Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Anti-infective therapy against SARS-CoV-2: some light at the end of the tunnel?

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Many examples of scientific accomplishments related to severe infectious diseases have been reported over the past decades. The HIV pandemic provides an illustration of the process for the discovery of antiviral therapies [1]. Compared to previous pandemics, the scientific and medical responses to Coronavirus Disease 2019 (COVID-19) have been amazingly swift, with more than 50,000 reports being published in the first months of the outbreak. However, no licensed anti-infectives are currently available for *Coronaviridae* therapy, and the conventional approach is based on alleviating clinical signs and providing supportive care. Where do we stand today in the race for developing drug regimens against the SARS-CoV-2 virus? The current paper attempts to summarise the trends in the development of anti-infective medications to counter the virus.

The SARS-CoV-2 virus belongs to the large *Coronaviridae* family, genus *Betacoronavirus*, subgenus *Sarbecovirus*. This organism possesses an unsegmented single-stranded RNA structure with four major structural proteins: nucleocapsid (N), spike (S), membrane (M) and envelope (E) [2–6]. The first step of the SARS-Cov-2 infection cycle starts with direct binding of the S-glycoprotein to the host angiotensin-covering enzyme 2 (ACE2) receptor (which is more highly expressed in the oral cavity than in the lung). This allows a change in S-glycoprotein conformation and cathepsin-L proteolysis of the S-glycoprotein to allow fusion between viral and host cell membranes. The next steps include endocytosis, which allows the release of the viral nucleocapsid into the cytosol of the infected cell, viral replication of RNA and protein syntheses, assembly of new viruses and their exocytosis [2–6]. Each step of SARS-CoV-2 replication is a potential target for anti-infective agents (Figure) [2–6].

Most of the treatment options and proposed strategies rely on repurposed drugs that have demonstrated in vitro activity against other coronaviruses during previous (SARS-CoV and MERS-CoV) outbreaks. Their effects against other emerging pathogens, mainly the Zika and Ebola viruses, have also led to the proposal of new antiviral medications [2]. These repositioning strategies could be considered time-saving approaches in the time-sensitive search for a COVID-19 therapy [6]. Finally, large in vitro screening tests are also being used to identify additional medications for the treatment of SARS-CoV-2, but it might be several years before emergence of new antiviral agents.

The methodology used in the previous studies deserves comment. The number of well-conducted randomised controlled trials remains scarce, regardless of the medications studied. A large heterogeneity in endpoints should be stressed in randomised and cohort studies: single or composite endpoints, clinical criteria (such as clinical improvement or worsening using various scales, death rate analysed at various dates, mechanical ventilation and/or its duration, delay of resolution of the symptoms), virological criteria (such as viral titre at various dates, negative PCR, duration of viral clearance), and safety outcomes (including adverse events). From the physician perspective, these various clinical surrogate endpoints question the potential therapeutic benefits of most evaluated drugs [7,8]. These structural deficiencies have been observed among many randomised clinical trials, but most cohorts share the same inconsistencies.

Several classes of well-known antiviral agents, such as oseltamivir, acyclovir, ganciclovir and ribavirin do not demonstrate any effect on SARS-CoV-2 [2,3]. Additional investigations are pending, such as a phase 1 study evaluating an inhaled ribavirin formulation for adult COVID-19 patients with respiratory distress [NCT04356677]. Among antiviral agents, targeted enzyme inhibitors (RNA-dependent RNA polymerase (RdRP) inhibitors and protease inhibitors) are being investigated in the search for potential activity against SARS-CoV-2 (Table) [2,3,5,6]. Remdesivir, initially developed for the Ebola virus, has demonstrated promising effects against SARS-CoV-2. While initial results did not show any improvement in symptoms or a reduction in mortality rate [9], preliminary results of the Adaptive COVID-19 Treatment Trial showed a shorter recovery time in the remdesivir group [10]. Recently, the United States of America Food and Drug Administration (US FDA) broadened the scope of the emergency use of remdesivir [11].

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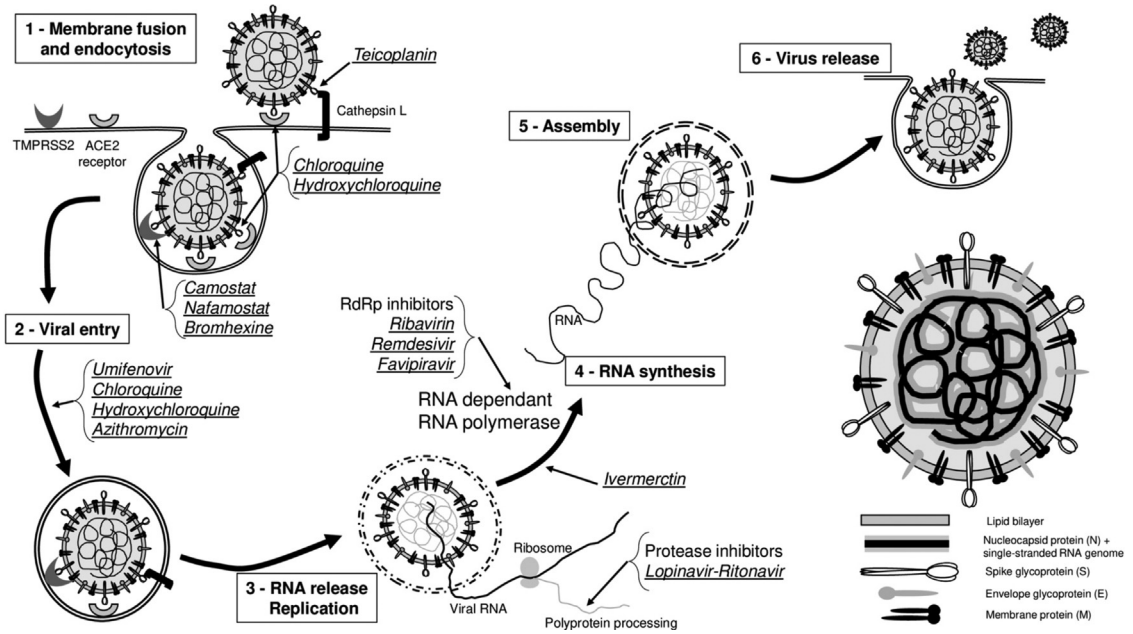

Fig. 1. SARS-CoV2 virus structure and possible therapeutic targets based on its structure, adapted from [2–6].
ACE:Angiotensin-converting enzyme 2 ; TMPRSS2: Transmembrane serine protease 2

In an open-label, randomised, controlled trial, patients treated with interferon-alfa and favipiravir, another RdRP inhibitor already approved for the treatment of influenza and tested against Ebola, had a shorter viral clearance time and a higher improvement rate, as determined by chest imaging [6]. Disappoint results have been achieved with protease inhibitors, another large category of medications that have investigated for their effects against SARS-CoV-2. The optimism surrounding lopinavir/ritonavir, a combination therapy of protease inhibitors initially used for HIV infection, was not confirmed, as the results were inconclusive [2,3,5,6]. Transmembrane protease serine 2 (TMPRSS2) is a serine protease required for the entry of SARS-CoV-2 into host cells and, as such, could be a potential target. Three TMPRSS2 inhibitors (camostat mesylate, used for pancreatitis in Japan, nafamostat, and bromhexine, used as a generic mucolytic) are currently under investigation in humans [6]. Umifenovir is an anti-influenza drug that acts as an ACE2 membrane fusion inhibitor. Only a small single-centre retrospective cohort has suggested that umifenovir decreases viral load more rapidly than lopinavir/ritonavir [6]. The currently available data are inconclusive in supporting its use [3,6].

Antibiotic agents have also demonstrated potential antiviral activity against SARS-CoV-2 (Table) [2–6]. Teicoplanin, a glycopeptide used for years against aerobic Gram-positive bacteria, inhibits S-glycoprotein cleavage by cathepsin-L. In vitro data suggest that teicoplanin exerts a 10-20-fold more potent inhibitory effect on protease capacity than other drugs [12]. Teicoplanin has been used as adjunctive therapy in a small cohort of 21 ICU patients, but no clinical trial is currently ongoing [13]. Two recently released lipopeptides (dalbavancin) and semisynthetic glycopeptides (oritavancin) with effects against Gram-positive bacteria have been shown to exert inhibitory effects against cathepsin-L in SARS-CoV and MERS-CoV in vitro and could be of interest for COVID-19 treatment. Azithromycin, a common antibiotic, has been used as an adjunctive therapy combined with hydroxychloroquine [2–6] because of its in vitro activity against the Zika and Ebola viruses, but proof of its activity against SARS-CoV-2 is scarce. Its use in association with hydroxychloroquine was initially justified to prevent bacterial superinfection [14]. Subsequent analyses of retrospective and prospective cohorts did not demonstrate any benefit, and azithromycin has even been shown to be associated with detrimental effects [2–6].

Antiparasitic drugs have also demonstrated interesting antiviral capacities (Table) [2–6]. Chloroquine and hydroxychloroquine are anti-malarial quinolines that increase the endosomal pH and inhibit the fusion of SARS-CoV-2 and host membranes, leading to impaired recognition of the ACE2 receptor by the virus. Both agents share similar antiviral activities, with hydroxychloroquine showing less toxicity than chloroquine. After the initial results of a retrospective analysis suggested that the combination of hydroxychloroquine and azithromycin has potential benefits [14] and because of the large controversies associated with this drug, several trials have been conducted, and many retrospective and prospective cohorts have been analysed. The first results did not show any significant difference in mortality rate or any evidence of a beneficial effect of this combination [2–6]. A meta-analysis reported that the combination of hydroxychloroquine and azithromycin significantly increased mortality in 11,932 hospitalised COVID-19 patients [15]. Recently, the US FDA issued a safety warning regarding the use of chloroquine and hydroxychloroquine for COVID-19 due to reports of serious heart rhythm problems [16] and has revoked their emergency use authorisation [17]. Ongoing prospective randomised control trials involving azithromycin with hydroxychloroquine will provide definitive insights into the safety and efficacy of this combination therapy [2–6].

Ivermectin, another antiparasitic agent approved for onchocerciasis, helminthiasis and scabies, has shown interesting in vitro effects against SARS-CoV-2 replication [2]. Nitazoxanide and its metabolite tizoxanide, which was initially developed for the treatment of protozoal infections, have broad spectrum in vitro antiviral activity [6]. Studies in animal models have suggested that these compounds exert inhibitory action against N-protein expression and inflammation. A clinical trial for COVID-19 patients

Table 1
: Medications with in vitro activity against SRAS-CoV-2 virus under investigation for treating COVID-19 infections. Adapted from [2–6]

Molecule	Mechanisms	Number of clinical trials enrolling*	Studies available with efficacy endpoint
Antiviral agent			
Remdesivir	RNA dependent RNA polymerase inhibitor	23	4 RCT, some concerns Clinical improvement proved**
Favipavir	RNA dependent RNA polymerase inhibitor	0	1 RCT No reduction of clinical recovery
Lopinavir/ritonavir	Inhibits viral protease enzyme Ritonavir inhibits lopinavir metabolism	42	4 RCT No evidence of clinical benefit
Umifenovir	Spike protein/ACE-2 membrane fusion inhibitor	1	1 RCT No clinical benefit
Nafamostat	Inhibits TMPRSS2	2	
Antibiotics			
Teicoplanin	Inhibits cathepsin L-mediated spike protein cleavage	0	Monocentric cohort study with biological outcome
Antiparasitic agent			
Chloroquine Hydroxychloroquine	Increases endosomal pH of phagolysosome interferes with viral fusion with cell; modifies ACE2 receptor; modifies protein degradation pathways	38	2 meta analyses of RCT No clinical benefit Serious alerts for safety endpoints
Ivermectin	Importing inhibitor α/β-mediated nuclear import	23	None

ACE-2: Angiotensin-converting enzyme 2; RCT: randomised controlled trial; TMPRSS2: Transmembrane serine protease 2
* last update: 10th September on clinicaltrial.gov; ** NIH NIAID ACTT-1, 2020

without comorbidities is planned to evaluate ribavirin in combination with both nitazoxanide and ivermectin [NCT04392427] [4].

This brief overview illustrates the deceptive reality, showing only a small handful of interesting anti-viral drugs under investigation. Results for moderate COVID-19 cases are scarce. In ICU patients with severe COVID-19, none of the drugs mentioned above have demonstrated a significant clinical impact. Most studies have focused on COVID-19 therapy, while prophylaxis for people at risk and/or health care workers has been neglected. Another source of concern is the fragmentation of the investigations, with small national/regional/institutional studies rather than large collaborative studies being performed. These scattered resources dramatically increase the inconsistency of most scientific results. Finally, the international "Infodemic" magnifies the entropy of the pandemic. Worldwide interest in COVID-19 management strategies has spread like wildfire across all kinds of media, with heated debates finally reaching the highest political leaders who give their opinion on the best regimens for COVID-19 cases.

Despite this sad overview and the limited number of methodologically rigorous studies, the COVID-19 pandemic has put a spotlight on the important developments of experimental and methodological tools for drug innovation. Living meta-analysis and artificial intelligence are two examples of advances for finding the "next new agent" to efficiently target SARS-CoV-2 [18,19]. In the interim, scientific rigor should remain our guide, with a cautious review of the literature, a careful analysis of breaking news, and therapeutic selection based on improving individual prognosis and limiting side effects [20].

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Philippe Montravers[a,b,c,*], Elie Kantor[a], Aurélie Gouel-Cheron[a,d,e]
[a]*Département d'Anesthésie-Réanimation, CHU Bichat-Claude Bernard, DMU PARABOL, HUPNVS, APHP, 75018 Paris France*
[b]*Université de Paris, 75018 Paris, France*
[c]*INSERM UMR 1152, Université de Paris,75000 Paris, France*
[d]*Institut Pasteur, Inserm UMR 1222, 75015 Paris, France*
[e]*National Institute of Allergy and Infectious Diseases, National Institutes of Health, Biostatistics Research Branch, Division of Clinical Research, Bethesda, MD, USA*

*Corresponding author at: Département d'Anesthésie-Réanimation, CHU Bichat-Claude Bernard, 46, Rue Henri-Huchard, 75018, Paris, France
E-mail address: philippe.montravers@aphp.fr (P. Montravers).

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