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DRUGS AND POTENTIAL VACCINE FOR COVID-19; STATUS SO FAR

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ABSTRACT

Coronavirus is spreading around the world, but there are still no vaccines to protect the body against the disease it causes, COVID-19. The coronavirus is mainly transmitted through droplets generated when an infected person coughs, sneezes, or exhales. As per WHO, as of 10.33.am CEST, July 11, 2020, India had 8,20,916 confirmed cases whereas globally there have been 12,286,264 confirmed cases of COVID-19, including 555,642 deaths. Majority of the world's population is still vulnerable to it. As far as total number of cases are concerned, India comes at number three after USA and Brazil. There are many ongoing clinical trials evaluating its potential treatments. Several pharma companies are working on antiviral drugs, some of which are already in use against other illnesses, to treat people who already have COVID-19. Drugs, including hydroxychloroquine, azithromycin and the nucleotide analogue remdesivir, are being actively tested, but none has been specifically approved for the disease. A vaccine would provide some protection by training people's immune systems to fight the virus so they should not become sick. The making of a vaccine takes many years and it passes through several clinical trials before coming in the market for human use. As COVID-19 has become pandemic, the researchers and scientist at the world level are working on potential treatments and vaccines. Some countries have announced their human trials also. In a recent news, Sinovac Biotech, a Beijing based company which is in the process of vaccine making, has claimed the success of their human trials. Similarly, Covaxine, the Indian vaccine candidate is also in the process of trials but it is too early to predict about the efficacy of the vaccine.

KEYWORDS: Covid-19, Vaccine, Corona Viruses, pandemic, hydroxychloroquine, chloroquine, azithromycin, remdesivir, SARS-CoV-2, nCoV, Sinovac, Covaxine

INTRODUCTION

Coronavirus disease (COVID-19) which is a newly emerged infectious respiratory disease caused by a newly discovered coronavirus (nCoV) has been declared as global pandemic by WHO on March 11, 2020. International Committee on Taxonomy of Viruses (ICTV) announced 'severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)' as the name of the new virus on 11 February 2020 because of its genetic resemblance to the coronavirus responsible for the SARS outbreak of 2003. The 2019-nCoV belongs to genus Betacoronavirus which is further distributed in five subgenera among which Sarbecovirus contains SARS-CoV and the novel coronavirus (2019-nCoV).[1] This virus is known to be transmitted through droplets generated when an infected person coughs, sneezes, or exhales.

India has reached at number three after America and Brazil being at number one and two respectively. Globally, as of 10:33am CEST, 11 July 2020, there have been 12,286,264 confirmed cases of COVID-19, including 555,642 deaths. At the same time, the total number of confirmed cases in India has been reported as 8,20,916. Majority of the world's population is still vulnerable to it (WHO, updated July 11, 2020, 10.33 am CEST; https://covid19.who.int/?gclid=Cj0KCQjwwr32BRD4ARIsAAJNf_3iUDqmISxbGZJGapcGFSixRoFZBX1hbetax4EMxmO5chtyWmkcsdYaAkMAEALw_wcB).[2]

Although several drugs, including hydroxychloroquine, azithromycin and the nucleotide analogue remdesivir, are being actively tested, none has been specifically approved for the disease. At present, all approaches that directly target the virus or block viral entry and the treatments that address the immunopathology of the infection have become a major focus in addition to the development of a vaccine.[3] To cope up with the situation, experimenting with the existing drugs without sufficient scientific evidence may pose several limitations. In reality, a vaccine takes an average of two to five years to develop. Similar is the scenario with COVID-19 vaccine.

Making of a vaccine

There are no drugs or other proven therapeutic options to prevent or treat COVID-19. Current clinical management includes infection prevention, supportive medical care including supplemental oxygen and mechanical ventilator support when indicated. As the virus is

novel, therefore, humans have no natural immunity to it, and researchers must start from square one to develop a vaccine to educate the immune system to defend itself from the virus.

In the making of a vaccine, scientists make sure that they are handling the latest version of the virus. The first important thing to begin the whole process is to know the gene sequence of the virus. For this purpose, researchers need to grow the virus, which may thrive in host organisms but is fragile outside of them, in cell culture. In addition, if they can establish a helpful animal model to use it to understand the viral mechanisms before developing the vaccine. All these steps are labor-intensive and time-consuming. Before beginning to develop the vaccine, researchers need to create multiple versions to find out that which version can trigger immunity against the virus without causing damage. Before human trials, its efficacy and safety is ensured. It undergoes various phases of trials and before its human trials, it is tested on animal models. According to CDC (Centers for Disease Control and Prevention), clinical development is a three-phase process. During Phase I, small groups of people receive the trial vaccine. In Phase II, the clinical study is expanded and vaccine is given to people who have characteristics (such as age and physical health) similar to those for whom the new vaccine is intended. In Phase III, the vaccine is given to thousands of people and tested for efficacy and safety (CDC, https://www.cdc.gov/vaccines/basics/test-approve.html).[4]

Human trials are not easy exercise. On how many human to go with, how much should be the dose and from where to bring the patients are some of the critical considerations. After several successful trials on human, it needs to get government approval for its market launch. This whole process takes several years.

The challenge in vaccine development consists in devising a vaccine strong enough to ward off infection without making the individual seriously ill. It is important to understand how a person becomes ill on attack by any bacteria or virus or other such component. Normally, the body is able to distinguish between self and non-self, but in persons with autoimmune disorders, normal bodily substances provoke an immune response, leading to the generation of autoantibodies. Antibodies that bind to a variety of exogenous antigens, such as those on bacteria, viruses, and fungi, as well as self-antigens (e.g., nucleic acids, phospholipids, erythrocytes, serum proteins, cellular components, insulin or thyroglobulin) account for a significant proportion of immunoglobulins in healthy individuals.[5]

In case of COVID-19 vaccine too, there are no easier or to be bypassed steps. The slightly better situation in this case is that unlike most of other viruses it is pandemic and the scientists of the whole world are burning mid night oil to find a solution at the earliest for their own survival. A team of Chinese researchers has already sequenced the SARS-CoV-2 virus. Multiple institutions are already working together to characterize the virus and test in animals. As SARS and SARS-CoV-2 share about 80-90 percent of their genetic code, researchers can build on the research done on SARS. The previously developed SARS-CoV vaccines were inactivated viruses that have been shown to induce the production of neutralizing antibodies. These antibodies target the spike protein on the capsid of the coronavirus so that it cannot bind to its cellular receptor and, consequently, it cannot enter the cell. With this similarity between the two viruses, we can hope the speedy development of the vaccine for COVID-19 but not less than a year.[6]

Status of Hydroxychloroquine and Azithromycin

Hydroxychloroquine is a form of chloroquine, which targets the parasite that causes malaria. It targets the asexual form of the malaria parasite in the red blood cell whereas, Azithromycin is an antibiotic used for the treatment of several bacterial infections. It prevents bacterial growth by interfering with their protein synthesis.

Dr. Anthony Fauci, the Director of the National Institute of Allergy and Infectious Disease, who claims to recover 80 Covid patients by giving them a combination of hydroxychloroquine and azithromycin, supports this medication. He has called his study as “anecdotal evidence”. A New York Family physician has made a similar claim. However, according to Sylvia, this could have been a coincident and patients were to recover at their own. In first study, sample size was very short and even it was not sure whether the patients were actual Covid patients. In the second study too, there was no control group and comparison could not be made between those who had the combination of hydroxychloroquine and azithromycin and the control group.[7]

On the other hand, according to Cennimo, Hydroxychloroquine and chloroquine are widely used antimalarial drugs that elicit immunomodulatory effects and are therefore used to treat autoimmune conditions and as inhibitors of heme polymerase, they are believed to have additional antiviral activity via alkalinization of the phagolysosomes. The latter inhibits the pH-dependent steps of viral replication.[8]

Wang et al. reported that chloroquine effectively inhibits SARS-CoV-2 in vitro.[9] Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.[10] The pharmacological activity of chloroquine and hydroxychloroquine was tested using SARS-CoV-2–infected Vero cells and Hydroxychloroquine was found to be more potent than chloroquine in vitro. A loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection.[11]

The U.S. Food and Drug Administration (FDA) (March 28, 2020) has, without having gone through a proper clinical trial, given emergency approval to distribute hydroxychloroquine to hospitals across the country (https://www.fda.gov/media/136534/download).[12] However, clinical trials for drugs exist for a reason. They have the same objective as those for vaccines: to ensure the drugs are efficacious and safe for a large, diverse population of patients.

Status of Remdesivir

Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV). Remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV.[13] Remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. It is further suggested that they should be assessed in human patients suffering from the nCoV disease.[9]

In a time of high stress, people tend to reach for easy and quick solutions. But SARS-CoV-2 is a virus and does not have any metabolic machinery. Little is known about how hydroxychloroquine and azithromycin act upon the virus so it remains unclear how they work against it. An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The experimental drug remdesivir has been authorized by US regulators for emergency use against COVID-19. On May 1st, 2020, the FDA issued an emergency use authorization for the investigational antiviral drug remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease (FDA, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.).[14] In a recent interview with Press Trust Of India (May 26, 2020), Ram Vishwakarma, Director of the Indian Institute of Integrative Medicine, CSIR,

Jammu, told that remdesivir is helping people recover faster, and is lowering the death rate among critically ill patients, and it can be life-saving.[15] Similar findings have also been supported by a recent study also.[16] At present, the combined use of anti-inflammatory and antiviral drugs may be more effective than using either modality alone.[3]

Body's immunity- an important role

Body's own immunity is proving very promising in case of COVID-19 so far. The development of immunity to a pathogen through natural infection is a multi-step process that typically takes place over 1-2 weeks. The body responds to a viral infection immediately with a non-specific innate response in which macrophages, neutrophils, and dendritic cells slow the progress of virus and may even prevent it from causing symptoms. This non-specific response is followed by an adaptive response where the body makes antibodies that specifically bind to the virus. These antibodies are proteins called immunoglobulins. This is called as humoral immunity. The body also makes T-cells that recognize and eliminate other cells infected with the virus. This is called cellular immunity. Studies show that people who have recovered from infection have antibodies to the virus. However, some of these people have very low levels of neutralizing antibodies in their blood, suggesting that cellular immunity may also be critical for recovery.[17] According to Poltorak, Professor of Immunology at Tufts University, Innate immunity is a person's inborn defense against pathogens that instruct the body's adaptive immune system to produce antibodies against viruses. He further adds that the killer is not the virus but body's own immune system.[18]

No study has evaluated whether the presence of antibodies to SARS-CoV-2 confers immunity to subsequent infection by this virus in humans. Therefore, work is being done on all fronts by the researchers and scientists of the world.

Future of COVID-19 vaccine

A vaccine would normally take years, if not decades, to develop. Researchers hope to achieve the same amount of work in only a few months. Research is happening at breakneck speed, about 100 groups around the world are researching vaccines, and some are now entering clinical trials. Scientists have fast-tracked every step in the discovery and testing process and hope to have a vaccine against nCoV2019 ready in 10 to 18 months.[19] Human trials have been announced by USA, UK and Australia and experts think a vaccine is likely to become available by mid-2021.[20] However, the scientists from WHO are now saying that pinning our hopes on a vaccine alone won't solve the crisis at large, and it could take anywhere

between 4-5 years to actually contain the virus at large. The other issues, which make it highly probable that the virus is here to stay, is the problem of mutation as reported in The Times of India (May 15, 2020).[21] According to The Indian Express (June 15, 2020), In a very recent revelation by Sinovac Biotech Ltd, A Beijing Based Company has claimed promising results with their CoronaVac vaccine for Covid-19. This Chinese firm has signed an agreement with a drug maker in Brazil to conduct the final phase of the three-part human testing of its CoronaVac vaccine. They have reported that the vaccine hasn't caused severe side effects and more than 90 per cent of people administered with the shot on a 14-day interval have induced neutralizing antibodies two weeks after inoculation. Sinovac's vaccine is among five Chinese experimental shots that have reached the crucial final stage of human testing before they can be approved for public use.[22]

Besides Sinovac, the vaccines developed by AstraZeneca-University of Oxford and Sinopharm of China National Pharmaceutical Group are the only other jabs in late-stage trials. Covaxin, the India's candidate for vaccine which has been cleared for Phase-I and Phase-II trials by the Drug Controller General of India, will be tested on more than 1,000 people in the two phases, as reported by Bloomberg. Jointly developed by ICMR and Bharat Biotech India Limited, Covaxin will be tested on 375 people in Phase I trial and on 750 people in the next phase, according to latest updates by The Indian Express (July 11, 2020).[23]

However, there is much more work to do including production, the safety of the trials, any side effects, pricing or transportation and chances seems high that corona virus may never really go away.

CONCLUSION

The making of vaccine is on the way but there are several challenges to meet. Body's immune system is proving promising so far. Therefore, emphasis should also be laid on strengthening it. As far as the recommendation of the existing drugs is concerned, there should be a better understanding of the drugs, especially combined use of drugs, before deployment to the general population, so that the drugs do not create more problems than they solve and become a problem bigger than the disease itself. With a vaccine still a long distance away, efforts to repurpose old medications used for other ailments provide hope of an early counter to COVID-19, placing the antiviral remdesivir on top of the list of possible

contenders although China based company Sinovac Biotech has claimed promising results with their vaccine CoronaVac which is ready for its final human trials.

Until something concrete comes to human reach, the safety guidelines issued by WHO needs to be followed strictly. These include, washing of hands with good soap repeatedly, using a good quality sanitizer, maintaining the social distancing of at least 3 feet, avoiding touching the eyes and nose and going to crowded spaces, and seeking medical intervention in case of coughing, fever and difficulty in breathing.

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Conflict of Interest

No conflict of interest.

REFERENCES

1. de Groot RJ, Baker S, Baric R, Enjuanes L, Gorbalenya A, Holmes K, Perlman S, Poon L, Rottier P, Talbot P, Woo PC. Family coronaviridae. In: King AMQ, Adams MJ, Cartens EB, Lefkowitz EJ (eds.), Virus Taxonomy, the 9th report of the International Committee on Taxonomy of Viruses. Academic Press, San Diego, CA., 2012; 806–828.
2. WHO. WHO Coronavirus Disease (COVID-19) Dashboard. Last updated 2020/7/11, 10.33 am. CEST. Available on; https://covid19.who.int/?gclid=Cj0KCQjwwr32BRD4ARIsAAJNf_3iUDqmISxbGZJGapcGFSixRoFZBX1hbetax4EMxmO5chtyWmkcsdYaAkMAEALw_wcB. Retrieved on July 11, 2020 at 6.49 pm
3. Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol, Apr 9, 2020; 1–2.
4. CDC (Centers for Disease Control and Prevention). Vaccine Testing and Approval Process. Available at; https://www.cdc.gov/vaccines/basics/test-approve.html. Retrieved on May 27, 2020 at 12.20pm.
5. Chen Y, Wang S, Lu S. DNA Immunization for HIV Vaccine Development. Vaccines, 2014; 2(1): 138–159.
6. Casali P, Schettino EW. Structure and function of natural antibodies. Curr Top Microbiol Immunol, 1996; 210: 167-79.

7. Sylviya He. April 7, 2020. Vaccine and Drug Development for COVID-19 – When the Cure Becomes the Problem. Available on https://www.technologynetworks.com/immunology/articles/vaccine-and-drug-development-for-covid-19-when-the-cure-becomes-the-problem-333159. Retrieved on May 6, 2020 at 6pm.
8. Cennimo DJ. May 4, 2020. What are the roles of hydroxychloroquine and chloroquine in the treatment of coronavirus disease 2019 (COVID-19). Available at; https://www.medscape.com/answers/2500114-197458/what-are-the-roles-of-hydroxychloroquine-and-chloroquine-in-the-treatment-of-coronavirus-disease-2019-covid-19, retrieved on May 7, 2020 at 1pm.
9. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 2020; 30: 269–271.
10. Vincent MJ, Bergeron E, Benjannet S, Erickson BR, Rollin PE, Ksiazek TG, Seidah NG, Nichol ST. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J., Aug 22, 2005; 2: 69.
11. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, Liu X, Zhao L, Dong E, Song C, Zhan S, Lu R, Li H, Tan W, Liu D. 2020. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis; ciaa237.
12. FDA. March 28, 2020. Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease. Available at; https://www.fda.gov/media/136534/download. Retrieved on May 7, 2020 at 1.30 pm.
13. Sheahan TP, Sims, AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Clarke MO, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med., 2017; 9: eaal3653.

14. FDA News Release. May 1st, 2020. Coronavirus (COVID-19) Update: FDA Issues Emergency Use Authorization for Potential COVID-19 Treatment. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment.). Retrieved on May 28th, 2020.
15. Press Trust of India. May 26, 2020. Clinical Trials are showing that Remdesivir can be like saving drug for COVID-19 infected patients. Available at; https://www.firstpost.com/health/clinical-trials-are-showing-that-remdesivir-can-be-life-saving-drug-for-covid-19-infected-patients-8406481.html. Retrieved on May 26, 2020 at 12.30 pm.
16. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, de Castilla DL, Finberg RW et al. for ACTT-1 group Members. May 22, 2020. Remdesivir for the Treatment of Covid-19 — Preliminary Report. The New England Journal of Medicine. 1-12.
17. Poltorak AS. May 24, 2020. The Print. Coronavirus isn't the killer, our immune response is. Available at; https://theprint.in/health/coronavirus-isnt-the-killer-our-immune-response-is/428214/. Retrieved on May 26, 2020 at 11 am.
18. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, Ling Y, Zhang Y, Xun J, Lu L, Jiang S, Lu H, Wen Y, Huang J. 2020. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv: 2020.03.30.20047365.
19. Sahadulla MI and Uduman SA. May 8, 2020. Scientific Challenges for a safe Covid-19 Vaccine. The Economic Times. Available at; https://health.economictimes.indiatimes.com/news/industry/scientific-challenges-for-a-safe-covid-19-vaccine/75595176. Retrieved on May 26, 2020 at 11.20 am.
20. Gallagher J. April 23, 2020. Coronavirus vaccine: When will we have one? BBC News. Available at; https://www.bbc.com/news/health-51665497. Retrieved on May 17, 2020 at 2.30.pm.
21. Timesofindia.com. May 15. 2020. Controlling coronavirus spread could take 4-5 years, can't depend on a COVID-19 vaccine alone, says WHO scientist. Avaialble at; https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/coronavirus-vaccine-covid-19-spread-latest-news-update-controlling-coronavirus-spread-could-take-4-5-years-cant-depend-on-a-covid-19-vaccine-alone-says-who-scientist/photostory/75759992.cms. Retrieved on May 26, 2020 at 2 pm.

22. The Indian Express.com. June 15, 2020. Coronavirus (Covid-19) vaccine status check: Moderna, Sinovac Biotech gear up for final phase trials. Available at; https://indianexpress.com/article/coronavirus/coronavirus-vaccine-moderna-sinovac-biotech-oxford-johnson-and-johnson-status-check-6458445/. Retrieved on June 15, 2020 at 1.30 pm.
23. The Indian Express. July 111, 2020. Coronavirus (Covid-19) vaccines latest updates: Covaxin to be tested on 375 people in Phase I; Moderna delays final phase trials. Available at; https://indianexpress.com/article/coronavirus/coronavirus-covid-19-vaccines-latest-news-covaxin-oxford-sinovac-moderna-gsk-sanofi-6494159/. Retrieved on July 11th, 2020.