Summary Report

Global COVID-19 Network | Webinar Learning Series

Treatment & Vaccine Development

Moderator

- **Dr. Subhash Hira** | Professor of Global Health, University of Washington, Seattle; Sambodhi/ISRN New Delhi

Speakers

- **Dr. Prashant Saxena |** Associate Director and Critical Care Head, Max Smart Hospital, India
- **Dr. Debashish Gupta** | Professor & Head, Department of Transfusion Medicine, Sree ChitraTirunal Institute for Medical Sciences and Technology, India
- **Dr. Ernesto T.A. Marques Jr.** | Associate Professor, Infectious Diseases and Microbiology, University of Pittsburg, USA

Discussion Summary

The fourth session of the COVID-19 Webinar Learning Series explored the theme of 'Treatment & Vaccine Development'. Medical and academic experts who are currently engaged in COVID-19 treatment and research shared learnings on the various therapies and drugs being used in patient recovery, as well as the roadmap to immunization, vaccine development and eventual rollout.

Dr. Prashant Saxena, currently engaged in treating COVID-19 patients in New Delhi, discussed the effectiveness of the various approved treatments and drugs being currently utilized in the treatment of patients. He discussed the phenomena of 'cytokine storms' in severe cases of COVID-19, which led to reduced transfer of oxygen in the lungs, clots in blood vessels, and damage to vital organs. The highly contested topic of 'relapse' and 'reinfection' was also touched upon, stating that despite its theoretical possibility no such instances have been recorded in India as yet.

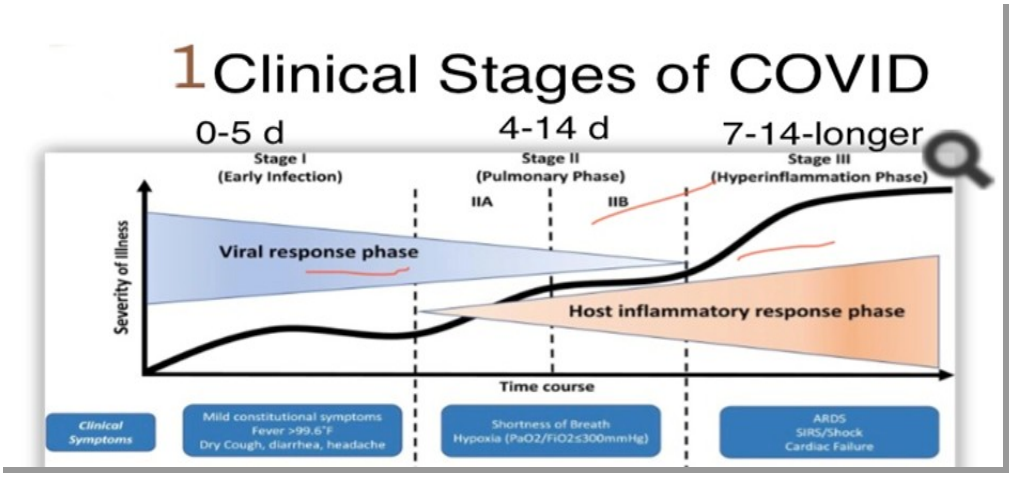
Dr. Debasish Gupta, being the first to introduce convalescent plasma therapy in the state of Kerala, shed light on the positive initial responses in using this therapy in treating severe cases of COVID. He emphasized the various steps and precautions to be taken while determining the eligibility of the donor as well as during and after the completion of the donation procedure.

Finally, Dr. Ernesto T.A. Marques Jr who had studied the developments leading up to the dengue vaccine, shared a realistic timeline for coronavirus vaccine along with concerns pertaining to its effectiveness. He spoke about the importance of studying the correlates of immunity and pathogenesis in COVID-19 that was taking time, and stressed the importance of designing human challenge models to study the effects of low immune responses elicited by the vaccine on the clinical outcomes of the COVID-19 infection. The latter studies will likely take 12-18 months at the earliest.

Dr. Subhash Hira-Moderator

Key takeaways

- The Clinical Stages of COVID illnesses occur in 15-20% of symptomatic cases. These are shown in the slide 1:
  - Stage 1: Viral response phase occurs in 0-5 days: fever, dry cough, diarr, headache, shivering, loss of smell, etc.
  - Stage 2: Pulmonary phase occurs in 4-14 days: breathlessness, X-ray /CT changes, hypoxia.
  - Stage 3: Hyperinflammation phase of Interleukin-storm occurs in 7-14-or longer days: ARDS, vessel clots, heart failure, stroke, etc.



Dr. Prashant Saxena

Key takeaways

- In India, we are using Hydroxychloroquine (HCQ), which is given to patients along with Azithromycin which is an antibiotic. We have seen that when both are combined, the killing of the virus is quickened.
- We are also using Oseltamivir, which is used for the treatment of flu such as H1N1. In India, we seem to have a mixed infection. You can be struck with COVID along with H1N1 infection, since both the clinical features are common. Once the H1N1 is negative, we stop the Oseltamivir.
- For the 5% of severe patients, we start with supportive care and take precautions to avoid aerosol dispersion to ensure that there is no transmission of infection to healthcare providers. We are managing them in negative pressure rooms and using ventilators.
- There has been some debate on whether Hydroxychloroquine (HCQ) is beneficial or not. There is no conclusive evidence against is usage as yet. In-vitro studies have shown that HCQ reduces viral shedding and also hampers replication. The only concerns are its cardiotoxicity. ECG baseline and for daily monitoring has to be done to determine its usage.
- Any inflammation in the body insights a cytokine storm. In COVID it has been seen that there is a cytokine storm which is modulated by T cells and inflammatory monocytes. There T cells and inflammatory monocytes gain access to the pulmonary circulation and reduce transfer of oxygen in the lung. The lack of oxygen due to the cytokine storm is the main reason that patients are dying due to COVID.
- Anti-Interlukin-6 (IL-6) drug named Tocilizumab is used to reduce the cytokine storm.

- A much talked about therapy is convalescent plasma. If a patient is recovering or has recovered, they tend to develop antibodies in the blood. This therapy has been attempted with Ebola, MERS, SARS-CoV, H1N1, etc. with variable success. We are using convalescent therapy for those patients who are not recovering through regular oxygenation. There are associated challenges in collecting this plasma, but there is enthusiasm amongst the public in using this therapy. We are still carrying out trials, but initial results are showing a positive trend.

- We have not seen any cases of reinfection so far, but it is possible to have reinfection. It is a viral illness and can thus happen again and again. The severity may be less, as the patient will develop antibodies, like it happens during flu.

- As for corticosteroids, we are only using them in very severe cases of COVID.

- It has been proved in many studies that Vitamin C improves mortality in cases of viral infection. Moderate dose of Vitamin C combined with thiamine has been shown to improve the results in patients. The available evidence is sufficient for us to administer the combination to all our patients.

- Thromboprophylaxis and anticoagulation are major issues. COVID patients tend to clot easily, and this is a major reason that patients are dying. It is important to carry out tests to determine whether patients have a tendency to clot, based on which we add molecules that prevent blood clotting for the patient.

- ECMO is a therapy where we artificially oxygenate blood. It is taken from the body, oxygenated, and then reintroduced into the body. This is a lifesaving therapy for patients with severe ARDS and refractory cardiovascular shock. This is reserved for very few cases. We have not used it yet for any patients.

- We have used Convalescent Plasma therapy in 25-odd patients. The initial response has been positive. The success of plasma therapy depends on when you start the plasma therapy. It is always wise to start the plasma therapy the moment you see clinical deterioration in the patient. We cannot wait for oxygenation to worsen as the damage done by COVID is very rapid. Within 24 hours the severely ill patient is close to death. It has to be a very early, calculated decision to initiate.

Dr. Debashish Gupta

Key takeaways

- **Convalescent plasma (CP) therapy is not a new concept. It has been used through the decades in treating Ebola, MERS, SARS, Chikungunya, Zika etc.**

- In a study conducted in China, it was found that with a transfusion of 200 ml of the plasma, the patient recovered within 3 days. There is positive response from the medical fraternity regarding the usage of convalescent plasma.

- There are two stages to determine usage of convalescent plasma therapy – (1) recruitment of COVID-19 recovered patient who is to be the plasma donor, and (2) identification and eligibility of COVID-19 patient for CP therapy.

- There are certain criteria to determine the eligibility of donors. They must be above 18 years of age, weighing more than 55 kgs. The recovered patients must not exhibit any COVID symptoms in 28 days after recovery, and if the plasma is extracted prior to 14 days then two consecutive PCR tests must confirm negative results.

- Any donors who have received transfusions in the last 8 weeks must be deferred from donating plasma.

- **COVID-19 plasma donors must make two visits unlike ordinary blood donors. The first is for pre-donation tests, which is highly recommended. The second is for collection of the convalescent plasma.**

- Plasmapheresis is the best method for plasma collection as it avoids wastage of red cells. The added advantage is that the plasma can be collected in a volume that can be divided into aliquots which can be used to treat two or three patients at a time. The volume of plasma collected should not exceed 1000 ml per sitting.

- One dose of 200 ml convalescent plasma is sufficient to treat a patient. But in some severe cases, we may need to administer another 200 ml of CP.

- We must transfuse plasma only in severe or life-threatening cases.

- Kerala is the first state where COVID-19 hit in India. We got approval from ICMR to start plasma therapy in April 2020. As of 11th May, ICMR has given approval to 76 centers across the country to conduct the convalescent plasma therapy.
- We are still in the experimental stage and have not carried out enough clinical studies to prove the safety and efficacy of the treatment. More testing and research is required to validate the general use. Until then, convalescent plasma therapy should be restricted only to actually indicated population of patients and should not be used for prophylactic purposes.

- **In terms of the success rate of plasma therapy, we have administered this to 4 patients who have all recovered. With the recent spurt in cases in Kerala, we may have to increase our use of CP therapy. We are monitoring all recovered patients who have undergone the therapy on a sustained basis.**

- A normal healthy donor can donate plasma every two weeks, and depending on other factors such as body weight, can go up to a maximum of 1000ml. However, in India, our guidelines do not permit donation of more than 500ml of plasma. In a year, a donor can only donate 12 times. The interval will have to be determined based on the donor's tolerance and their recovery pattern.

Dr. Ernesto T.A. Marques Jr

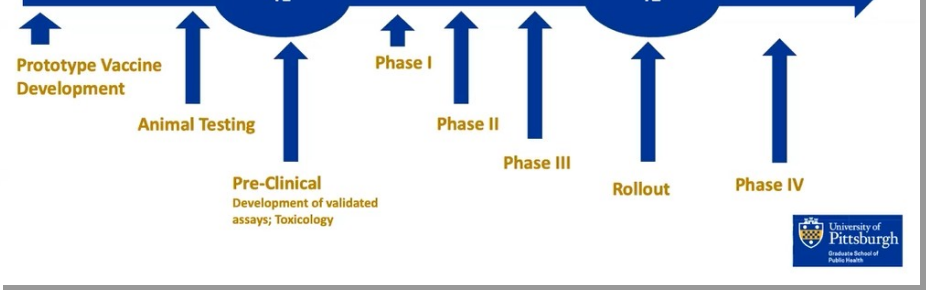
Key takeaways

- **I think the vaccine will be the best solution in dealing with this pandemic. We will be living with this disease for a very, very long. The way to come back to how life used to be in 2019 is through a vaccine.**

- **There are a lot of vaccines being developed. Probably a 100 different vaccines currently which are at various stages of clinical trials. Some of them show early signals of immunogenicity, which are encouraging.**

- There are about 20 vaccines in phase1, with around 31 in phase 1/2 combined.

- Normal vaccine development, in our recent history, has taken almost 20 years. An example is the development of tetravalent dengue vaccine by Sanofi.



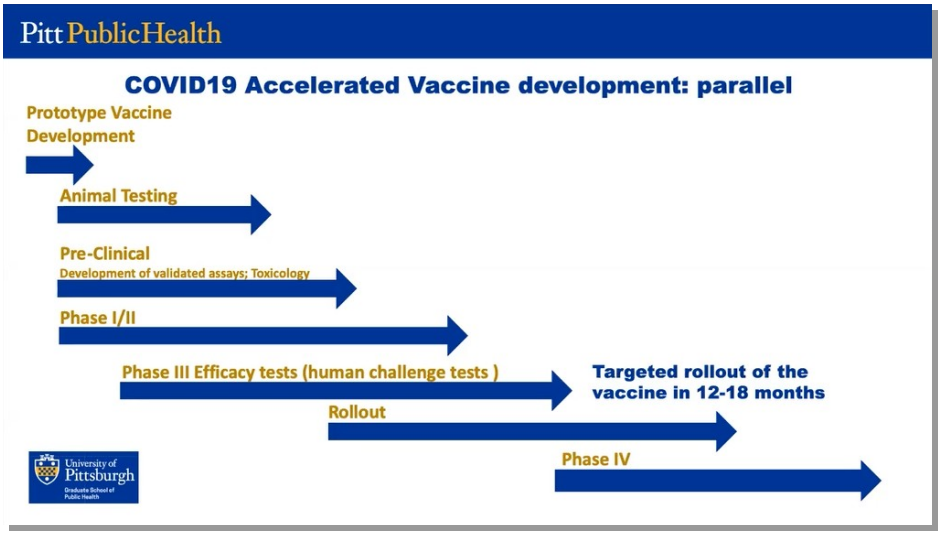
- Apart from assessing the biodistribution, toxicology etc., the efficacy and the safety of the vaccine are important. For the dengue vaccine neutralization was the preferred method. At the time it was believed that if you have strong neutralizing antibodies, you are protected. Phase 1 trials show great immunogenicity, good safety profile, no adverse effects. In phase 2, based on phase 1 encouraging results, they started largescale immunization of people, including children. Phase 2 was largely successful, but certain results showed that the vaccine was only partially effective. This was not enough to stop the immunization, and phase 3 was started. In total, vaccine was given to 40,000 individuals. 2-3 years later, sufficient data was available that the vaccine was of no significant risk and the vaccine was approved and rolled out. However, by the time the vaccine was registered and distributed, things changed.

- **There are lessons to be learnt from the dengue vaccine. Vaccine efficacy is dependent on previous exposure. If you had dengue and took the vaccine you were protected, but if you never had dengue and took the vaccine you had greater risk.**

- For the dengue vaccine, it was observed that the vaccine mediated protection was only for a limited and partial duration. There was a significant drop in antibody titers five years after immunization. The efficacy of the vaccine was also highly dependent on whether there was previous exposure or not.

- **Coming to the COVID-19 vaccine development, everything is being done parallelly. Prototype development, animal testing, clinical trial, everything is being done simultaneously. This means that you don't take experiences and learnings from one phase to the next.** You are learning everything at the same time. Gold-standard reference samples with excellent characterization is required. This takes time.

- One way to speed up the test is to conduct structured human exposures, or 'human challenge tests'. Humans are to be immunized and then exposed to COVID-19 virus. The outcome is then studied. A subset of phase I/II subjects are taken and passed through to this phase. The expectation is that post the human challenge tests, which should be in next Mar-May 2021, thereafter, we can start rolling out the vaccine if all went well.



The missing Links in vaccine development…

- At this stage, the correlates of immunity, or how the immune system can protect you from infection, is not clearly understood.

- Understanding mucosal immunity is essential in the case of COVID-19. We need to study this profoundly.

- We also need to study the role of T-cell responses. The mechanisms associated with pathogenicity needs to be understood.

- COVID19 natural infection induces moderate/weak antibody responses. Fraction of individuals produce very low levels and less than 30% produce high levels of IgM. The fact that many individuals do not illicit any IgM response is a bit concerning for 2 reasons. Is it because we are not having enough activation of B-cells, or is it because we are boosting memory B-cell response through previous exposure to coronavirus?

- **How can we start reducing risks in the COVID-19 vaccine? My first suggestion is based on the experience from the dengue vaccine. It is important to use more biologically relevant cell types, such as those from human lung and respiratory mucosa that express ACE and FcyR receptors.**

- It is important to carefully design human challenge models to study the effects of low immune responses elicited by the vaccine on the clinical outcomes of the COVID-19 infection.

- **What is a reasonable timeline for the vaccine? It will be an unprecedented vaccine development from start to rollout. In my perspective, we can have effective antigen formulation by next spring, 2021. This does not mean the vaccine would be safe and we don't know how efficacious it would be. The rollout will have to be very careful. It's not going to be like the typical vaccine development. We are flying blind at present !**