Review Article

A Review on Current Therapeutic Options for COVID-19

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ABSTRACT

The world is ravaged by SARS-CoV-2 infection with more than 45 million cases and 1 million deaths worldwide. And the rate of infection is nowhere appears to slow down. This unprecedented magnitude of pandemic in recent times pushed the world into a state of despair. Currently no treatment is approved and most of the choices are under clinical trials. All the treatment options have to pass through the rigorous studies to get approved. This must take a very long time. In this article, we are evaluating some of the therapeutic options available currently to tackle the COVID-19 at least until a definite treatment or vaccine is available. And we tried to present the differences between flu and COVID-19 and also the past Coronavirus epidemics versus the COVID-19.

Keywords: COVID-19, SARS-CoV-2, Coronavirus, Pandemic, Epidemic.

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FLU vs. COVID-19

Flu and COVID-19 both are respiratory diseases of viral infection. Symptoms and manifestations of the COVID-19 are also similar to Flu. Flu is caused by Influenza virus mainly Influenza A and Influenza B. And the COVID-19 is caused by a novel Coronavirus (SARS-CoV-2). Coronaviruses are a large family known to us for many years. Normally Flu symptoms would appear in 1-4 days but in COVID-19 it may range from 1-14 days indicating that they have developed some evading techniques from the immune system. Flu patients experience symptoms abruptly but in COVID-19 patients experience the symptoms gradually. And shortness of breath is more common with COVID-19 patients. Also COVID-19 is more severe than flu as 15% of COVID-19 patients hospitalized and 5 % require ventilator support, as per WHO. And also mortality is more in COVID-19 than flu as per the initial research.

History and epidemiology of past Coronavirus pandemics

Human Coronavirus first characterized in the 1960s and is popularly known for causing upper respiratory tract infections in children. Recent years saw Corona epidemics like SARS in 2003, MERS (Middle Eastern Respiratory Syndrome) in 2012. Since 2003 five new human Coronaviruses have been identified. The 2003 SARS outbreak put the animal Coronavirus in focus.

The SARS virus was easily grown in tissue culture and enabled its genomic sequencing quickly. And it significantly differed from already known human and animal Corona viruses made it into a new group.

The reported SARS infections were 8098 with 774 related fatalities that affected 29 countries in the 2003-04 outbreak.[1] The case fatality ratio was 11% according to the WHO.

And 2494 infections with 858 related fatalities were reported with 2012 MERS outbreak that affected 27 countries. Case fatality ratio was 34.4% according to the WHO.

As of October end, 45 M cases with nearly 1.2 M deaths were reported due to SARS-CoV-2 affecting 213 countries. Case fatality ratio is 6.84. The rate of admission in ICU in the hospitalized patients for pneumonia is 25.9%. And 25% of patients developed ARDS (acute respiratory distress syndrome).[2]

38 pregnant women with SARS-CoV-2 infection were studied and found that unlike SARS and MERS, COVID-19 did not lead to maternal deaths and in similar to SARS and MERS, SARS-CoV-2 did not pass through placenta to infect fetus. At this point of time there is no evidence that SARS-CoV-2 can infect fetuses by intrauterine or trans placental transmission. Additional information is required to confirm this.[3]

One striking difference between past Corona virus epidemics and COVID-19 is Patients with COVID-19 become fairly infectious even before they start experiencing symptoms. But in SARS and MERS patients became infectious when they were quite sick. The sick people were recognized and treated or at least infection could be prevented to other people by isolating them. But COVID-19 patients tend to infect others even before they start experiencing symptoms and most of the cases go

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unrecognized and keep on infecting others. Even Though fatality rate for COVID-19 is less, it resulted in more deaths as patients often go unrecognized and infect more numbers of people.

Antiviral treatment

Ubiquitous use of influenza drug Tamiflu / Oseltamivir may not act against novel Coronavirus as it is highly selective to Influenza. Initial research by Hong Kong University, School of Public Health found that Tamiflu does not have any antiviral effect on SARS-CoV-2.[4] Several drug regimens of Tamiflu are currently under clinical trials, more information on effects of Tamiflu against novel Coronavirus will be revealed later.

Many antiretroviral drugs are currently under study for their antiviral property against novel Coronavirus. Lopinavir/Ritonavir along with Ribavirin showed decreased fatality rate and disease course in an open label trial in SARS patients in 2003.

Galidesivir is a broad spectrum antiviral drug that acts by inhibiting nucleoside RNA polymerase. Survival benefits of this drug have already been noted against Zika and Ebola virus. Currently it is in an advanced stage of development.

Among all the drugs, currently under trials, the most promising one is the Remdesivir. It was developed by Gilead pharmaceuticals to treat Ebola but found to be ineffective. It is currently under trials to find its efficacy on the novel Coronavirus. One double blind RCT study is currently in phase III involving 761 patients in multiple hospitals of Wuhan. In another study it was found that intravenous Remdesivir did not statistically decrease mortality or did not show clinical improvement in severe cases.[5] In another clinical trial conducted in USA in more than 1000 patients it was observed that Remdesivir improved the recovery of the patients with COVID-19 and it was statistically significant.[6] For placebo treated patients duration of recovery was 15 days while patients on Remdesivir recovered in 11 days on an average. And also it decreased the mortality but it was not statistically significant. Later the trial was stopped on ethical grounds to give treatment to patients on placebo group with Remdesivir as it was found effective. And FDA has given the emergency use authorization for Remdesivir to treat COVID-19.

Another antiviral drug, Favipiravir is also one of the promising options. This drug has already been approved by The National Medical Products Administration of China. A study conducted in Shenzhen, Guangdong province involving 70 patients reported that Favipiravir is effective in treating COVID-19 with minimal side effects.[7] In another open-label controlled study also suggesting that Favipiravir is associated with faster rate of viral clearance and clinical improvement. Radiological findings also showed the difference between control arm and treatment arm. And also treatment group reported minimal side effects.[8]

Hydroxychloroquine

Hydroxychloroquine showed its inhibitory effect on viral cell entry and replication in vitro. In 100 patients of COVID-19 it showed positive results in both virological and clinical outcomes.

In another non randomised open-label study involving 36 patients it was reported that Chloroquine had significant effects in reducing nasopharyngeal swab positivity for SARS-CoV-2. In this study 14 patients were treated with Chloroquine alone and 6 patients with Chloroquine and Azithromycin and the remaining 16 patients were in the control group. All patients in concurrent therapy with Chloroquine and Azithromycin had negative viral swabs for SARS-CoV-2 after treatment for 6days. In the Chloroquine alone group, 8 out of 14 were tested negative. And in the control group 2 out of 16 tested negative for SARS-CoV-2. This study has limitations for lack of blinding and limited sample size and many more clinical trials are underway as this is a topic of interest for many scientists.[9]

Another study reported that high Chloroquine dosages should not be given to critically ill patients of COVID-19 owing to its potential safety issues like cardiac toxicity. Particularly chloroquine should not be combined with Azithromycin or Oseltamivir for their potential side effects due to drug-drug interactions. And suggested this should not be a cause for concern in less severe COVID-19 patients.[10]

In a study involving small sample size it was found that Chloroquine was effective in reducing viral load and also caused disappearance of virus. This effect of chloroquine was enhanced by combining with Azithromycin.[11]

Immunosuppressants

It was reported that 4 COVID-19 patients in ICU with Pneumonia/ARDS were treated with Eucilizumab and all of the patients were recovered after being treated with Eucilizumab and found that inflammatory marker levels were reduced. C-reactive protein decreased from 14.6 mg/dl to 3.5 mg/dl. Eucilizumab has the potential to be a key player in treatment of COVID-19. Ongoing trial SOLID C-19 will reveal more information.[12]

The drugs being used by rheumatologists appear to be promising in treating COVID-19.[13]

Immunosuppressors or Immunomodulators have shown some efficacy against SARS-CoV-2 in various invitro and in animal studies and also in some case series reports. Pro inflammatory conditions of high levels of IL and TNF are demonstrated in patients suffering from COVID-19. Moreover high levels of ILs and TNF were found in patients requiring ICU. This provides the rationale for using the immunosuppressants in COVID-19 patients.[14]

Effective host immune system is the key in deciding the severity and outcome of COVID-19. However excessive production of inflammatory mediators, cytokines causing cytokine storm which is responsible for multiorgan failure.

Immunomodulators like chloroquine , IL-1 and IL-6 antagonists and antirhematic drugs can be considered for treating COVID-19 patients especially in severely ill patients.[15]

Vaccines

It appears that SARS-CoV-2 have developed some immune system evading techniques as it is obvious that incubation period for flu is around 1-4 days but for SARS-CoV-2 is about 1-14 days.

There are several candidates that promise to offer protection against COVID-19 including live virus, recombinant protein subunits, and nucleic acid candidates. But these candidates need to undergo additional manufacturing steps and toxicological studies for safety. This would take a long time.

And also one should not forget that every decade is facing a Corona pandemic for ex. SARS in the 2000s, MERS in 2010s and now SARS-CoV-2. That's why to have a stockpile of broad spectrum vaccines against emerging viruses is the essential one. For that global coordination, funding and political commitment is necessary.[16]

Selection of target antigens for a vaccine is based on studies conducted on SARS and MERS. Full spike S1 is considered as a better option as it contains a receptor binding domain. Thus virus attaching to receptors could be prevented. Inactivated vaccines are the most conventional type and easily produced. These are produced by treating the virus with heat / chemicals. In the past SARS and MERS pandemics, inactivated vaccines were developed and found effective in all animal models. Interestingly for Zika virus, DNA vaccines were the first to enter clinical trials. mRNA vaccine design is considered the new development technology and having better stability and protein translation capability.[17]

Nevertheless inactivated vaccines should be developed and simultaneously focus should be on live attenuated or sub protein component or nucleic acid vaccines.[18]

Convalescent plasma therapy

The lack of vaccine or definitive treatment is forcing us to look at passive immunization. In SARS patients the efficacy of convalescent plasma therapy (CPT) was recorded in reducing the length of stay and mortality. If this therapy found effective in clinical trials, there will be an urgent need to establish plasma banks without any delay. Monoclonal antibodies (MAB) against targeted viral proteins can be rapidly produced and these are important to identify the epitopes that confer protective and cross reactive immune response. These MABs could help in design vaccine and can act as immunoprophylactics.[19]

Current understanding of COVID-19 specific immunity is limited. In a study, plasma collected from 8 patients of newly recovered COVID-19 and all of them have SARS-CoV-2 specific humoral and cellular immunity components. In another 6 patients of recovered COVID-19, even after 2 weeks found to have high titers of IgG. In the total 14 patients, 13 found to have serum neutralizing activity. And this would be encouraging to develop a vaccine or to practice the passive immunization treatment.[20]

In a study of 6 COVID-19 patients with respiratory failure, plasma therapy was given at a median of 21.5 days after finding the initial viral shedding. All of them tested negative for SARS-CoV-2 by 3 days of infusion but eventually 5 patients died. In conclusion, Plasma therapy is effective in viral clearance but ineffective in reducing mortality in critically ill stage COVID-19 patients. Thus Plasma therapy need to initiated at earlier stage.[21]

In one review, it was reported that with the available scientific data CPT appears to be safe and clinically effective and reduces mortality. Also stated that large scale multi centre RCT s are required to establish efficacy.[22]

In a case series of 5 critically ill patients of COVID-19, CPT has been given. All were having pneumonia and ARDS (acute respiratory distress syndrome) and were on antiviral treatment. Despite that, their entire situation was rapidly progressive, eventually to be kept on ventilator. In this uncontrolled study clinical improvement was seen for all of them after the CPT was given.[23]

DISCUSSION

Lopinavir/Ritonavir along with Ribavirin showed positive results in SARS patients and more information with SARS-CoV-2 is yet to come.

Recent study in the USA found that Remdesvir gave statistically significant clinical improvement in CoVid-19 patients but this drug may not be a game changer as it did not decrease the mortality in that study. Favipiravir appears to be promising as per the available information and currently it is in an advanced stage of clinical trial.

Vaccine may not be available immediately at least until the first wave of SARS-CoV-2 pandemic ends. But nevertheless having a stockpile of broad spectrum vaccines against Coronavirus is important as every decade is facing a Corona pandemic. Right now focus should be on 1st generation vaccine types like whole cell inactivated vaccines as they are relatively easily produced and simultaneously dna/rna/viral protein vaccines are also should get developed.

As developing a vaccine is time consuming focus should be shifted to passive immunity against SARS-CoV-2. Historically passive immunity is a proven concept but with its own risk involved and to implement this a lot of obstacles are there like donor availability, lack of technical equipment. Now many clinical trials are undergoing and preliminary results suggest that patients with moderate to severe disease are more likely to get benefit from transferring antibodies compared with patients already progressed to advanced stage.

Addition of immunosuppressants should also be considered to treat severely ill patients of COVID-19 as

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high levels of inflammatory mediators are found in ICU patients with Corona infection and Cytokine storm leading to multiorgan failure.

Hydroxychloroquine in combination with Azithromycin is proven effective in small clinical trials in inhibiting viral entry and replication but recent studies show concerns relating to safety issues. Hydroxychloroquine has been in the market for years with relatively low risk of toxicity but nonetheless cautiously be used in patients with predisposing factors to cardiac and renal problems and not suggested to use in critical patients of COVID-19.

As per the current knowledge, treatment regimen may contain Hydroxychloroquine in combination with Azithromycin and either of the antiviral drugs Remdesivir or Favipiravir. Immunosuppressants should also be considered in seriously ill patients along with the regimen as immune components are the major culprits in most cases for the multiorgan failure. If the disease is still progressing from moderate to severe stage convalescent plasma therapy should seriously be considered as it may not reduce mortality if already progressed to advanced stage.

CONCLUSION

SARS-CoV-2 pandemic is not the first and certainly not the last pandemic the world has seen. Focus should be on not only to tackle COVID-19 but also should be on strengthening the health systems globally.

Globally coordinated research organization is needed to combat any anticipated pandemic in near future by developing a pool of vaccines against emerging viruses.

And some countries are relying only on lockdown to contain the virus but this approach may not sustain in the long run. People's lifestyle should have to undergo a radical change and hygiene should be a part of every one's daily life.

Immediate focus should be on purifying and mass production of antibodies of COVID-19 to reduce the mortality as currently it is the promising option available. Simultaneously health institutions should conduct RCTs (randomized control trials) on various therapeutic options available to practice evidence based medicine.

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