembolic complications in COVID-19: report of the national institute for public health of the Netherlands. Radiology. 2020:1-15. https://doi.org/10.1148/radiol.2020201629
70. Richardson PG, Ho VT, Giralt S, Arai S, Mineishi S, Cutler C et al. Safety and efficacy of defibrotide for the treatment of severe hepatic veno-occlusive disease. Ther Adv Hematol. 2012;3(4):253-65. https://doi.org/ 10.1177/2040620712441943
71. Richardson PG, Soiffer RJ, Antin JH, Uno H, Jin Z, Kurtzberg J et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. Biol Blood Marrow Transplant. 2010;16(7):1005-17. https://doi.org/10.1016/j.bbmt.2010.02.009

72. Cai J, Ribkoff J, Olson S, Raghunathan V, Al-Samkari H, DeLoughery TG et al. The many roles of tranexamic acid: an overview of the clinical indications for TXA in medical and surgical patients. Eur J Haematol. 2020;104(2):79-87. https://doi.org/10.1111/ejh.13348

73. Luan J, Lu Y, Jin X, Zhang L. Spike protein recognition of mammalian ACE2 predicts the host range and an optimized ACE2 for SARS-CoV-2 infection. Biochem Biophys Res Commun. 2020;526(1):165-9. https://doi.org/10.1016/j.bbrc.2020.03.047

74. Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z et al. Structural and functional basis of SARS-CoV-2 entry by using human ACE2. Cell. 2020;18(4):894-904. https://doi.org/10.1016/j.cell.2020.03.045

75. Kai H, Kai M. Interactions of coronaviruses with ACE2, angiotensin II, and RAS inhibitors: lessons from available evidence and insights into COVID-19. Hypertens Res. 2020:1-7. https://doi.org/10.1038/s41440-020-0455-8

76. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020:1-4. https://doi.org/10.1002/ddr.21656

77. Patel AB, Verma A. COVID-19 and angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what is the evidence? JAMA. 2020:1-2. https://doi.org/10.1001/jama.2020.4812

78. Gehring G, Rohrmann K, Atenchong N, Mittler E, Becker S, Dahlmann F et al. The clinically approved drugs amiodarone, dronedarone and verapamil inhibit filovirus cell entry. J Antimicrob Chemother. 2014;69(8):2123-31. https://doi.org/10.1093/jac/dku091

79. Scaglione F, Petrini O. Mucoactive agents in the therapy of upper respiratory airways infections: fair to describe them just as mucoactive? Clin Med Insights Ear Nose Throat. 2019;12:1-9. https://doi.org/10.1177/1179550618821930

80. Steiropoulos P, Tzouvelekis A, Bouros D. Formoterol in the management of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2008;3(2):205-15. https://doi.org/10.2147/copd.s1059

81. Ichinose F, Roberts Jr JD, Zapol WM. Inhaled nitric oxide: a selective pulmonary vasodilator: current uses and therapeutic potential. Circulation. 2004;109(25):3106-11. https://doi.org/10.1161/01.CIR.0000134595.80170.62

82. Chen X, Xu Z, Zeng S, Wang X, Liu W, Qian L et al. The molecular aspect of antitumor effects of protease inhibitor nafamostat mesylate and its role in potential clinical applications. Front Oncol. 2019;9:1-12. https://doi.org/10.3389/fonc.2019.00852

83. Nishimura H, Yamaya M. A synthetic serine protease inhibitor, nafamostat mesilate, is a drug potentially applicable to the treatment of ebola virus disease. Tohoku J Exp Med. 2015;237(1):45-50. https://doi.org/10.1620/tjem.237.45

84. Yamaya M, Shimotai Y, Hatachi Y, Kalonji NL, Tando Y, Kitajima Y et al. The serine protease inhibitor camostat inhibits influenza virus replication and cytokine production in primary cultures of human tracheal epithelial cells. Pulm Pharmacol Ther. 2015;33:66-74. https://doi.org/10.1016/j.pupt.2015.07.001

85. Deeks ED. Cobicistat: a review of its use as a pharmacokinetic enhancer of atazanavir and darunavir in patients with HIV-1 infection. Drugs. 2014;74(2):195-206. https://doi.org/10.1007/s40265-013-0160-x

86. Moreno-Ajona D, Pérez-Rodríguez A, Goadsby PJ. Gepants, calcitonin-gene-related peptide receptor antagonists: what could be their role in migraine treatment? Curr Opin Neurol. 2020;33(3):309-15. https://doi.org/10.1097/WCO.0000000000000806

87. Dubowchik GM, Conway CM, Xin AW. Blocking the CGRP pathway for acute and preventive treatment of migraine: the evolution of success. J Med Chem. 2020. https://doi.org/10.1021/acs.jmedchem.9b01810

88. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA. 2000;283(20):2701-11. https://doi.org/10.1001/jama.283.20.2701

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Authors' Contribution

PaumgarttenI FJR – Conception, planning (study design), acquisition, analysis, data interpretation and writing of the work. Delgado IF, Pitta LR, Oliveira ACAX - Conception, planning (study design), acquisition, analysis, data interpretation. All authors approved the final version of the work.

Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.