

Review Article

Numerous Vaccine and Drug Trials for Covid-19 in the World: A Review

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ABSTRACT:

As an emerging infectious disease, coronavirus diseases 2019 (COVID-19) seriously threatens human health around the world. Due to the urgent situation of treatment and prevention and control of the disease, it is necessary to research and develop effective intervention methods of COVID-19 to facilitate disease control. There are at least eight types of vaccines being tried against the coronavirus, and they rely on different viruses or viral parts. While finding effective drugs is no easy feat on its own, it is also only at best a single step on a long journey towards taming the COVID-19 beast. Manufacturing, regulatory approval, and supply and access decisions are also going to need collective solutions, as will vaccine and diagnostic development. Again, as a preventive measure, strict vigilance of viral changes in different hosts for prediction of an event is important.

Key words: Coronavirus, Vaccine, clinical trials, SARS-CoV-2.

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INTRODUCTION

Coronaviruses (CoVs) have a single-stranded RNA genome (size range between 26.2 and 31.7 kb, positive sense), covered by an enveloped structure. The shape is either pleomorphic or spherical, and it is characterized by bears club-shaped projections of glycoproteins on its surface (diameter 80–120 nm).¹ Among all the RNA viruses, the RNA genome of CoV is one among the largest. The number of open reading frames (ORFs) in the CoV genome ranges from six to ten.² CoV genetic material is susceptible for frequent recombination process, which can give rise to new strains with alteration in virulence.³ There are seven strains of human CoVs, which include 229E, NL63, OC43, HKU1, Middle East respiratory

syndrome (MERS)-CoV, severe acute respiratory syndrome (SARS)-CoV, and 2019-novel coronavirus (nCoV), responsible for the infection with special reference to the involvement of the respiratory tract (both lower and upper respiratory tract), e.g., common cold, pneumonia, bronchiolitis, rhinitis, pharyngitis, sinusitis, and other system symptoms such as occasional watery and diarrhoea. Among these seven strains, three strains proved to be highly pathogenic (SARS-CoV, MERS-CoV, and 2019-nCoV), which caused endemic of severe CoV disease.⁴

STRUCTURE OF CORONAVIRUS

The most important structural proteins of CoV are spike (S) protein (trimeric), membrane (M) protein,

envelop (E) protein, and the nucleocapsid (N) protein. Some of the viruses such as beta-CoVs also have hemagglutinin esterase (HE) glycoprotein.³The RNA genome of CoV has seven genes that are conserved in the order: ORF1a, ORF1b, S, OEF3, E, M, N in 5' to 3' direction. The two-third part of the RNA genome is covered by the ORF1a/b, which produces the two viral replicase proteins that are polyproteins (PP1a and PP1ab). Sixteen mature non-structural proteins (NSPs) arise from further processing of these two PPs. These NSPs take part in different viral functions including the formation of the replicase transcriptase complex. The remaining genome part of the virus encodes the mRNA which produces the structural proteins, i.e., spike, envelope, membrane, and nucleocapsid, and other accessory proteins.⁵ Another important envelop-associated protein which is expressed by only some strains of CoV is the HE protein. The RNA genome of CoV is packed in the nucleocapsid protein and further covered with envelope. Knowledge about the structure, metabolic pathways of CoV, and pathophysiology of CoV-associated diseases is important to identify possible drug targets.⁶ Various treatments have been suggested and applied to control COVID-19 based on previous experiences with other viral infections. Studies are being carried out involving monoclonal

antibodies, stem cells, traditional medicines, antiviral drugs as well as vaccine development for containing coronavirus.⁷ (Table 1 and 2) On March 13, the United Nations Foundation, the Swiss Philanthropy Foundation, and the World Health Organization (WHO) have created the SOLIDARITY Response Fund in order to raise money to support studies on COVID-19.⁸ On March 18, WHO indicated that the first trial supported by the Fund would be an adaptative study performed in ten countries, namely Argentina, Bahrain, Canada, France, Iran, Norway, South Africa, Spain, Switzerland, Thailand. India joined the trial on March 27.

Remdesivir (GS-5734) is by far the most promising drug that exhibits broad-spectrum antiviral activities against RNA viruses. It is a pro-drug, whose structure resembles adenosine. Therefore, it can incorporate into nascent viral RNA, and further inhibit the RNA-dependent RNA polymerase. This results in premature termination of the viral RNA chain and consequently halts the replication of the viral genome. Importantly, it has been previously shown to exhibit antiviral activities against different coronaviruses, including SARS-CoV and MERS-CoV, in vitro and in vivo. In a recent in vitro study, Remdesivir was also shown to inhibit SARS-CoV-2. Remdesivir is now being tested in multiple trials in different countries.⁹

Table 1- Registered ongoing Vaccine trials around the world.

S.no.	Vaccine trials	Pharmaceutical company/ Academic institutions
1	Fusogenix DNA vaccine	Entos
2	ChAdOx1 nCov-19	Oxford university
3	Gimsilumab	Roivant Sciences
4	AdCOVID	Altimmune
5	TJM2	I-Mab Biopharma
6	Coronavirus vaccine (produced virus like particles of the coronavirus)	Medicago
7	AT-100	Airway Therapeutics
8	TZLS-501	Tiziana Life Sciences
9	OYA1	OyaGen
10	BPI-002	Beyond Spring
11	Intranasal coronavirus vaccine	Altimmune
12	INO-4800	Inovio pharmaceuticals and Beijing Advaccine Biotechnology
13	NP-120 (Ifenprodil)	Algeron Pharmaceuticals
14	APN01	University of British Columbia and APEIRON Biologics
15	mRNA-1273	Moderna and Vaccine Research Centre
16	Avian Coronavirus infectious bronchitis virus vaccine (IBV)	MIGAL Research Institute
17	TNX-1800	Tonix Pharmaceuticals
18	Brilacidin	Innovation Pharmaceuticals
19	Recombinant subunit vaccine	Clover Pharmaceuticals
20	Oral recombinant vaccine	Vaxart
21	Leronlimab	CytoDyn
22	Linear DNA vaccine	Applied DNA Sciences and Takis Biotech
23	BXT-25 (to treat late stage ARDS)	BIOXYTRAN
24	MERS coronavirus vaccine to treat COVID-19	Novavax
25	INO-4700	Inovio Pharma

Table -2 Ongoing Drug trials for treating COVID-19 and its complications around the world

S.No.	Drug trials	Pharmaceutical companies
1	Remdesivir (GS-5734)	Gilead Sciences
2	Actemra (to treat coronavirus related complications)	Roche
3	Galidesivir	Biocryst Pharma
4	REGN3048-3051 and Kevzara	Regeneron
5	SNG001	Synairgen Research
6	AmnioBoost	Lattice Biologics
7	Lopinovir-Ritonavir (Kaletra)	Abbvie

DISCUSSION

In the months since COVID-19 has spread, researchers have launched more than 180 clinical trials of everything from repurposed antivirals and immunomodulators to unproven cell therapies and vitamin C. A further 150 trials are preparing to recruit patients. Up to 90% of new entrants into clinical trials never make it to approval, and so investigators want to have as many shots on goal as possible. Scientific understanding of COVID-19 is also changing so quickly that it makes sense to keep options open.¹⁰ All vaccines aim to expose the body to an antigen that won't cause disease, but will provoke an immune response that can block or kill the virus if a person becomes infected. There are at least eight types being tried against the coronavirus, and they rely on different viruses or viral parts. A virus is conventionally weakened for a vaccine by being passed through animal or human cells until it picks up mutations that make it less able to cause disease. Codagenix in Farmingdale, New York, is working with the Serum Institute of India, a vaccine manufacturer in Pune, to weaken SARSCoV2 by altering its genetic code so that viral proteins are produced less efficiently. In case of Inactivated virus vaccines, the virus is rendered un-infectious using chemicals, such as formaldehyde, or heat. Making them, however, requires starting with large quantities of infectious virus.¹¹ At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. The nucleic acid is inserted into human cells, which then churn out copies of the virus protein; most of these vaccines encode the virus's spike protein. RNA and DNA based vaccines are safe and easy to develop: to produce them involves making genetic material only, not the virus. But they are unproven: no licensed vaccines use this technology.¹² Around 25 groups say they are working on viral vector vaccines. A virus such as measles or adenovirus is genetically engineered so that it can produce coronavirus proteins in the body. These viruses are weakened so they cannot cause disease. There are two types: those that can still replicate within cells and those that cannot because key genes have been disabled. Many researchers want to inject coronavirus proteins directly into the body. Fragments of proteins or protein shells that mimic the coronavirus's outer coat can also be used. At least seven teams are developing vaccines using the virus

itself, in a weakened or inactivated form. Many existing vaccines are made in this way, such as those against measles and polio, but they require extensive safety testing. Sinovac Biotech in Beijing has started to test an inactivated version of SARSCoV2 in humans.¹³ In the registered clinical trials, intervention/treatment methods mainly include: antiviral drugs, such as: rheticvir, abidol, fabiravir etc., antimalarials like- chloroquine phosphate hydroxychloroquine, chloroquine etc., antiviral drug combination biological agents, for example: lucotinib combined with mesenchymal stem cell therapy, recombinant cytokine-gene derived protein injection combined with abidol or lopinavir/ritonavir, recombinant virus macrophage inflammatory protein for aerosol inhalation injection or lopinavir/ritonavir tablets combined with thymosin A1, lopinavir/ritonavir and interferon- α 2b, biological agents (products), for example: uterine blood stem cells, interferon, cord blood mononuclear cells, cord mesenchymal stem cell-conditioned medium, recombinant cytokine gene-derived protein, immunoglobulin, etc. and steroid therapy, for example, glucocorticoid (intervention in critical patients).¹⁴ While finding effective drugs is no easy feat on its own, it is also only at best a single step on a long journey towards taming the COVID-19 beast. Manufacturing, regulatory approval, and supply and access decisions are also going to need collective solutions, as will vaccine and diagnostic development.¹⁰

CONCLUSION

Drug discovery against the CoV is a challenging job owing to frequent recombination events. The development of a vaccine is another important aspect. We need more structural biology details and details of the life cycle of the CoV, which can speed up the drug/vaccine development process against CoV. Again, as a preventive measure, strict vigilance of viral changes in different hosts for prediction of an event is important.

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