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Vaccine Approaches for Pandemic COVID-19: An Overview

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ABSTRACT

The coronavirus strain, SARS-CoV-2 causative agent of the pandemic viral pneumonia disease COVID-19, identified in the late 2019. Unfortunately, there is no vaccine or therapeutics available to control the disease. Although, earlier research efforts of SARS pandemic (2003) provides the precious information to the researchers for fast track vaccine development. Research efforts for vaccine development of COVID-19 pandemic are unprecedented in terms of promising time period. The inactivated whole virus-based SARS-CoV-2 vaccine is first one developed and entered into clinical trial.

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However, later on after announce of complete genome sequence of SARS-CoV-2, vaccine based on recombinant viral vector, nucleic acid and immunogenic fragment also introduced. Previous experience of undesired immunopotentiation in SARS-CoV studies represents, vaccine safety should be the main concern. Researchers believe that next generation vaccine approaches using recombinant technology such as viral vector or subunit protein-based vaccine will be more effective and safer. This review describes brief information of the major vaccine candidates and the current scenario of vaccine approaches against COVID-19 pandemic.

Keywords: COVID-19, Vaccine, SARS-CoV-2

1 Introduction

The pandemic COVID-19 disease caused by severe acute respiratory syndrome corona virus-2 (SARS-CoV-2) started in December 2019 from Wuhan, China, later on within few months this infectious disease spread in all over the world [1]. SARS-CoV-2 belongs to the family coronavirdae in the genus betacoronavirus. It poses positive-sense single-stranded RNA genome, approximately 29,903 bp nucleotides long [2], including four major structural proteins, viz., spike (S), membrane (M), envelope (E) and nucleocapsid (N), sixteen non-structural proteins (nsp1-16) and five to eight accessory proteins [3]. High predominance and wide distribution of coronaviruses influence the genetic diversity and frequent recombination in genome, increase the risk of pandemic situation [2, 4]. Coronaviruses is constitute of the subfamily Orthocoronavirinae, and classified into four genera including alpha, beta, gamma and delta [5]. Infectious disease caused by corona viruses have been identified in several avian hosts as well as in various mammals, including camels, bats, masked palm civets, mice, dogs, and cats [6]. Total seven human coronaviruses have been identified till date, including the new pandemic SARS-CoV-2, which is close similar to human severe acute respiratory syndrome corona virus (SARS-CoV), a species of coronavirus which infects humans, bats, and camels [7]. SARS-CoV, first identified in the year 2003, which causes severe acute respiratory syndrome (SARS) and shows unique pathogenesis as respiratory tract infections [8]. Human SARS-CoV is believed to be originate from animal as evidenced >99% nucleotide homology with SARS-CoV–like virus, recovered from palm civets or other animals of china meat market [9]. Symptoms as common cold and headache with mild illness have been reported in human corona virus infection. Although, infections of SARS, MERS, and COVID-19 have been reported to the most life-threatening disease, infected person may have severe symptoms like pneumonia and acute respiratory distress syndrome [10].

Presently COVID-19 is terrific for the world and precipitously transmission of virus from infected individuals or from aerosol droplets has been reported earlier [11]. Asymptomatic nature of virus and human to human transfer by sneezing droplets makes the situation terrific that results spread of the disease worldwide. Typical clinical symptoms of disease are dry cough, fever, breathing difficulties and pneumonia [12, 13]. In last two decades, acute viral respiratory disease following by pandemic SARS-CoV (2003) and MERS-CoV (2012) causes illness and death of the individuals due to weak immune system or respiratory tract infection [14]. Present scenario of COVID-19 shows situation is pandemic; globally more than 60, 57,853 confirmed cases including 3, 71,166 deaths have been reported to WHO since December 2019 to 2nd JUN 2020. Pandemic situation caused the travel restriction and nation wise lock down in many countries that also cause economic loss internationally [15]. Vaccine development is only the way to restrict the pandemic situation; an effective vaccine strategy is required that induce the cell-mediated immunity and deliver the antibody responses against SARS-CoV-2 in vaccinated host. Presently no approved cure is available for SARS-CoV-2; although, scientists from all over the world are giving their best efforts to develop protective vaccine or therapeutics. As per the newsletter of Coalition for Epidemic Preparedness

Innovations (CEPI) at least 115 vaccine projects are in progress. However, 78 projects reported as actively running, in which many are in preclinical stage and some of these have been entered into clinical stage [17].

2 Vaccine Approaches

Development of effective vaccine to prevent infection of SARS-CoV-2 is urgently required, as the world is becoming victim of the pandemic COVID-19. There are many strategies are use as routine method of vaccine development for virus diseases such as live-attenuated vaccine, inactivated whole virus vaccine, recombinant viral vector based vaccine, nucleic acid based vaccine and immunogenic fragment based vaccine [18]. The present economic impact and human life threat due to the COVID-19 is forcing to the researchers for moving towards the next-generation vaccine approaches, that are usually based on genomics and structural biology. Many of these approaches are not currently allowed as licensed vaccine. Although, experience of success in case of malaria vaccine e.g. RTS,S/AS01 and HIV vaccine encourages researchers to exploit the opportunities for next-generation vaccine approaches that support to early development platforms [19, 20]. Complete genome sequence of SARS-CoV-2 shares 79.6% and 96.2% nucleotide sequence identity with SARS-CoV and RaTG13 bat coronavirus, respectively [21]. Numerous nucleotide sequence based study also indicates that the bat might be a probable origin of SARS-CoV-2 [22, 23]. Nucleotide sequence study of surface glycoprotein spike (S) revealed ~72% nucleotide sequence similarity between SARS-CoV-2 and SARS-CoV [24, 25]. It also has been confirmed that S protein of SARS-CoV-2 attach on host cell by angiotensin converting enzyme-2 (ACE2), the same cell entry receptor used by SARS-CoV, to spread the disease [26]. Research studies in last two decades done for vaccine development of SARS allows researcher to use already shaped groundwork of vaccine strategy, on the basis of SARS genome identity with COVID-19 [27]. Although, a new vaccine will require careful safety evaluations for immunopotentiation that may found in the form of increased infectivity or eosinophilic infiltration, which occur after immunizations with whole virus vaccines or recombinant vaccines [28]. In India, seven different industries (Zydus Cadila, Serum Institute of India, Biological E, Bharat Biotech, Indian Immunologicals, Mynvax and Hester Biosciences) are in race to develop a better vaccine candidate with support from the government organizations and academic institutions, researchers are working on 14 vaccine candidates on different levels [29]. However, more than 100 companies from all over the world are also working on different projects, in which mostly are in preclinical evaluation stage and ten in clinical evaluation stage as per the report of WHO and CEPI, 2 Jun 2020 [16]. Scientists are using specific significance platform for early development of an effective vaccine e.g. whole virus inactivated and live attenuated vaccine, Nucleic acid (DNA, RNA) vaccine and viral vector based recombinant vaccine. A brief of these strategies is described here and vaccines that are presently in clinical evaluation listed in table-1.

2.1 Whole-Virus live and Inactivated Vaccines

Purified virus is grown on tissue culture and inactivates by heat or chemically after harvest, a traditionally classical method of inactivated vaccine development. There are several advantages of inactivated vaccine such as; it does not need any genetic manipulation, cost effective and good safety profile [30]. However, it requires live virus culture that generates the risk of high-level containment. Safety and efficacy of inactivated COVID-19 vaccine have been confirmed by multinational companies in animal model [17]. Vaccine candidate PicoVacc has been reported earlier for partial and complete protection against SARS-CoV-2 in macaques following by testing neutralizing antibodies protection in ten representative strain of SARS-CoV-2 [31]. In response to the outbreak of SARS-CoV2, University of hong kong have developed a vaccine candidate based on the live attenuated influenza virus platform, they adapted it to express the surface protein of SARS-CoV-2, this vaccine will be consider as flu-based vaccine and can combine with any

seasonal flu vaccine strains [32]. A "codon deoptimization" technology to attenuate viruses has developed by Codagenix and the same strategy is using for exploring COVID-19 vaccine [33]. Inactivated vaccine developed by Wuhan Institute of Biological Products/Sinopharm, Beijing Institute of Biological Products/Sinopharm and Sinovac are presently in clinical evaluation trial phase-1.

Table 1: COVID-19 vaccine development programs under clinical evaluation [16]

Vaccine type	Candidate type	Developer	Current stage of clinical evaluation
Non-Replicating Viral Vector	ChAdOx1-S	University of Oxford/AstraZeneca	Phase2b/3
	Adenovirus Type 5 Vector	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 2
RNA	LNP-encapsulated mRNA	Moderna/NIAID	Phase 2
	3 LNP-mRNAs	BioNTech/Fosun Pharma/Pfizer	Phase 1/2
DNA	DNA plasmid vaccine with electroporation	Inovio Pharmaceuticals	Phase 1
Inactivated	Inactivated	Beijing Institute of Biological Products/Sinopharm	Phase 1/2
	Inactivated	Wuhan Institute of Biological Products/Sinopharm	Phase 1/2
	Inactivated	Institute of Medical Biology , Chinese Academy of Medical Sciences	Phase 1
	Inactivated + alum	Sinovac	Phase 1/2
Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	Novavax	Phase 1/2

2.2 Nucleic acid vaccines

Nucleic acid vaccine is a major concern for licensing, till now there is no nucleic acid based vaccine is licensed for human. Pandemic situation needs fast track vaccine development, and nucleic acid platforms may be a solution for the same. The Innovation and Value Initiative (IVI), created a DNA-based vaccine candidate (INO-4800) targeting SARS-CoV-2 S protein, recently they demonstrated that vaccination with INO-4800 generates robust neutralizing antibodies and T cell responses against SARS-CoV-2 in mice and guinea pigs [34]. Moderna/NIH and CureVac are working on development of mRNA vaccine, and clinical trial of Moderna's candidate vaccine mRNA-1273 has been performed earlier [35]. Another vaccine candidate BNT162 developed by BioNTech, Fosun Pharma and Pfizer is also in clinical trial phase 1/2 (ClinicalTrials.gov Identifier: NCT04368728) to determine the safety, immunogenicity and optimal dose level [36].

2.3 Subunit vaccines

Immunogenic studies of MERS and SARS represented the S protein and its fragments, S1, S2, RBD, and N protein, are major targets for developing vaccines. So it is expected for COVID-19 vaccines, the similar regions of SARS-CoV-2 could also be considered as key targets for effective vaccine development [37, 38]. However, global production capacity might be limited and integrity of antigen or epitope also needs to confirm. Subunit vaccines elicit an immune response against the S-spike protein and prevent its docking with the host ACE2 receptor [39]. Previous research studies have been demonstrated the subunit vaccines based on recombinant S or S1 protein found effective in case of SARS-CoV and MERS-CoV [40]. Clover Biopharmaceuticals is developing a subunit vaccine consisted trimerized SARS-CoV-2 S-protein by using their patented Trimer-Tag technology [41]. The receptor-binding domain (RBD) was identified earlier in SARS-CoV-2 S protein and suggested that S1 subunit consists of the RBD, which mediates virus entry into host cells through ACE2 receptor [42, 43]. The significance of RBD provides the rationale for choosing RBD as a prime target for subunit vaccine. In case of early SARS coronavirus vaccine research, undesired immunopotentiation is a major issue reported in whole virus or complete S protein based vaccines [28]. RBD-based vaccine also provides an advantage to minimize the host immunopotentiation. An Immunogenic vaccine candidate, virus-like nanoparticles based on SARS-CoV-2 S-protein recombinant expression developed by Novavax and the construct is in clinical trial phase-1 [44]. Industries and academic organizations such as expresS2ion, iBio, Novavax, AdaptVac, Biological E Ltd, Baylor College of Medicine, University of Queensland, and Sichuan Clover Biopharmaceuticals are also in preclinical phase [17]. The long-term protective immunity and presence of induced neutralizing antibodies reported, when SARS-CoV RBD proteins administrated in animal models [45]. Thus, S1 subunit targeted antibodies against SARS-CoV-2 would be effective to provide protection and treatment of COVID-19.

2.4 Vaccines based on viral vector (replicating and non-replicating)

Recombinant viral vectors based vaccines have prospective for therapeutic use; they facilitate intracellular antigen expression and enhance immunogenicity without an adjuvant following by induced cytotoxic T lymphocyte (CTL) response [46]. MERS-CoV S glycoprotein expressed in Ankara and adenoviruses based recombinant vectors and demonstrated immunogenicity in mice [47]. Thus, viral vectors provide a promising tool for protective vaccine strategy. The first COVID-19 vaccine candidate based on adenovirus vector developed by Chen Wei group and human clinical testing on 16 March 2020 (ClinicalTrials.gov Identifier: NCT04313127). Recombinant adenovirus vaccine candidate, Ad5-nCoV developed by Cansino Biologics Inc. / Beijing Institute of Biotechnology, the recent clinical trial phase-2 of the same demonstrates that a single dose Ad5-nCoV vaccine produces virus-specific antibodies and T cells in 14 days [46]. Vaccine

candidates based on lentivirus vector namely, COVID-19/aAPC and LVSMENP- DC also have been developed by Shenzhen Geno-Immune Medical Institute and clinical trial for the same is in progress (ClinicalTrials.gov Identifier: NCT04276896; NCT04299724).

3 Conclusion

Scientist, doctors, medical staff and other social activist organization from all over the world are involved as frontline corona warriors against COVID-19. Although, successful research on different vaccine approaches are in progress for eliminate the pandemic situation. Hard work and efforts done in the last two decades for coronavirus strains such as SARS and MERS provide knowledge and ideas for effective vaccine development. Vaccine candidates, including inactivated whole-viruses, live viruses, recombinant protein subunits, and nucleic acids may offer better protection against pandemic COVID-19. However, research studies of coronaviruses demonstrate that vaccine based on subunit protein will be more effective than other candidates. Vaccine approaches currently in progress have their advantages and disadvantages. Consequently, it is the priority that vaccine prepared by any of the promising approach will require a carefully evaluation for safety and efficacy. The data presented in this review provides a judicious summary on efforts to develop a vaccine for the SARS-CoV-2.

4 Competing Interests

The authors declared that no conflict of interest exists.

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