

Treatment of Covid-19 Infection. A Rationale for Current and Future Pharmacological Approach

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Abstract

Global efforts at this time are focused concurrently on containing interhuman spread of this virus and mitigating the impact of this virus. Treatments exist. Health officials from WHO have noted that Remdesivir has demonstrated efficacy in treating the coronavirus infection. The US commenced clinical trials in humans at to test the safety and efficacy of the drug. The first patient to be administered the drug is an evacuee from the Diamond Princess cruise ship. The National Medical Products Administration of China has approved the use of, an anti-viral drugs, as a treatment for coronavirus. Favilavir and Umifenovir are approved for marketing in the treatment of influenza and is one of the four drugs showing efficacy against the coronavirus in human trials. The other three are Chloroquine, Remdesivir and Lopinavir. The medicines were widely used to treat patients who showed resistance to Tamiflu and Relenza Rotadisk, both of which are medications used to treat and prevent influenza caused by influenza A and B viruses. Favilavir (Avigan) has been adopted by both Japan and China as an experimental drug to treat patients suffering from severe COVID-19. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro* and in latest clinical trials. [6,13,14]. Already existing antiretroviral Protease Inhibitors might be also effective in this situation. A HIV protease inhibitor, Lopinavir is being studied along with Ritonavir for the treatment of MERS and SARS coronaviruses. The repurposed drug is already approved for the treatment of HIV infection under the trade name Kaletra. The combination is listed in the WHO list of essential medicines. Lopinavir is believed to act on the intracellular processes of coronavirus replication and demonstrated reduced mortality in the non-human primates (NHP) model of the MERS. Umifenovir (Arbidol) is used primarily as an antiviral treatment for influenza, similarly to Tamiflu, but also showed anti-coronavirus activity. Its use is only in China and Russia, since not approved by neither the FDA nor the EMA.

Keywords: COVID-19 Infection; Remdesivir; Favilavir; Umifenovir

Introduction

This review article is proposing a current opinion and a concise clinical algorithm for discovery, risk assessment, specimen collection and processing, and last but not least - effective treatment of the current COVID-19, with already existing and proven therapies. An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The SARS-CoV-2 belongs to Betacoronavirus which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon B 1b, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. In many studies, were evaluated the antiviral efficiency of five FDA-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine, plaquenil and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV *in vitro* [7,14].

Given the scale and rapid spread of the 2019 novel coronavirus (2019-nCoV) acute respiratory disease, there is an immediate need for medicines that can help before a vaccine can be produced. Results of rapid sequencing of 2019-nCoV, coupled with molecular modelling based on the genomes of related virus proteins, have suggested a few compounds that are likely to be effective, including the anti-HIV Lopinavir plus Ritonavir combination. The suppression of Cytokine Release Syndrome, 'cytokine storm' is of utmost importance to prevent morbidity and mortality in ICU settings in ARDS cases. As the existing antivirals, many anti-inflammatory drugs approved for treatment of RA can be useful in that purpose, but again after repurposing and approval. A pathophysiological approach, diminishing MAS and CSS in the treatment of COVID-19 will be exposed here, reminding that the Coronavirus Treatment Could Lie in Existing Drugs - antiviral and immunomodulatory [33]. The virus-induced innate immune response is devastating, not the virus itself.

Some authors do not recommend use of a high-flow nasal cannula or non-invasive ventilation until the patient has viral clearance. Supporting the recommendation of the authors, we would like to add some points in relation to the use of high-flow nasal oxygen therapy and non-invasive ventilation in patients with COVID-19 infection. Non-invasive NIV ventilation is not recommended for patients with viral infections complicated by pneumonia because, although non-invasive ventilation temporarily improves oxygenation and reduces the work of breathing in these patients, this method does not necessarily change the natural disease course [50]. Except in cases of ventilator shortage and impossibility to react otherwise, but in all cases not to choose firstly, mostly in ER settings and not in ICU isolated box, because may contribute to spread the viral droplets in the air and contaminate more people, doing more harm than good.

Real-time reverse transcriptase RT-PCR

In RT-PCR (reverse transcriptase PCR), the RNA template is first converted into a complementary DNA (cDNA) using a reverse transcriptase. The cDNA is then used as a template for exponential amplification using PCR. QT-NASBA is currently the most sensitive method of RNA detection available [15]. The use of RT-PCR for the detection of RNA transcript has revolutionized the study of gene expression real-time reverse transcriptase RT-PCR (sometimes even called quantitative real-time RT-PCR, is often abbreviated as qRT-PCR.

The emergence of novel fluorescent DNA labeling techniques in the past few years have enabled the analysis and detection of PCR products in real-time and has consequently led to the widespread adoption of real-time RT-PCR for the analysis of gene expression. Not only is real-time RT-PCR now the method of choice for quantification of gene expression, it is also the preferred method of obtaining results from array analyses and gene expressions on a global scale. Currently, there are four different fluorescent DNA probes available for the real-time RT-PCR detection of PCR products: SYBR Green, TaqMan, Molecular Beacons, and Scorpions. All of these probes allow the detection of PCR products by generating a fluorescent signal. While the SYBR Green dye emits its fluorescent signal simply by binding to the double-stranded DNA in solution, the TaqMan probes, Molecular Beacons and Scorpions generation of fluorescence depend on Förster Resonance Energy Transfer (FRET) coupling of the dye molecule and a quencher moiety to the oligonucleotide substrates [15]. Shortly, the qRT-PCR is of utmost importance for exact diagnosis and subsequent proper treatment.

The second major pillar in the process is the CT chest imaging. Even one study of 1,014 patients published on the 26 of February 2020 in Radiology, supposes that chest CT outperformed RT-PCR lab testing in the diagnosis of COVID-19. Chest CT has a high sensitivity for diagnosis of COVID-19. Chest CT may be considered as a primary tool for the current COVID-19 detection in epidemic areas [16]. Maybe it is wiser to use both, while many other pathogens may produce the same patterns on chest CT scans. They report that chest CT had higher sensitivity for diagnosis of COVID-19 as compared with initial reverse-transcription polymerase chain reaction (RT-PCR) from swab samples in the epidemic area of China. With analysis of serial RT-PCR assays and CT scans, 60% to 93% of patients had initial positive chest CT consistent with COVID-19 before the initial positive RT-PCR results. 42% of patients showed improvement of follow-up chest CT scans before the RT-PCR results turning negative [16].

The aim of this review article is to provide a already existing actual practical approach, including the treatments proven yet again after the first SARS CoV outbreak and confirmed as such with high efficacy and very efficient after 10 - 14 days of application, with significant

clinical benefice, disappearance of viral load in the respiratory secretions and symptom improvement. SI. qRT-PCR becomes again negative after the resolution of the LRT symptoms and signs (cough, dyspnea and hypoxemia) and the lung infiltrates on chest X-rays or CT scans.

Multiple drugs for COVID-19 under clinical and laboratory investigation <https://www.genengnews.com/news/coronavirus-treatment-could-lie-in-existing-drugs/> [33].

The fundamental pathophysiology of severe viral pneumonia is severe ARDS - SARS. Men and people of an older age (> 65 years) are more likely to develop ARDS than women or those of a younger age. Therefore, it is reasonable that the mortality at 28 days of severe COVID-19 pneumonia is similar to the mortality of severe ARDS, which is near 50% [17]. But not acceptable. Low tidal volume 6 ml/kg PBW Vt (lung-protective) ventilation (LTVV) with higher PEEP - 10 cm H₂O is associated with decreased ventilator-induced lung injury (VILI) and acute respiratory distress syndrome (ARDS) progression as well as a shorter length of stay (LOS).

Why different coronaviruses vary in severity

There are seven coronaviruses known to infect people. Four of them-229E, NL63, OC43 and HKU1-typically cause a cold and only rarely result in death. The other three-MERS-CoV, SARS-CoV, and the new SARS-CoV-2, COVID-19-have varying degrees of lethality. In the 2003 SARS outbreak, 10 percent of infected people died. Between 2012 and 2019, MERS killed 23 percent of infected people. Although the case fatality rate of COVID-19 is lower, the virus has already killed more people than the other two outbreaks combined, which some have attributed to the pathogen's fast transmission and long 14 days incubation period [24].

The ACE2 gene encodes the angiotensin-converting enzyme-2, which has been proved to be the receptor for both the SARS-coronavirus (SARS-CoV) and the human respiratory coronavirus NL63. Recent studies and analyses indicate that ACE2 could be the host receptor for the novel coronavirus 2019-nCoV/SARS-CoV-2 [22]. Previous studies demonstrated the positive correlation of ACE2 expression and the infection of SARS-CoV *in vitro*. The East Asian populations have much higher AFs (allele frequencies) in the eQTL variants associated with higher ACE2 expression in tissues, which may suggest different susceptibility or response to SARS-CoV-2 from different populations under the similar conditions [22,23]. The cold-causing coronaviruses, as well as many other viruses that cause common colds, are typically restricted to the upper respiratory tract, that is, the nose and sinuses. Both SARS-CoV and SARS-CoV-2, however, are capable of invading deep into the lungs, something that is associated with more severe disease.

One possible reason for this is that the virus binds to the ACE-2 receptor on human cells in order to gain entry. This receptor is present in ciliated epithelial cells in the upper and lower airway, as well as in type II pneumocytes, which reside in the alveoli in the lower airway and produce lung-lubricating proteins - the surfactant. It's loss causes atelectasis, shunt and ARDS. The type II pneumocytes are very important for lung function, so this is part of why the lower respiratory disease can be so severe [25].

The new coronavirus also appears to use the ACE-2 receptor, which may help partially explain why, like SARS, it is more deadly than the other four coronaviruses [29]. Those pathogens use different receptors, except for NL63, which also uses the ACE-2 receptor but binds to it with less affinity. MERS is thought to use an entirely different receptor - dipeptidyl peptidase-4 (DPP4), which is also present in the lower airways. It's inhibitors - the gliptins, are a class of oral hypoglycemics that block the enzyme dipeptidyl peptidase-4 (DPP-4) and are used to treat diabetes mellitus type 2.

The fact that SARS-CoV-2 targets ACE2 receptors could be significant. For instance, ACE2 is on a sex-linked chromosome, meaning that women express the receptor at higher levels than men. But according to Wu's data, men have worse COVID-19 outcomes than women [29]. Men take more ACEI and ARB as hypertension and heart failure treatment [29].

And then there's the issue of ACE inhibitors. Renin-angiotensin-aldosterone system inhibitors, which include ACE inhibitors, cause an increase in the expression of ACE2 receptors, according to a recent comment in Nature Reviews Cardiology [29].

For the current COVID-19, caused by SARS-CoV-2, we consider the options of 1) drug repurposing, 2) developing neutralizing monoclonal antibody therapy, 3) oligonucleotide strategy targeting the viral RNA genome and 4) using a recombinant human Angiotensin Converting Enzyme 2 (rhACE2). Only the first approach will be widely exposed here.

Using oligonucleotides against 2019-nCoV-2 RNA genome will block the virus to produce receptor-binding spikes. One option is the use of small interfering RNA (siRNA) or antisense oligonucleotides (ASO) to combat the virus by targeting its RNA genome [26].

Blocking agents that bind to ACE2 receptor is logical to propose. It is a biologic that blocks 2019-nCoV-2 entry using a soluble version of the viral receptor, (ACE2), fused to an immunoglobulin Fc domain (ACE2-Fc), providing a neutralizing antibody, while also helping to recruit the immune system to build lasting immunity. The Ab will block the viral spike - ACE2 binding and subsequent ALI (acute lung injury).

APEIRON Biologics AG, a biotechnology company with an approved product on the market as well as a broad preclinical and clinical pipeline, today announced the launch of a Pilot investigator-initiated clinical trial (IIT) with APN01, a recombinant human angiotensin-converting enzyme 2 (rhACE2), to treat patients with severe coronavirus infection in the People’s Republic of China. The ACE2 receptor is expressed in human airway epithelia as well as lung parenchyma and was previously identified as the gateway, which the SARS virus uses to infect the cells. ACE2 is also the critical receptor for the new virus 2019-nCoV to enter human cells. Thus, treatment with recombinant human ACE2 could be used to not only block viraemia but also protect lungs from injury. APEIRON currently has the full licenses, clinical data and protocol from GSK, GMP production technology and stored GMP grade rhACE2 available for immediate use in trials in China. The drug candidate is administered intravenously as an infusion and has shown safety and tolerability in 89 patients and volunteers [27].

A major drawback which potentially retards proper diagnosis and foster virus spread is the rarity and distance of/to Certified Centers to send the specimens. Also, the swabs and oro-nasal secretions are positive before the serum conversion. That causes undiagnosed and untreated, when they are easy treatable, cases and spread of the disease. Coronavirus testing kits have not been widely and evenly distributed to the hospitals and public health labs. Those without these kits must send samples all the way to certified labs, rather than testing them on site, wasting precious time as the virus spreads.

Singlean launched the latest Rapid On-site test for #COVID-19 [05/03/2020]. Compared to PCR test, the IgG/IgM blood test is easier to sampling and have sooner result.

Singlean Medical’s COVID-19 IgG/IgM Rapid Test Cassette (Whole Blood/Serum/Plasma) is an assay for the rapid, qualitative and differential detection of IgG and IgM antibodies to 2019 Novel Coronavirus in human whole blood, serum or plasma.



Figure 1

The fast test cassette, part of the kit, can detect the virus in just 2 - 15 minutes. It might be a solution for transport and waste of time waiting for results, the patients left untreated.

Between 25% and 50% of COVID-19 patients present with underlying conditions.

Case Fatality Rates (CFR) have been:

- 6% higher in patients with hypertension
- 7.3% higher in patients with diabetes
- 10.5% higher in those with established CVD.

Also increased CFR is noted in CKD, old age, smokers, cancer patients and other serious comorbidities.

17% of patients develop arrhythmias and 7% experience acute cardiac injury.

Deaths from Covid-19 are due to:

1. Respiratory distress (SARS) secondary to cytokine storm syndrome (CSS) which is an excessive response to the viral attack.
2. Fulminant myocarditis and cardiogenic shock.
3. Multiorgan failure due to CSS (high SOFA score).

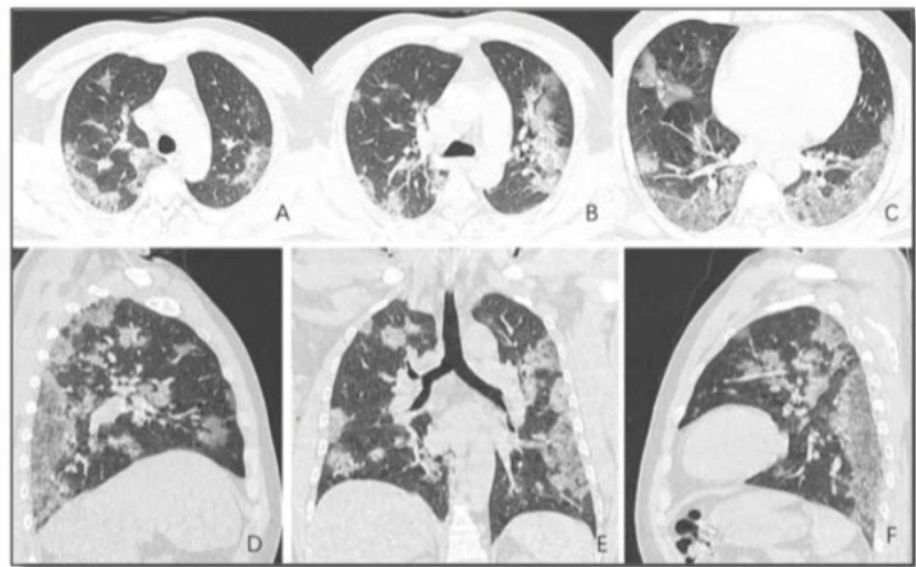


Figure 2: COVID-19 SARS - severe lung injury on CT axial and coronal images - alveolar infiltrative consolidations and GGO (ground glass opacities) bilaterally peripherally.

Laboratory diagnosis

Blood tests elevated

C-reactive protein, CD4, CD8, interleukin-6 (IL-6), D-dimers, ferritin, troponin, BNP.

All Covid-19 patients sick enough for hospitalization should be given a serum ferritin blood test. Elevated serum ferritin values are a good first screening tool for the possibility of a cytokine storm syndrome (CSS or CRS) in sick patients with high fevers. A good predictor for later complications.

All pointing to an acute inflammatory hyperresponse. Besides SARS this inflammation may cause multiorgan damage, myocardial damage (elevated pro-BNP and troponin). There may be some evidence of lung fibrosis, but the myocardial injury - the troponin and pro-BNP elevation - will usually normalize after discharge so no need to keep patients hospitalized until these values are normal.

Laboratory tests which to be conducted at admission are including - a complete blood count, serum biochemistry, and identification of other respiratory pathogens such as influenza A virus (H1N1, H3N2, H7N9), influenza B virus, respiratory syncytial virus, parainfluenza virus, and adenovirus. Routine microbiological testing for banal flora, TB, whooping cough, fungi, opportunistic infections must be made and eliminated before the beginning of COVID-19 treatment, because of the sometimes immunosuppressive nature of the latter (anti-IL-6 IV Mab Actemra). Concomitant use of antibiotics when needed is advised in the setting of bacterial superinfection or coinfection or prolongation of the illness with CRP > 30 mg/L more than 7 days.

Below are the protocols for treatment already used in China epidemic outbreak and proven effective. Others are in current studies in Europe, waiting for (re)-approval. More of the new proposals mentioned after the protocols are studied for now only in laboratory conditions and hopefully theoretically and empirically efficient. Much remains to be done for that new molecules to obtain their approval and clearance to mass use by the regulatory and sanitary institutions worldwide. Multiple and diverse researches are on their way, including vaccine pharmacodesign and production. While waiting for that unique drug or vaccine we are disposing of repurposed and efficient treatments which allowed the cure for 80% of Chinese patients.

Specimen collection

The nasopharyngeal or oropharyngeal swabs are proceeded as follows:

- If positive repeat every 3 days until negative (during the treatment also).
- If negative repeat second test after 24 hours.
- If two consecutive tests are negative isolation can be discontinued.

To be able to provide effective treatment we must understand the underlying mechanisms a provoking the injury. In this case in the COVID-19, the SARS CoV-2 (19) is not directly cytopathogenic - it is the immune response of the organism that causes the organ injury and failure and the complications. Thus, immunosuppression in the ICU cases can be beneficial.

We will focus on three topics - Antivirals, Anti-inflammatory (anti ARDS/SARS) drugs and Ventilation strategies:

- Antivirals are two groups - 1. Repurposed already approved existing antivirals and 2. Novel antiviral treatments under study.

- Anti-inflammation immunomodulatory medications, approved mostly for RA for now, represent a pathophysiological approach, suppressing the CSS, ARDS and MAF - again we have a repurposing which makes sense, but no clinical trials supporting that Ventilation in ICU.

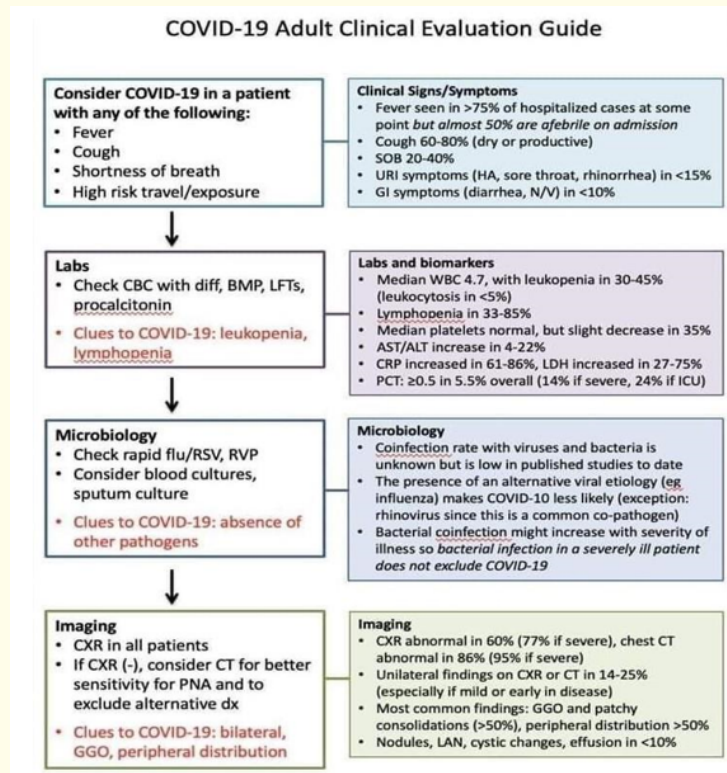


Figure 3: UCSF - COVID-19 Clinical Working Group. Updated March 4, 2020. <https://www.ucsf.edu/coronavirus#tabs-1>

The pathophysiology of COVID with SARS lies in the Hemophagocytic Lymphohistiocytosis HLH, a.k.a Macrophage Activation Syndrome MAS or Hemophagocytic Syndrome HPS. In its essence it is a clinical syndrome resulting from immunologic hyperactivation provoked by hyperstimulated macrophages. These hyperstimulated macrophages recognize and engulf the neutrophils, both acting in the first line of the innate immunity, which phagocyte the virus particles. The ingested neutrophils release massively large amounts of pro-inflammatory cytokines (IL-1, IL-6, IL-8) thus provoking the CSS, CRS - Cytokine Storm Syndrome, Cytokine Release Syndrome which is the direct cause of the bilateral lung injury - ARDS and multiorgan failure MAF, not the virus itself.

The Results of HLH/MAS - Hyper acute phase reaction:

- High fever
- Shock, capillary leak syndrome, ARDS
- Cytopenias

- Abnormal liver test (synthesizes all acute phase reactants)
- Disseminated intravascular coagulation - DIC syndrome
- Delirium, seizure
- Lymphadenomegaly, hepatomegaly, splenomegaly, (RES hypertrophic reaction, MAS)
- Markedly elevated Inflammatory markers (ferritin, CRP, procalcitonin)
- Multiorgan failure MOF including cardiomyopathy and myocarditis
- Death.

The severe lymphopenia is an initial finding, followed after several days by hyperlymphocytosis - both lineages CD4 and CD8. The potential risk factors are older age > 70y, high SOFA score and D-dimer greater than 1 µg/ml. High ferritin bodes bad outcome too.

Actemra (Tocilizumab) and Kevarza (Sarilumab) were first approved by the FDA as anti-interleukin (IL)-6 receptor blocking agents for the therapy of rheumatoid arthritis, now it is used for treatment of severe COVID-19 with serious lung damage and elevated IL-6 [42]. It may be applied IV 8 mg/kg once or 800 mg IV repeated TID only one day in most severe cases.

A vascular leakage therapy (Q BioMed and Mannin Research) is being developed. It targets the angiotensin-Tie2 signaling pathway to reduce endothelial dysfunction [48].

Tiziana’s anti-IL-6R MAb binds to both the membrane-bound and soluble forms of IL-6R and rapidly depletes circulating levels of IL-6 in the blood. The Canadian company TIZIANA’s anti-IL-6R MAB Foralumab is an immunomodulator. It binds to CD3 epsilon. An excessive production of IL-6 is regarded as a key driver of chronic inflammation and is believed to be associated with severe lung damage observed with COVID-19 infections and acute respiratory illness. A recent Chinese study also reported that COVID-19 infection caused clusters of severe respiratory illness such as severe acute respiratory distress syndrome (ARDS) [41,42]. <https://www.pharmaceutical-technology.com/.../roche-actemra> [42].

Anakinra (Kineret) is an IL-1 alpha and beta receptor antagonist that may be used in MAS to prevent CSS [43]. The dose recommended is 3 - 4 mg/kg/day SC, 7 days or as needed.

One interesting aspect of the implication of AI proposed in the treatment regimens is the anti-inflammatory drug. That makes sense, but no study for now for confirming practical benefits. The Baricitinib (Olmiant) is a JAK, AAK and GAK kinases inhibitor, in blocking these pathways, predominantly JAK 1/2 it diminishes the inflammatory ravages to lung and heart, by suppressing CSS (Figure 3). Doses recommended are once per day 4 mg PO. The 2 mg tablet PO is recommended for patients > 75 years old. An additive effect with other immunosuppressants cannot be excluded [44]. Baricitinib shows dual antiviral and anti-inflammatory activity *in vitro* and in February 2020 it was suggested as a potential treatment for the Coronavirus disease 2019 [45]. Beware latent TB, herpes and hepatitis reactivation.

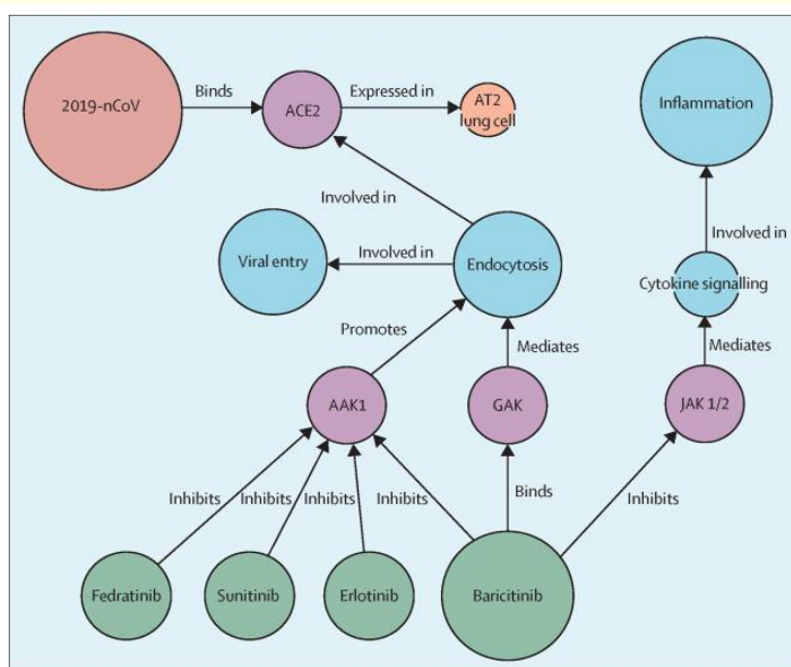


Figure 4: Effect on Baricitinib on COVID-19 and CSS by suppressing JAK 1/2 kinases pathway *The Lancet*. doi:10.1016/S0140-6736(20)30304-4 [45].

Most viruses enter cells through receptor-mediated endocytosis. The receptor that 2019-nCoV uses to infect lung cells might be ACE2, a cell-surface protein on cells in the kidney, blood vessels, heart, and, importantly, lung AT2 alveolar epithelial cells (Figure). These AT2 cells are particularly prone to viral infection.³ One of the known regulators of endocytosis is the AP2-associated protein kinase 1 (AAK1). Disruption of AAK1 might, in turn, interrupt the passage of the virus into cells and also the intracellular assembly of virus particles [46].

Fulminant myocarditis is primarily caused by infection with viruses. It arises quickly, progresses rapidly, and may lead to severe heart failure or circulatory failure presenting as rapid-onset hypotension and cardiogenic shock, with mortality rates as high as 50% - 70%.

To maintain blood pressure and to reduce the necessity of frequent bedside monitoring low-medium dose Noradrenalin is given 4 - 7 days.

The treatment depends on clinical stage and severity at the time of presentation. Isolation, antiviral and anti-inflammatory immunomodulator drugs and adequate oxygenation are of primary concern.

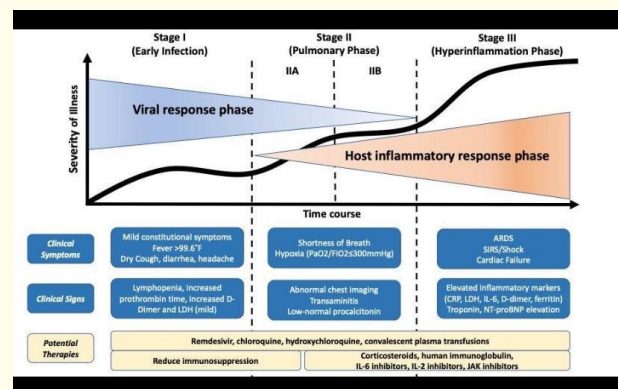


Figure 5: Temporal sequence of events in COVID-19 infection.

The course of COVID -19 may be divided in two phases - virological, in the beginning, from day 1-5, and immunological, from day 6-7 onwards. The primary goal of antiviral treatment is of course the first phase - to inhibit viral replication and subsequent immune overreaction and cytokine storm. In the second phase which clinically manifests itself as CSS and ARDS there is no interest of antivirals. This may be the explanation of the failure to succeed the first Chinese Kaletra trial - this antiviral drug was introduced on day 10 when the virological phase was already exceeded. After 10 days of clinical symptoms the probability that an antiviral drug may be effective diminishes progressively. In contrast, at that moment systemic antiinflammatory drugs will be of greater interest in order to prevent or treat the CSS, which is the direct cause of the high mortality rate.

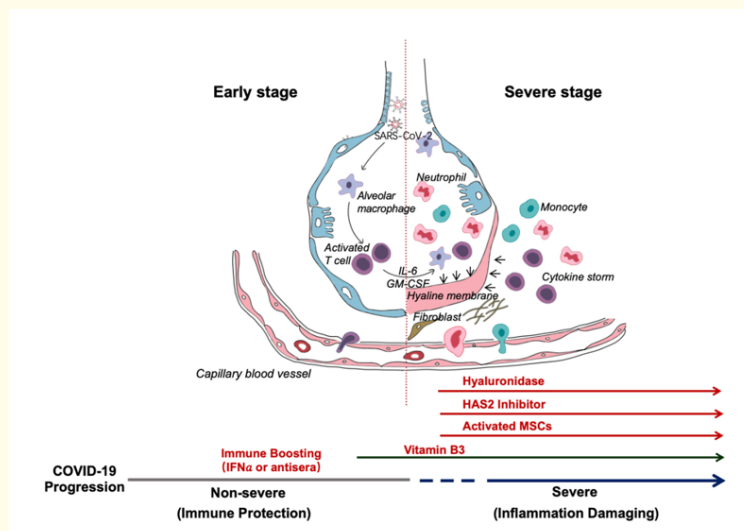


Figure 6: The immune damage second phase and its pharmacological approach [53].

We believe that the two-phase division is very important: the first immune defense-based protective phase and the second inflammation-driven damaging phase. Medical staff should try to boost immune responses and suppress viral replication during the first, while suppressing immune response in the second phase. Since nicotinamide - Vitamin B3 is highly lung protective, it should be used as soon as coughing begins.

Bromhexin also, an OTC mucolytic drug may be efficient in addition to fluidifying mucus, to inhibit entry by blocking membrane receptor mediated entry via TMPRSS2. Bromhexine hydrochloride (BHH) as an ingredient in a mucolytic cough suppressant is also effective to attenuates prostate cancer metastasis in mice. Furthermore, it shows specific inhibition of TMPRSS2 (IC50 = 0.75 μM). Given that BHH is an FDA-approved drug with no significant adverse effects, it could be used for treatment of influenza virus and coronavirus infections as an inhibitor of TMPRSS2.[52]

IV Hyaluronidase to dissolve hyaline membranes[54]

In the 1970s, hyaluronidase was investigated as a potential treatment for myocardial infarction. Unsurprising in the context of our current understanding of thrombus formation, the benefit in this condition was moderate; however, a number of published studies demonstrate the safe use of hyaluronidase in this emergency setting. Doses of 500IU/kg were used and administered as an intravenous bolus over 1-2 minutes. The dose was repeated seven times at 6-hour intervals. The half-life in the circulation is approximately 2 to 5 minutes. Adverse events related to the hyaluronidase were reported as mild. There were no cases of anaphylaxis. [54]

A preliminary skin test for hypersensitivity to Hydase/Hyalase can be performed. The skin test is made by an intradermal injection of approximately 0.02 mL (3 Units) of a 150 Unit/mL solution. A positive reaction consists of a wheal with pseudopods appearing within 5 minutes and persisting for 20 to 30 minutes and accompanied by localized itching. Transient vasodilation at the site of the test, i.e., erythema, is not a positive reaction.

For a 70kg adult, this would approximate 10 ampules of Hydase, a commercially available powder form of hyaluronic acid (Wockhardt Ltd., Mumbai, India), and a total dose of 15,000IU. Into each ampule, 1mL of normal saline for injection is injected, the powder rapidly dissolves, the solution is withdrawn, and this process is repeated until a total bolus of 15,000IU in 10mL of saline has been prepared. An intravenous cannula is inserted and the bolus is given followed by a 10mL flush. The patient remains supine, and adrenaline and oxygen are available in the event of anaphylaxis which is rare if previous skin testing were performed.

1. Treatment of COVID-19 upper respiratory tract infection (Fever, runny nose, cough, without CT lung infiltrate + positive qRT-PCR)

Hydroxychloroquine (Plaquenil) PO 400 mg BID day1 followed 200 mg BID for 4 days

+/-

Tamiflu PO 150 mg BID for 5 days or Arbidol 200 mg TID 5 days

OR

Plaquenil HCQ maintenance dose 200 mg BID for 10 days +/- Tamiflu or Arbidol 5d

OR

Chloroquine phosphate CQ PO 500 mg BID 5 for days

+/-

Oseltamivir (Tamiflu) PO 150 mg BID for 5 days.

Plaquenil sulfate HCQ is three time more efficient than Chloroquine phosphate CQ [41].

2. Treatment of COVID Pneumonia - CT bilateral Lung infiltrate + positive qRT-PCR - but without SARS, patient on spontaneous ventilation SaPO2 > 92% on air, and capable to swallow medication

HCQ Plaquenil 200 mg TID for 5 days

+

Azithromycin 500 mg OD day 1 then 250 OD for 5 days [51] - the citation is 51 for that treatment.

Kaletra 400/100 BID for 14 days

+

HCQ Plaquenil 200 mg TID for 5 days

Lopinavir/Ritonavir (Kaletra) PO 200/50 mg 2 tabs BID or 400/100 mg 1 tab BID 14d

+/-

Oseltamivir PO 150 mg BID for 5 days or HCQ 200 mg BID or Arbidol 200 mg TID

OR

Kaletra PO 400/100 mg BID for 14 days + IntronA 5 MIU nebulization BID 5-7 d + Tamiflu 150 mg BID for 5 days or Arbidol 200 mg TID for 7 days

OR

Atazanavir (Reyataz) PO 400 mg OD with food for 14 days

+/-

Oseltamivir (Tamiflu) PO 150 mg BID for 5 days or IntronA 5MUI nebulized BID

OR

Atazanavir boosted: 1. +Cobicistat 300/150 mg OD or 2. +Ritonavir 300/100 mg OD

+/-

Chloroquine PO 250 mg BID for 5 days /or Tamiflu 5 days / or Plaquenil 200 mg BID

OR

Darunavir/Cobicistat (Rezolsta) PO 800/150 mg OD for 14 days

+/-

Chloroquine PO 250 mg BID for 5 days / Tamiflu 5 days / or Plaquenil 200 mg BID

+/-

Interferon alpha 2b (IntronA) 5M IU BID aerosol nebulization for 5 to 7 days

OR

Plaquenil HCQ 200 mg BID + IntronA 5MIU BID aerosol + Arbidol 200 mg TID for 5d

OR

Remdesivir IV - 200 mg on day 1 infused for 30 min, followed by 100 mg IV OD for a total of 10 days. Exists in 100 mg in 10 ml glass vials.

OR

HCQ Plaquenil 200 mg TID for 10 days

+

Azithromycin 500 OD on day1 followed by 250 mg OD for total of 5 days [51].

3. SARS of COVID-19 in ICU on LTVV MV (low tidal volume lung protective ventilation - Vt 6 - 4 ml/kg PBW, PEEP 10 - 15 cm H₂O, Plateau < 25 cm H₂O)

Remdesivir IV - 200 mg on day 1 infused for 30 min, followed by 100 mg IV OD for a total of 10 days. Exists in 100 mg in 10 ml glass vials. 14 days treatment is for Ebola. And above the 3rd ventilation ARDS section.

+ Corticosteroids IV Methylprednisolone 40 mg q12h BID for 5-7 days

OR

Dexamethasone IV 20 mg OD d1 - d5, then 10 mg IV OD d6 - d10 [20]

+/- Tocilizumab (Actemra) 8mg/kg IV in 100ml normal saline for 60 minutes IV infusion in ICU settings, once only. In severe cases can be repeated TID or augmented up to 800 mg TID one day only.

Foralumab - anti IL-6R Mab and Kevzara (Sarilumab) are not FDA approved for that.

Anakinra 3 - 4 mg/kg/daily SC in divided doses - BID or TID

HCQ Plaquenil 200 mg TID for 10 days

Baricitinib (Olmiant) 4 mg PO once daily for 7 - 10 days. 2 mg > 75 years old pts

IntronA can be applied SC - 3MUI to 5MUI SC per day for 5-7d.

To intubate if after 15 minutes of face mask with FiO₂ of 60% the patient has SaPO₂ < 95%, PaO₂/FiO₂ < 200, RR > 25 - 30/min. A good compliance sign is if the inspiratory pressure - P plateau is < 25 - 27 cm H₂O (easy to ventilate lungs) with driving Pressure < 13 cm H₂O. Limit and monitor volume administration. Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion. Ventilation Vt of 6 - 4 ml/kg with minimal RR to reach pH > 7.2 Use high PEEP (13 - 15 cm H₂O). The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets. In adult patients with severe ARDS, prone ventilation for 12 - 16 hours per day is recommended.

If the hospital is run out of ventilators, NIV - BIPAP or CPAP may be tried, but not if pH < 7.2 and SaPO₂ < 94% with 5l O₂/min or he-

modynamically instable, also jet ventilation and ECMO are considered according to clinical scenario. Patient on HFNO and NIV are closely monitored for clinical deterioration. Adult HFNO systems can deliver up to 60 L/min of gas flow and FiO_2 up to 1.0. Because of uncertainty around the potential for aerosolization, HFO, NIV, including bubble CPAP, should be used with airborne precautions until further evaluation of safety can be completed. Compared with standard oxygen therapy, HFNO reduces the need for intubation. Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), hemodynamic instability, multiorgan failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia. Patients receiving HFNO should be in a monitored setting and cared for by experienced personnel capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Evidence-based guidelines on HFNO do not exist, and reports on HFNO in patients infected with other coronaviruses are limited. NIV guidelines make no recommendation on use in hypoxemic respiratory failure (apart from cardiogenic pulmonary oedema and postoperative respiratory failure) or pandemic viral illness (referring to studies of SARS and pandemic influenza). Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate in patients with other viral infections such as MERS-CoV who receive NIV.

Patients receiving a trial of NIV should be in a monitored setting and cared for by experienced personnel capable of performing endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Patients with hemodynamic instability, multiorgan failure, or abnormal mental status should likely not receive NIV in place of other options such as invasive ventilation.

In situations where mechanical ventilation might not be available, bubble nasal CPAP may be used for severe hypoxemia and may be a more readily available alternative in resource-limited settings.

Avoiding use of chest CT for progress evaluation of the lung pathology helps to contain the illness. Chest X ray and LUS is enough, in attempt to limit the spread intra hospital wards and personnel.

Alvesco (ciclesonide), an inhaled corticosteroid for asthma treatment, apparently helped improve the symptoms of patients who developed the novel coronavirus disease COVID-19, according to a report posted on the website of the Japanese Association for Infectious Diseases. Teijin Pharma will supply 20,000 cans of its inhaled corticosteroid Alvesco (ciclesonide) to the Japanese government as part of measures against the spread of the novel coronavirus after reports on the drug's potential as a COVID-19 treatment, the company announced in Pharma Japan article: <https://pj.jiho.jp/article/241623>. Alvesco (ciclesonide), has demonstrated its inhibitory effect against the replication of the novel coronavirus, according to researchers at the National Institute of Infectious Diseases (NIID).

Antiviral Interferons Alpha and Beta in sole application are not proven superior to other drugs listed above until now but can be associated to other treatments in selected cases.

The effects of interferon alfa 2b lie in activation of protective mechanisms of virus-free cells that prevent the virus entry and assembly of virions and in their immunomodulating effect - Interferon alfa 2b activates macrophages, T cells and NK cells, increases phagocytosis and antigen processing and presentation mediated by major histocompatibility complex (MHC) and stimulates proliferation and differentiation of bone marrow cells, therefore enhancing the mechanism of antiviral protection.

The α 2b-interferon (IntronA) atomization inhalation/aerosol BID can be considered (5 million UI per time for adults, diluted in sterile injection water; twice a day nebulization can be added to Lopinavir/Ritonavir orally, 400/100 mg twice daily. In France there is an ongoing clinical trial associating the β 1a-interferon (Rebif) SC every other day to Kaletra PO. IntronA alternatively can be applied SC - 3MUI to 5MUI SC per day for 5-7d.

HIV drugs for coronavirus treatment - a HIV protease inhibitor, Lopinavir is being studied along with Ritonavir for the treatment of

MERS and SARS coronaviruses. The repurposed drug is already approved for the treatment of HIV infection under the trade name Kaletra. The combination is listed in the WHO list of essential medicines. Lopinavir is believed to act on the intracellular processes of coronavirus replication and demonstrated reduced mortality in the non-human primates (NHP) model of the MERS.

Rezolsta tablets is the European market name for Prescobix, Prezista in the US. Atazanavir exists as capsules - Reyataz, Evotaz. PI's may be boosted or not. Most frequently they are, either with Cobicistat or Ritonavir in fixed dose combinations.

As a general rule, the protocols used in China include 14 days a sole or boosted protease inhibitor PI - i.e. Kaletra 400/100 +/- Chloroquine CQ or Plaquenil HCQ BID [36] (low dose if added to PI's) + Tamiflu 150 mg BID, or Arbidol 200 mg TID + Interferon alpha aerosol BID or sole IV Remdesivir for 10 days. Booster denotes pharmacokinetic enhancer - which may be a CYP3A4 inhibitor to increase plasma concentration and bioavailability of the first PI - Cobicistat, Tybost, or second but at low dose PI - Ritonavir, as in Kaletra with Lopinavir, and in Anzavir-R - Atazanavir plus Ritonavir. Evotaz is fixed association of Atazanavir plus Cobicistat [4,5,14]. When a booster is present in prefabricated association tablet, the dose of the PI diminishes as a result of improved plasma levels and efficacy. The 400 mg OD sole Atazanavir becomes a 300 mg OD combined tablet. The inclusion of a booster does not changes/diminishes the length of the treatment. It remains two weeks, with or without PO Chloroquine 500 mg or Tamiflu 300 mg daily, administered in two takes and added concomitantly for 7 and 5 days respectively [19].

Concomitant use of Ritonavir-boosted, Cobicistat-boosted, or unboosted Atazanavir, Darunavir and Lopinavir with drugs that are potent inducers of CYP3A (e.g. nevirapine, rifampin, St. John's wort [*Hypericum perforatum*], triazolam) since such use may decrease Atazanavir exposures resulting in possible loss of virologic response. Cobicistat is a CYP3A4 and CYP2D6 (at lesser degree) inhibitor. Kaletra augments the plasma levels of Chloroquine, Metformin, Beta-blockers, Statines, Midazolam and Dexamethasone. Thus, association Kaletra + Chloroquine is to be monitored, CQ used in lower doses - 250 BID in the place of 500 BID when sole or if not monitored to be avoided. Ocular potential adverse effects are non-negligible - retinitis and keratitis, cardiac complications may provoke unnecessary risk also.

The Chloroquine phosphate CQ and Hydroxychloroquine HCQ [36,37] - a widely used anti-malarials and autoimmune disease drugs, has recently been reported as a potential broad-spectrum antiviral drug. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV. Chloroquine would stand out by showing effectiveness on several tables: "to contain the evolution of the pneumonia, to improve the condition of the lungs, to make the patient negative for the virus and to shorten the duration of the illness". Another positive point for chloroquine, "it costs less and it is a drug that has been around for a long time and has proven itself, which we know is safe in terms of benefit/risk balance", add the cited scientists [6,8,9] Both are prone to ophthalmic and cardiac adverse effects in high concentrations.

Hydroxychloroquine HCQ Plaquenil (EC₅₀ = 0.72 μM) was found to be more potent than chloroquine (EC₅₀ = 5.47 μM) *in vitro*. Based on PBPK models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance. Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 *in vitro* [40].

The IV antiviral Remdesivir, which has already obtained three patents in China for the treatment of the coronavirus also obtains good results [4,11,14]. Remdesivir, a nucleotide analog, is an investigational broad-spectrum antiviral treatment. It was previously tested in humans with Ebola virus and Marburg virus disease and has shown promise in animal models for treating Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), which are caused by other coronaviruses [12,13,30]. Remdesivir, being IV drug and is diluted in Cyclodextrin, is formally contraindicated in dialyzed patients, those with moderate renal failure must be taken with precaution. Hepatic cytolysis with ASAT and ALAT > 5N is contraindication also. Cyclodextrins are cyclic oligosaccharides used for the improvement of water-solubility and bioavailability of drugs. Because of the diverse types of interactions of cyclodextrins may cause renal

tubular vacuolization and renal failure.

Remdesivir (formerly GS-5734) is a prodrug of a modified adenine nucleoside analog GS-441524. Remdesivir undergoes efficient metabolic conversion in cells and tissues to active nucleoside triphosphate metabolite that inhibits viral RNA polymerases, but not host RNA or DNA polymerases. Remdesivir exhibits a potential for clinical efficacy against Ebola virus and other filovirus infections. Current trials for qRT-PCR proven COVID-19 are in progress [4,13,33,35].

Antibiotics with a double action - Chloroquine CQ, HCQ and Remdesivir successfully inhibited the 2019n-CoV virus in an in vitro model. Added to this, teicoplanin (Targocid), oritavancin, dalbavancin, monensin (all antibiotics) and ememetine (once used against parasitic diseases) could be reused, repurposed to treat a coronavirus infection. These molecules have managed to inhibit more coronavirus as well as other viral infections, specifies in a study published in the International Journal of Infectious Diseases. The antibiotics mentioned would therefore have a double action. They could be used to treat viral and bacterial co-infections, or to prevent patients from being infected a second time [31-34].

The 2019-nCoV belongs to Betacoronavirus which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial. In many studies, were evaluated the antiviral efficiency of five FDA - approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV *in vitro* [7,14,17]. Most patients in seven hospitals in Zhejiang province in eastern China (89%) received antiviral treatment, predominantly Lopinavir/Ritonavir alone or in combination with alpha-interferon, Arbidol (Umifenovir), or both. Antibiotics and corticosteroids were given to 45% and 26%, respectively Only one patient needed intensive care with mechanical ventilation. No deaths occurred as of the report.

Umifenovir (Arbidol) 200 mg TID, inhibits membrane fusion. and prevents contact between the virus and target host cells. Fusion between the viral capsid and the cell membrane of the target cell is inhibited. This prevents viral entry to the target cell, and therefore protects it from infection. Some evidence suggests that the drug's actions are more effective at preventing infections from RNA viruses than infections from DNA viruses [18]. The drug may be described as analog with similar efficacy to Tamiflu. Umifenovir is used primarily as an antiviral treatment for influenza. The drug has also been investigated as a candidate drug for treatment of hepatitis C. In 2007, Arbidol (umifenovir) had the highest sales in Russia among all over-the-counter drugs. Also in routine use in China, but not present in European markets [19].

More recent studies indicate that umifenovir also has *in vitro* effectiveness at preventing entry of Ebolavirus Zaire Kikwit, Tacaribe arenavirus and human herpes virus 8 in mammalian cell cultures, while confirming umifenovir's suppressive effect in vitro on Hepatitis B and poliovirus infection of mammalian cells when introduced either in advance of viral infection or during infection.

As well as specific antiviral action against both influenza A and influenza B viruses, umifenovir exhibits modulatory effects on the immune system. The drug stimulates a humoral immune response, induces interferon-production, and stimulates the phagocytic function of macrophages [18,19].

Umifenovir is used primarily as an antiviral treatments for influenza. The drug has also been investigated as a candidate drug for treatment of hepatitis C [12].

More recent studies indicate that umifenovir also has in vitro effectiveness at preventing entry of Ebolavirus Zaire Kikwit, Tacaribe arenavirus and human herpes virus 8 in mammalian cell cultures, while confirming umifenovir's suppressive effect in vitro on Hepatitis B

and poliovirus infection of mammalian cells when introduced either in advance of viral infection or during infection.

Notably, two compounds remdesivir (EC₅₀ = 0.77 μM; CC₅₀ > 100 μM; SI > 129.87) and chloroquine (EC₅₀ = 1.13 μM; CC₅₀ > 100 μM, SI > 88.50) potently blocked virus infection at low-micromolar concentration and showed high SI (symptom improvement) [10,13].

The Chinese National Health Commission said in the recently published online treatment guidelines for the virus that Tocilizumab, which is Mab anti-IL-6 can be used to treat patients with coronavirus with severe lung damage (ALI) and high IL-6 levels - 'cytokine storm'. Cytokine release syndrome (CRS) caused by interleukin 6 (IL-6) oversecretion is involved in the development of immunological and inflammatory reactions. Tocilizumab binds soluble as well as membrane bound interleukin-6 receptors, hindering IL-6 from exerting its pro-inflammatory effects. In March 2020, China approved tocilizumab for the treatment of inflammation in patients with the corona virus SARS-CoV-2. As of March 2020, there is no evidence whether this treatment is effective. Chinese health officials say that only a few patients have been asked to use this medicine [28]. Italy began clinical trial with Tocilizumab (Actemra, RoActemra) 8 mg/kg IV once in ICU. This Mab may reactivate TB and hepatitis, thus it is necessary to verify serologically potential latent infections before use [42].

In one study half of the patients were given antiviral agents, and more than half were given intravenous glucocorticoids. Patients treated with Lopinavir were from an ongoing clinical trial registered on Chinese Clinical Trial Registry (ChiCTR2000029308). Remdesivir was given to the first patients with SARS-CoV-2 pneumonia in the USA [4]. Trials on Remdesivir are about to recruit both mild to moderate patients (NCT04252664) and severe patients (NCT04257656) infected with SARS-CoV-2. Although, intravenous glucocorticoids were commonly used in patients with severe SARS or MERS pneumonia, their dosage remains controversial and their use to treat SARS-CoV-2 infection is also controversial. Lung protective Mechanical Ventilation is the main supportive treatment for critically ill patients. An ongoing clinical trial (NCT04244591) might shed some light on the safety and efficacy of these drugs as treatment [17].

Concerning the corticosteroids, there is a proven inverse relationship between the dosage and long duration of bolus corticosteroid use and mortality and survival in SARS. The sooner, the lesser and shorter, the better and faster the gain, prognosis and cure rate eventually. Another study finds that early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS [20]. In a multicentre, randomised controlled trial in a network of 17 intensive care units (ICUs) in teaching hospitals across Spain in patients with established moderate-to-severe ARDS (defined by a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 mm Hg or less assessed with a positive end-expiratory pressure of 10 cm H₂O or more and FiO₂ of 0.5 or more at 24h after ARDS onset). Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10. Patients in both groups were ventilated with lung-protective mechanical ventilation [20]. May be the SARS will remain the sole indication for their systematic use.

Favilavir is the first approved coronavirus drug in China. The National Medical Products Administration of China has approved the use of Favilavir, an anti-viral drug, as a treatment for coronavirus. The drug has reportedly shown efficacy in treating the disease with minimal side effects in a clinical trial involving 70 patients. The clinical trial is being conducted in Shenzhen, Guangdong province [14]. Favilavir/Favipiravir, also known as T-705 or Avigan, is an antiviral drug that was originally developed by Toyama Chemical of Japan (owned by Fujifilms) with activity against many RNA viruses.

The antiviral is a pyrazine carboxamide derivative that has been demonstrated to be effective against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus as well other flaviviruses, arenaviruses, bunyaviruses and alphaviruses. Activity against enteroviruses and Rift Valley fever virus has also been demonstrated and it has limited efficacy against Zika virus. In mouse models, it was also proven to be effective against Ebola.

The antiviral drug Galidesivir (BCX4430) has shown broad-spectrum activity against a wide range of pathogens including coronavirus. It is a nucleoside RNA polymerase inhibitor that disrupts the process of viral replication [14].

A team of German virology, genomic and pharmaceutical scientists at the Leibniz Institute for Primate Research has identified an existing Japanese drug called Camostat Mesylate (trade name: Foipan) that could treat the Covid-19 disease by blocking the SARS-CoV-2 binding and entry through ACE2. Moreover, Camostat mesylate inhibited infection of important target cells like human lung epithelial cells. Research findings showed that SARS-CoV-2 requires a cellular protein or protease present in the human body called TMPRSS2 to enter hosts' cells. This protease is a potential target to block for therapeutic intervention. Since Camostat mesylate has already been tested in

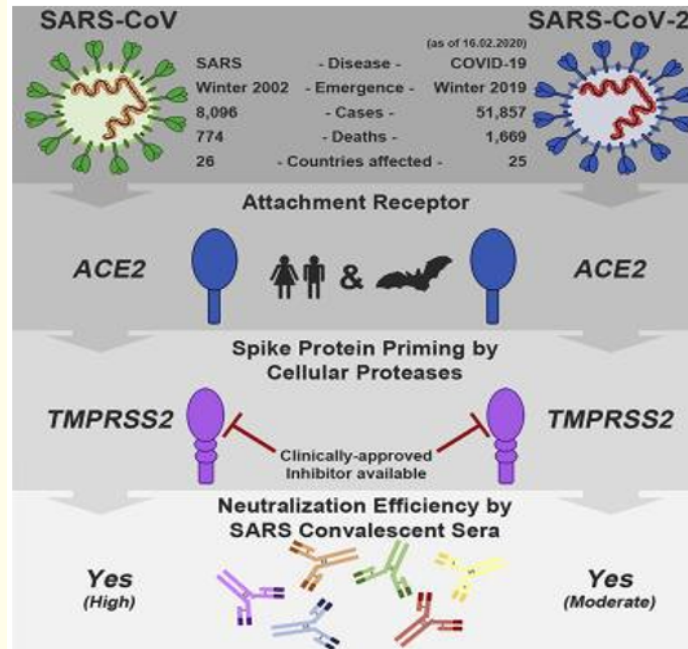


Figure 7 : Camostat mesylate (Foipan) blocks the entry of SARS-CoV-19 in the cell [39]. The Cellular Serine Protease TMPRSS2 Primes SARS-2-S for Entry, and a Serine Protease Inhibitor Blocks SARS-CoV-2 Infection of Lung Cells.

people, and was already approved by the Japanese FDA although not specifically for the treatment of COVID-19 disease, it could be easily repurposed [38]. In this context, it is noteworthy that the serine protease inhibitor Camostat mesylate, which blocks TMPRSS2 activity (Kawase., *et al.* 2012, Zhou., *et al.* 2015), has been approved in Japan for human use, but for an unrelated indication. This compound or related ones with potentially increased antiviral activity (Yamamoto., *et al.* 2016) could thus be considered for off-label treatment of SARS-CoV-2-infected patients [38,39]. It is approved for now in Japan for the treatment of pancreatitis.

An *in vitro* study shows that Camostat reduces significantly the infection of Calu-3 lung cells by SARS-CoV-2, the virus responsible for COVID-19.

The leronlimab (PRO 140), a CCR5 antagonist, as a potential coronavirus drug [14].

Brilacidin, a defensin mimetic drug candidate, as a potential treatment for coronavirus. Brilacidin has shown antibacterial, anti-inflammatory and immunomodulatory properties in several clinical trials [14]. As mentioned in the same review, there is a list of future major coronavirus drugs that pharmaceutical companies across the world are developing and that have the potential to become major coronavirus vaccines or antivirals for treating the contagious coronavirus infection.

Ifenprodil (NP-120; Algenon Pharmaceuticals) is a N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist. NMDA is linked to inflammation and lung injury. An injectable and long-acting oral product are under production to begin clinical trials for COVID-19 and acute lung injury [47].

Rintatolimod - The toll-like receptor 3 (TLR-3) agonist rintatolimod (Poly I:Poly C12U; Ampligen; AIM ImmunoTech) is being tested as a potential treatment for COVID-19 by the National Institute of Infectious Diseases (NIID) in Japan and the University of Tokyo. It is a

broad-spectrum antiviral agent [49].

Besides the already existing drugs, with variable efficacy which is determined by the need for MV and ARDS development, a new molecular viral target exists and give optimism. A potential drug target has been identified in a newly mapped protein of SARS-CoV-2, the virus that causes the coronavirus disease first discovered in 2019 (known as COVID-19). The structure was solved by a team including the University of Chicago, Argonne National Laboratory and the University of California, Riverside School of Medicine [21].

The protein Nsp15 from the new coronavirus is 89% identical to the protein from the 2010 outbreak of SARS. Studies published in 2010 on the SARS virus revealed that inhibition of Nsp15 can slow viral replication. This suggests drugs designed to target Nsp15 could be developed as effective drugs against COVID-19.

This new structure was solved by the group of University of Chicago Prof. Andrzej Joachimiak, director of the Structural Biology Center at Argonne's Advanced Photon Source, in conjunction with the Center for Structural Genomics of Infectious Diseases. Dr. Joachimiak is a co-director of the center [21].

"The newly mapped protein, called Nsp15, is conserved among coronaviruses and is essential in their lifecycle and virulence," said Joachimiak. "Initially, Nsp15 was thought to directly participate in viral replication, but more recently, it was proposed to help the virus replicate possibly by interfering with the host's immune response" Joachimiak added. The structure of Nsp15 is the first structure solved by the center.

SARS-CoV-2 is thought to infect host cells through ACE2 to cause COVID-19, while also causing damage to the myocardium, although the specific mechanisms are uncertain. Patients with underlying CVD and SARS-CoV-2 infection have an adverse prognosis. Therefore, particular attention should be given to cardiovascular protection during treatment for COVID-19 [29]. The mechanism of acute myocardial injury caused by SARS-CoV-2 infection might be related to ACE2. ACE2 is widely expressed not only in the lungs but also in the cardiovascular system and, therefore, ACE2-related signaling pathways might also have a role in heart injury. Other proposed mechanisms of myocardial injury include a cytokine storm triggered by an imbalanced response by type 1 and type 2 T helper cells and respiratory dysfunction and hypoxemia caused by COVID-19, resulting in damage to myocardial cells [29].

Conclusion

Many more drugs and vaccines are on their way to the clinical trials [14] but even in the present, in everyday clinical practice, we are disposing with enough potent therapeutic arsenal to treat effectively or at least to diminish the severe lung injury and the need for MV and to improve prognosis, which might be not so grim if treated timely and properly, using the clinical experience of the teams of practitioners and researchers worldwide in their quest for better and even more efficient treatments and vaccines against COVID-19.

According to China National Center for Biotechnology Department head Zhang Xinmin, Favilavir demonstrated encouraging profile with mild adverse reactions in coronavirus patients in trials in Shenzhen, Guangdong province [14].

The three drugs showing efficacy currently are anti-malaria drugs Chloroquine and Plaquenil, Gilead's experimental IV drug Remdesivir and Protease Inhibitors, boosted or not. Favilavir (Favipiravir) is ready for use, but Interferons need more to be done in order to prove clinical efficacy. Corticosteroids are aimed at the immune response, not to virus itself and must be wisely selected in complicated and ventilated ARDS cases.

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