Mini Review
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COVID-19: An Immunological Perspective

Summary

The dilemma posed by the pandemic of COVID-19 is unprecedented in our lifetime. The number of treatment modalities that have advanced for testing demonstrates the widespread international cooperation to respond to the crisis. This review aims to distill some of the key responses to this pandemic. Included is a brief background to the virus, and its mechanism of action. Most importantly, it includes an overview of some of the key efforts that are being made by the medical and scientific community to develop treatments and vaccines to arrest the rise of the pandemic and, ultimately, cure the disease.

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Background

The corona virus (CoV) belongs to a large family of viruses that has been defined as a novel respiratory tract virus common in many different animals including camels, cattle, cats, and bats. These viruses rarely infect and cause illness in humans, but when it occurs, ranges widely in severity. The first known severe illness emerged in 2003 with Severe Acute Respiratory Syndrome (SARS) and was followed by Middle East Respiratory Syndrome (MERS) in Saudi Arabia in 2012. The most recent outbreak is a novel strain that also causes severe illness and is termed SARS-CoV-2 or COVID-19. The name originates from the bulb-tipped spikes that project from the virus's surface giving the appearance of a corona surrounding it.[1]

Mechanism of action

The research community has responded very rapidly to sequencing the COVID-19 virus genome. Within a month of sequencing, scientists revealed the genetic template for spike proteins, projections on the outside of the virus, which allows it to grab and penetrate the host cell. The receptor-binding domain (RBD) has evolved to target angiotensin-converting enzyme 2 (ACE-2), a receptor involved in regulating blood pressure.[2]

The infection begins when the long spike proteins that protrude from the virus particle latch on to the ACE-2 protein. From this point, the spike transforms, unfolding and refolding itself using coiled spring-like parts that start out buried at the core of the spike. The reconfigured spike hooks and docks the virus particle to the host cell. This forms a channel allowing the viral genetic material into the unsuspecting cell, in the case of COVID-19, type II lung cells. As with SARS, most of the damage in COVID-19 results from the immune system going into overdrive to stop the virus from spreading.[3] The influx of immune cells to the infected tissue cause enormous amounts of damage in the process of cleaning out the virus, infected cells, and bacterial infections, with potentially lethal consequences.

Potential treatments

The clinical features of COVID-19 range from moderate (cough, mild fever) to severe (pneumonia and acute respiratory distress syndrome (ARDS)). Diagnosis is made by testing specimens using a Real-Time Reverse Transcriptase (RT-PCR) diagnostic kit. There are several therapeutic modalities that are currently under investigation. The following sections outline some of the main strategies deployed to treat the disease.

Antivirals: Antiviral drugs stop the virus from replicating. Although there are currently no antivirals that specifically target COVID-19, drugs that have been used to treat other viral infections are being tested. These drugs must target the specific phase of the virus's life cycle necessary for it to reproduce and, critically, must kill the virus without killing the host cell required for its survival.

An example of an antiviral that is under investigation is remdesivir. It is a nucleoside analogue and broad-spectrum antiviral that shuts down viral replication by inhibiting a key viral enzyme, the RNA polymerase. Human clinical trials are underway. Although one report suggested that the treatment did not improve patients' condition,[4] preliminary data from other trials indicate that it may become a potential treatment.

Favipiravir is an antiviral that also works by the selection inhibition of RNA-dependent RNA polymerase. It has been approved in China earlier this year for the treatment of novel influenza and is also currently undergoing clinical trials to treat COVID-19.

The list of compounds that could make an effective COVID-19 treatment grows longer each day. It has been reported that administrating the antiviral EIDD-2801 improved pulmonary function, reduced virus titer and body weight loss in mice infected with the virus.[5] Moreover, an inhibitor of the cellular serine protease TMPRSS2, which primes the virus for entry into the cell, has been shown to block infection of lung cells.[6]

Anti-inflammatories/antibodies: Anti-inflammatories are used to treat patients once the immune system is overwhelmed. After the immune system recognizes the potential threat, in this case a viral or secondary bacterial infection, it elicits the overproduction of immune cells. This in turn leads to the production of their activating compounds called cytokines, referred to as a "cytokine storm". One class of cytokine, chemokines, is specific for attracting cells to sites of infection and inflammation. Several types of cells are able to secrete these chemotactic cytokines, including phagocytic cells such as macrophages, neutrophils, and endothelial cells.

Several anti-chemokine drugs exist and are FDA approved. They are used to treat diseases such as autoimmune diseases like rheumatoid arthritis, and work by dampening the effects of the

cytokine storm. One of the most notable of these is anti-IL-6 or IL-6-receptor (R) blocking antibodies like tocilizumab (Actemra). This drug is currently approved for treating the cytokine storm resulting from cancer treatments.[7] Others include siltuximab (Sylvant) and sarilumab (Kevzara), that are FDA-approved for various conditions, including rheumatologic disease and the lymphoproliferative disorder Castleman's syndrome. These drugs also work by blocking IL-6/IL-6 (R). Although the anti-malaria drug, hydroxychloroquine, has been promoted as a potential treatment, there is no conclusive data at this point. It will take the results of ongoing clinical trials to determine whether it will become a viable therapy.

Another group of antibody-based treatments use the convalescent plasma (plasma from recovered COVID-19 patients). This treatment involves administering the plasma into someone infected with the virus. Antibodies from the recovered individual should weaponize the patient's immune system by neutralizing the virus. Studies are currently underway to test the efficacy of this particular treatment. People who have fully recovered from COVID-19 for at least two weeks and are eligible to donate blood are encouraged to consider donating plasma. Individuals must have had a prior diagnosis of COVID-19 documented by a laboratory test and meet other donor criteria. One unit (200mL) of convalescent plasma is considered a therapeutic dose. The most important criteria for recipient eligibility include laboratory confirmed COVID-19 and the symptoms must be severe or immediately life-threatening.

Manufactured monoclonal antibodies are antibodies developed in mice and then modified into drugs that can be injected into patients. A manufactured antibody, or a mixture of manufactured antibodies, may have a more consistent impact than blood plasma and can also be used off-the-shelf. Antibodies against EBOLA were successfully developed. A similar strategy is underway to treat COVID-19 by binding viral proteins.[8]

Vaccines

Vaccines ultimately offer the most appealing and robust therapeutic modality as they prevent the disease from taking hold in the first place. The global vaccine R&D effort in response to the pandemic is unprecedented in terms of scale and speed. At the time of writing, there are currently 115 vaccine candidates (with more coming onstream), 73 of which are confirmed as active and are currently at exploratory or preclinical stages, 5 are in human clinical trials.[9]

Another key development with respect to vaccines is the range of technology platforms being evaluated, including nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating), recombinant protein, live attenuated virus, and inactivated virus approaches. In addition to the platforms under investigation, another mechanism of enhancing immunogenicity are adjuvants. These enhance the immune response to lower doses, enabling vaccination of a larger number of people without compromising immune protection.

Conclusion

This pandemic, striking globally in such a relatively short-time frame, has focused the minds of politicians, physicians, and scientists to come up with solutions. The research community has responded very rapidly and learned about structures of the virus spike protein and ACE-2 protein just over a month after the genetic sequence became available. The World Health Organization (WHO) and others want to repurpose drugs that are already approved for other diseases and have acceptable safety profiles. It is likely that a combinatorial approach utilizing different treatment modalities will be most successful. For example, utilizing drugs that target both the virus directly and the resultant downstream cytokine storm. Moreover, it is recommended that a strict test, isolate and contact tracing strategy be deployed in the event of a second wave of COVID-19.

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Conflict of interest

There is no conflict of interest.

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