Understanding Current and Future Therapeutic Options for COVID-19

In recent weeks, the world has welcomed very positive and much anticipated news on the COVID-19 vaccine front. At least two high-profile vaccines (mRNA vaccines from Pfizer/BioNTech and Moderna) have been authorized for use by global regulatory authorities in the US, UK, and some countries in Europe and Asia. Even though vaccines are now available to some, it will take months before the entire US population has been vaccinated, due to logistics and limited supply. As Europe and the US encounter some of the worst outbreaks of the virus since last spring, physicians and scientists continue to look for new and re-purposed therapeutics to treat COVID-19 patients.

With ongoing widespread outbreaks of COVID-19, people will continue to get sick and require life-saving treatment until there is sufficient herd immunity through a combination of immunizations and naturally acquired immunity. Ultimately, symptom-based therapeutics will save thousands of lives before we reach population-level immunity.

This blog reviews the current state of treatments and therapeutic research related to COVID-19. This is not intended to be an exhaustive discussion of all interventions being studied or used for the disease but provides a summary of some common treatment perspectives. As COVID-19 research continues to evolve, this discussion will likely shift. Ultimately, individual treatment strategies are the responsibility of physicians.

Current Treatment Options for the Three Stages of COVID-19

In the early days of the COVID-19 pandemic, there were many unknowns. As with any novel pathogen, a lot of attention was initially focused on characterizing the molecular signature of SARS-CoV-2 to better understand its origin and how to treat it. Through swift efforts in virology, it quickly became clear to researchers and physicians that we were dealing with a novel coronavirus. Coronaviruses are a large family of viruses that can cause mild to severe respiratory illness in humans.

Before 2002, endemic coronaviruses were known to cause mild symptoms associated with the common cold. Two new coronaviruses emerged in the 2000s, SARS-CoV and MERS-CoV (commonly called SARS and MERS), that were associated with much more severe,

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even fatal, disease. While the spread of SARS and MERS was limited compared to our current pandemic, all of these viruses have the potential to cause fatal illness with a plethora of respiratory and non-respiratory symptoms.

Early in the pandemic, physicians noted that asymptomatic or mildly symptomatic infection was common, but they also recognized a pattern of disease progression in those patients who developed severe COVID-19 symptoms. In an article published in March 2020, Siddiqi et al. (2020) proposed a clinical staging system, with three escalating phases of COVID-19 disease progression, that hinges on "distinct clinical findings, response to therapy, and clinical outcome."

STAGE I (EARLY INFECTION)

Stage I represents the time from onset of inoculation (first encounter with the SARS-CoV-2 virus) through early establishment of the disease. Common hallmark symptoms of this stage include rapid viral replication in the respiratory system, lymphopenia (or a reduced amount of certain white blood cells in the blood) and onset of mild, non-specific symptoms like malaise, fever, and dry cough. Treatment at this stage has focused on reducing the viral load and treating the mild symptoms.

Therapeutics that may be effective during Stage I (particularly for high-risk individuals) include therapies like polyclonal and monoclonal antibodies, and (rarely) convalescent plasma. Standard cold and flu medicines may also be used with the advice of physicians. These include non-steroidal anti-inflammatory drugs (NSAIDS) like acetaminophen, ibuprofen and naproxen for pain management and fever reduction, and drugs like guaifenesin and dextromethorphan for moderating wet and dry coughs, respectively.

STAGE II (PULMONARY PHASE)

COVID-19 that progresses to Stage II is characterized by more serious symptoms. These individuals are said to have moderate disease with pulmonary involvement, and some may experience hypoxia (oxygen deprivation due to inadequate respiration). During this stage, patients also experience a more severe cough and difficulty breathing. As the body's immune system targets the viral infection in the lungs, inflammation can increase markedly as evidenced by opacities upon chest imaging.

Many of the same therapeutics mentioned for the treatment of Stage I are also used in patients that progress to Stage II. Further interventions in Stage II include the use of the antiviral, remdesivir (in hospitalized patients), supplemental oxygen for patients with reduced blood oxygen, and the introduction of corticosteroids like dexamethasone. There is some debate among experts as to exactly when in the course of disease corticosteroids should be started. Dexamethasone has proven effective in reducing mortality by preventing aberrant, destructive immune responses; however, the inherent risk of introducing immunosuppressive drugs too soon is that viral clearance could be halted prematurely, allowing viral loads to rebound. As with all therapeutics, physicians must weigh the pros and cons for each individual patient.

STAGE III (HYPERINFLAMMATION PHASE)

The symptoms associated with Stage III COVID-19 are much more serious. Acute respiratory distress syndrome (ARDS) is one life-threatening complication associated with advanced COVID-19. ARDS is defined by widespread lung injury and an inability to supply the body with enough oxygen to sustain basic organ functions. Late-stage COVID-19 is also known to be associated with septic shock and cardiovascular events, among other systemic conditions.

Perhaps one of the most distinct features of Stage III disease cannot be observed through symptoms alone, but through blood biomarkers. An out-of-control immune response, also called a "cytokine storm," is a common feature of the worst cases of COVID-19. While corticosteroid administration can help modulate some inflammatory activity, physicians have also looked to cytokine inhibitors to reduce the levels of pro-inflammatory cytokines that are found in high concentrations in the blood of patients with severe COVID-19.

As with corticosteroid use, the introduction of cytokine inhibitors is a complex balancing act. On one hand, we know that cytokines are implicated in the immune-mediated destruction of lung cells in COVID-19; but, on the other hand, we do not fully understand the relationship between different cytokines or the inflammatory processes that are at play in severe disease. Inhibiting a single type of cytokine may prove ineffective or even detrimental.

Unlike in mild to moderate COVID-19 patients, antiviral therapies may be ineffective at altering the course of disease in Stage III COVID-19 patients. In most cases of Stage III, the primary viral infection has taken a backseat to the hyperinflammatory processes in terms of perpetuating illness.

An intervention that is used almost exclusively in patients experiencing the most severe complications of COVID-19 is mechanical ventilation. Ventilators can be helpful in preventing widespread organ failure and allowing time for the lungs to heal, but their use is rarely seen as a viable long-term solution and has been the subject of some controversy in recent months.

Future COVID-19 Treatments

The list of new and repurposed drugs being investigated for possible treatment of COVID-19 is lengthy. As of January 2021, there are currently over 4,000 studies on ClinicalTrials.gov, including 173 vaccine studies, 1,387 drug studies, and 516 mapped drug names. Preclinical data and clinical trial results emerge for new experimental therapeutics regularly. The World Health Organization (WHO) maintains an exhaustive list of COVID-19 clinical trials here. The U.S. FDA Coronavirus Treatment Acceleration Program (CTAP) also features an overview of the types of drugs being studied for the treatment of COVID-19 which include:

- Antiviral drugs
- Immunomodulators
- Cellular and gene therapies
- Neutralizing antibodies

ANTIVIRAL DRUGS

In vulnerable populations and individuals with multiple risk factors for severe COVID-19, the best way to prevent health deterioration after exposure is to limit viral replication before it prompts an uncontrollable immune response. While remdesivir has shown mixed results (positive effect vs. no significant effect) in improving clinical outcomes, the ideal COVID-19 antiviral drug would meet the following criteria:

- Immediate availability (prescription or over-the-counter access) after exposure to fight off the virus before it multiplies in large numbers in the lower respiratory tract. Keeping the viral load low early on gives the immune system time to mount a measured response to clear the virus. Success of these therapeutics would be greatly improved with widespread deployment of rapid antigen testing for at-home use.
- Ease of administration in either pill or nasal spray formulations so that the drug can be administered readily outside clinical settings. Current antivirals for COVID-19 require IV infusions and are reserved for inpatients.
- High affinity or specificity for the SARS-CoV-2 virus. Future antiviral development for COVID-19 will need to focus on delivering the drug to the correct cells in a form that can be readily used to disrupt viral processes; a combination therapy targeting two or more viral processes may prove most effective. The ideal antiviral should also show activity against possible SARS-CoV-2 variants, with minimal risk for driving mutation through artificial selective pressure.
- Lastly and most importantly, future antivirals need to be safer and more effective than other standard care options. Ideal antivirals would be given soon after exposure to prevent the onset of severe symptoms, and side effects of the antiviral will need to be minimal to justify the inherent risk of drug intervention in patients not yet showing severe symptoms. Studies should include large, diverse populations and explore potential drug interactions.

There are ongoing clinical trials for antivirals that check some of these boxes, but the search for a highly effective drug or combination of drugs remains elusive.

IMMUNOMODULATORS

In a disease like COVID-19, which is greatly exacerbated by dysfunctional immune responses, it is no surprise that immunomodulators are garnering attention from drug developers. There are several of these drugs currently in development for COVID-19, but none have been authorized yet by the FDA.

Most of the work with immunomodulators so far has focused on cytokine and kinase inhibitors. These drugs bind to and block chemical messengers and enzymes that are thought to perpetuate out-of-control immune responses, like in severe COVID-19 cases. Thus far, our limitations in deploying effective immunomodulators are the result of knowledge gaps in how to recognize and when to treat cytokine storms, which can be difficult to predict and have a rapid onset. Furthermore, once started, cytokine storms can make stabilizing a patient's health difficult.

CELLULAR AND GENE THERAPIES

Cellular and gene therapies are relatively new to the medical world and are not here for COVID-19 yet, but it is possible to envision a genetic approach to treating COVID-19 or similar infectious diseases because of "proof-of-concept" in the Pfizer and Moderna vaccines. These vaccines are not true gene therapies because they do not modify DNA or gene expression; instead, they use manufactured mRNA to exploit the cell's normal protein-making processes. The proteins produced are recognized by the body's immune system as foreign, and a targeted, memory-based immune response can be activated by future exposure to the virus. As we learn more about the role of genetics in COVID-19, we may also be able to better treat and prevent the disease in uniquely susceptible individuals.

Future cellular therapies may be useful for COVID-19, as well. AlloVir and Baylor College of Medicine are partnering to develop virus-specific T cells (VSTs) which may prove useful in the fight against many viral diseases, including COVID-19. By "priming" donor T cells against the virus of interest, in this case SARS-CoV-2, and then administering these cells to COVID-19 patients, AlloVir hopes to prevent the development of severe disease in high-risk patients. A Phase I, dose-finding study is ongoing since the company received the IND approval from the FDA in 2020.

NEUTRALIZING ANTIBODY THERAPIES

Unlike cellular and gene therapies, neutralizing antibody therapies for COVID-19 are here now. In fact, at least one therapy, bamlanivimab, has received emergency use authorization from the FDA "for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients." The drug is intended for patients who are at high risk for progressing to severe COVID-19 and/or hospitalization, and like with antivirals, it is assumed that earlier treatment is most effective at preventing negative outcomes.

Antibody therapies work by jumpstarting your body's healthy immune response to the viral invasion. Because SARS-CoV-2 is new and our bodies have never encountered it before, it takes time for us to generate a targeted defense against it. Antibody therapies provide your body with these "armies of viral warriors," which are artificial proteins that are specifically engineered to bind to and neutralize the novel coronavirus. For now, antibody therapies specifically target the current spike protein of the virus, which it uses to enter human cells, but future antibody cocktails may bind different spike sequences and even more sites on the virus, offering better protection from severe COVID-19 disease and any future viral variants.

Conclusions

The COVID-19 pandemic remains a problem throughout the world. Despite the tremendously positive news of safe and effective vaccines being administered to thousands of people every day, the novel coronavirus will continue to spread until global herd immunity is reached – a goal that may not be attained for quite some time. Even then, public health professionals will need to stay vigilant of possible viral mutations. Having multiple reliable therapeutics in our COVID-19 arsenal will help us to quickly gain control of future outbreaks.

We have learned a lot about COVID-19 and how best to treat it during different stages of disease progression; however, it is important to continue researching new and more effective ways to treat COVID-19 and other infectious diseases. Antivirals, immunomodulators, cellular and gene therapies, and neutralizing antibodies are just a few of the therapies that may hold promise for treating COVID-19.

Nuventra has experience with many different types of COVID-19-related programs, including new and repurposed drugs. Contact one of our senior consultants today for help with your program.