Fight against SARS-CoV-2: treatments and prevention. What are the pros and cons of drug therapies?

Field: Science Output

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Abstract

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has recently emerged as the etiological agent of Coronavirus Disease 2019 (COVID-19), which causes serious respiratory illness such as pneumonia and lung failure. COVID-19 pandemic represents most probably the greatest global public health crisis of this generations since the pandemic influenza outbreak of 1918.

No proven effective therapies for this virus currently exist. Besides the novelty of this virus and its related disease, it is now emerging a rapid expanding knowledge regarding SARS-CoV-2 virology that is providing a significant number of potential drug targets. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlights both - the need and capability to produce high-quality evidence even in the middle of a pandemic.

Introduction

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019, and has since spread worldwide.

The new CoV, which belongs to betacoronaviruses based on sequence analysis, can infect the lower respiratory tract and cause pneumonia in human, but it seems that the symptoms are milder than SARS and MERS (Middle East Respiratory Syndrome Coronavirus) [1].

At the moment, there is no single specific antiviral therapy for CoV and the main treatments are supportive.

Emerging data suggest that many patients infected with COVID-19 may die due to an excessive response of their immune system, characterized by the abnormal release of circulating cytokines, termed cytokine release syndrome (CRS). CRS plays a major role in the deterioration of COVID-19 patients, from pneumonia through acute respiratory distress syndrome (ARDS), cumulating in systemic inflammation and ultimately multi-system organ failure.

COVID-19 Viral Lifecycle and Potential Drug Targets

Unravelling which cellular factors are used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets.

SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Following receptor
binding, the virus particle uses host cell receptors to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein. Once inside the cell, viral proteins are synthesized that encode the enzyme that catalyzes the virus replication (replicase-transcriptase complex), which leads to RNA synthesis via its RNA polymerase. Eventually structural proteins are synthesized to complete the assembly and release of viral particles. These viral lifecycle steps provide potential targets for drug therapy (Figure 1) [1][2][3].

![Figure 1. Viral Lifecycle and Potential Drug Targets.](image)

Cellular and viral factors used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets (credit: James M. Sanders, PhD, PharmD; Marguerite L. Monogue, PharmD; Tomasz Z. Jodlowski, PharmD; James B. Cutrell, MD. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). A Review. JAMA, 2020; 323(18):1824-1836).

Inhibition of the viral proteins (Protease inhibitors as Lopinavir) or the RNA genetic material (Ribavirin) are potential targets of drugs that prevent viral replication by blocking the crucial enzymes. In addition drug targets include the inhibitors of viral cell entry (Camostat mesylate) and the membrane fusion of the viral envelope (Arbidol).

The massive production of pro-inflammatory cytokines (cytokine storm) has been associated with the immunopathogenesis and high mortality rate of SARS-CoV.

Many cytokines take part in the “cytokine storm” in COVID-19 patients, among which a crucial role seems to be played by IL-6, whose increased levels in the serum have been correlated with respiratory failure and adverse clinical outcomes. This suggests a crucial role for IL-6, classifying it as a potential target for COVID-19 targeted therapy (Tocilizumab and Sarilumab). Those monoclonal antibodies are under way for clinical trials for the management of COVID-19 patients with severe respiratory complications [4].
General treatment for viral infection

Based on the SARS-CoV-2 lifecycle, several trials are currently ongoing in order to study the response of the virus to different pharmacological therapies. Since SARS-CoV-2 is a new and relatively unknown virus, most clinical trials are based on molecules that are known to have effect against other well-known viruses and related diseases. Such therapies can be used to relieve COVID-19 related symptoms or can be directed to the virus itself, targeting a particular protein or other molecular structures.

**Antiviral Therapies**

Several drugs that were used to treat other coronaviruses related respiratory syndromes (e.g. SARS or MERS) have been repurposed to treat COVID-19. Such molecules can interfere with the virus infection in different phases (Figure 1): binding of the virus to the host cell, endocytosis (entrance of the virus inside the cell) of the virus, replication and translation of the viral genome, assembling of codified viral protein into a new-born virus [2]. Coronavirus specific treatment can thus include inhibitors of viral proteases or nucleosides analogs.

**Antibiotics**

Antibiotics have no effect on viruses since they are directed against bacteria. Nevertheless, bacterial co-infections are quite common during viral infections and antibiotics can prevent, in patients with low immune function, these bacterial co-infections whilst strengthening the immune support, leading to a better recovery. Antibiotics that were used in COVID-19 patients are cephalosporins, carbapenems and quinolones [5].

**Immunoenhancers**

Since the viral infection can trigger to an exaggerated and amplified activation of the Immunological System of the host, other therapies are dedicated to control such immune response that can damage multiple organs (e.g. “cytokine storm”) [6]. Other therapy that is used for viral infection is related to the use of interferons that, on the other hand, help the innate immune response.

**Gammaglobulins**

Treatment with gammaglobulins is a well-known therapy for many diseases. The rationale for this treatment is that antibodies from recovered patients may help with both free virus and infected cell immune clearance. In theory, the benefits of this therapy would accrue primarily within the first 7 to 10 days of infection, when viremia is at its peak and the primary immune response has not occurred yet. Being the outbreak relatively recent, commercial preparations of this virus-specific antibodies are still not available [2]. As soon as the pool of patients who have recovered from COVID-19 globally increases, several safety and efficacy trials of this modality are ongoing through the use of hyper-immune plasma.

**Fusion proteins**

Other than drugs that are already known in R&D and clinical fields, some other new developments are ongoing in the biotechnologies. Since SARS-CoV-2 requires binding to ACE2 receptor to infect humans, a proposed ACE2-IgG1 fusion protein has been hypothesized to exert neutralization potential of the virus [7].
The Table 1 below shows the results of the main Clinical Trials performed during the first months of the virus spread.

![Table 1. Summary of Treatment and Clinical Outcomes from early COVID-19 Clinical Series](adapted from JamesM. Sanders, PhD, PharmD; Marguerite L. Monogue, PharmD; Tomasz Z. Jodlowski, PharmD; James B. Cutrell, MD. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19). A Review. JAMA, 2020; 323(18):1824-1836)

### Clinical Pharmacologic Treatments

**AIFA authorizations for Covid-19 disease**

In a relevant section AIFA provides updates about the drugs used outside clinical trials (off-label use), such as those marketed for other indications that are made available to patients, even in the absence of a specific therapeutic indication for COVID-19, based on scientific evidence often rather limited. Those drugs are listed below:

- **Azithromycin**: it lacks the evidence of efficacy in the treatment of COVID-19 and the several side effects of the antibiotic allow to recommend the use of the antibiotic only in cases of bacterial overlaps.

- **Lopinavir/Ritonavir**: the association used in the treatment of HIV can be considered, limiting it to patients COVID-19 of less severity, in the early stages of the disease.

- **Darunavir/Cobicistat**: the anti-HIV therapy of darunavir/cobicistat can be considered as an alternative to lopinavir/ritonavir when later it is not tolerated for diarrhoea.

- **Low-molecular-weight heparin (LMWH)**: used in venous thromboembolism and pulmonary embolism, it can be considered early in the disease when pneumonia is present and one
occurs hypomobility of the patient with lodging. In this phase, the LMWH must be used prophylactic dose in order to prevent venous thromboembolism; in the more advanced stage it can be used at therapeutic dose in patients hospitalized to contain thrombotic phenomena as a consequence of hyperinflammation.

**Bites from ongoing clinical trials**

Out of several ongoing clinical trials noteworthy is the first potential drug **LY-CoV555** emerged from the collaboration between Lilly and AbCellera specifically designed to treat the virus. It is a neutralising immunoglobulin G1 monoclonal antibody directed against the spike protein of SARS-CoV-2.

The RECOVERY study, launched in March, is one of the largest randomized controlled trials in the world for coronavirus treatments that report the potential of the cheap and widely available steroid (Dexamethasone) to cut deaths by one-third among patients critically ill with COVID-19 [9].

**Conclusion**

Despite the fact that SARS-CoV-2 spread is new and most of its details are not very well known yet, during the last months there has been a significant development and research on various therapeutics, with some of them being quite promising. There have been several Clinical Trials on COVID-19 patients using some of well-known small molecules or other kinds of therapies (e.g. hyper-immune plasma) and many of them have been reported to be very promising, too. However, the lack of clinical evidence, due to the short period of time that this virus and its related pathogenicity has been known, may lead to unpredictable clinical prognosis, thus no therapy has been elected as first-choice yet. Many progresses shall still be made and particular care shall be used considering that some drugs may lead to severe side effects that can be even more dangerous than the virus itself if not well administered.

**Glossary**

- **ACE2**: Angiotensin-Converting Enzyme 2
- **AIFA**: Agenzia Italiana Del Farmaco (Italian Drug Agency)
- **ARDS**: Acute Respiratory Distress Syndrome
- **CoV**: Coronavirus
- **COVID-19**: Coronavirus Disease 2019
- **CRS**: Cytokine Release Syndrome
- **HIV**: Human Immunodeficiency Virus
- **IFN**: Interferon
- **Ig**: Immunoglobulin
- **IL**: Interleukin
- **LMWH**: Low-Molecular-Weight Heparin
- **MERS**: Middle East Respiratory Syndrome
- **RNA**: Ribonucleic Acid
- **S**: Spike Protein
- **SARS**: Severe Acute Respiratory Syndrome
SARS-CoV-2  Severe Acute Respiratory Syndrome Coronavirus 2
TMPRSS2  Type 2 Transmembrane Serine Protease
TNF  Tumor Necrosis Factor

References

[8] www.aifa.gov.it
[9] www.nature.com