The Current Therapeutic and Vaccine Pipeline of COVID-19

Asama Mukherjee

International Institute of Innovation and Technology, DH Block Action Area 1, Newtown, Kolkata 700156, West Bengal, India.

Abstract

The COVID-19 pandemic has posed a menace to human life worldwide. This has triggered the thrust for the development of effective therapeutics and vaccines based on varied strategies. The trend for the repurposing of approved molecules or those already in the clinical stage of development for other indications has been currently explored to facilitate speedy identification of safe and effective drugs. Passive immunization through use of monoclonal antibodies and convalescent plasma therapy has been an investigational treatment from our previous knowledge of SARS and MERS. The landscape for vaccine development represents several novel agents based on diverse technologies that have already entered into fast track clinical trials. A new paradigm for identifying safe and immunogenic vaccines may be achieved through adaptive development and innovative regulatory process to address the unmet need in a short span compared to the conventional timeframe. This article aims to consolidate the status of the therapeutics and vaccines in the developmental pipeline for COVID-19.

Key words: COVID-19, Coronavirus, Remdesivir, Hydroxychloroquine, Vaccine development.

Introduction

The novel corona virus disease (referred to as COVID-19) outbreak occurred in December 2019 with its epicenter at Wuhan, the capital city of Hubei province in China, the causative agent being novel corona virus (1). The disease is characterised by acute to severe respiratory illness along with fever, dry cough, fatigue, nasal congestion, sore throat and diarrhoea. The novel virus has been named SARS-CoV-2 by the Coronavirus Study Group (CSG) of International Committee on Taxonomy of Viruses (ICTV) due to its resemblance with the RNA genome of the SARS coronavirus (SARS-CoV), which made its appearance in the early 2000s. Both of these viruses are of zoonotic origin belonging to the family *Coronaviridae*. Since its outbreak there has been an exponential rise in the number of cases worldwide. On March 11, the World Health Organization (WHO) declared the outbreak as pandemic. The severity of the disease appears to be associated with age, with the elderly most at risk. The Case Fatality Rate (CFR) is also more pronounced in patients with comorbidities including cardiovascular, diabetes, chronic respiratory disease, hypertension, and cancer.

Currently the World Health Organisation (WHO) has designed the technical guidance (2) on the preparedness, readiness and response action. Several guidelines have been

implemented for pandemic control and infection prevention such as screening, hand sanitising, social distancing, isolating affected people, disease containment and on the proper use of Personal Protective Equipment (PPE). Clinical management using several non-pharmacologic treatment approaches such as fluid support, oxygen and ventilation support as well as compassionate use of several chemical agents (3,4) and therapies (5,6) is currently recommended for patients. However, a robust and rapid pipeline of therapeutics and vaccine has been created on priority basis to address the state of emergency.

The Coronavirus structure and genome

The virus is an enveloped structure with a positive sense, single stranded RNA of size ranging between 26-32 Kilobases. The genome encodes for both structural and non-structural proteins. At the 5′ end the open reading frame encodes a polyprotein which is processed by viral proteases to cleave into 16 non-structural proteins needed for replication and transcription process. The structural proteins encoded within the 3′ end of the viral genome are the membrane protein (M), envelope (E) protein, nucleocapsid (N) protein and spike protein (S) that are critically important for viral attachment, entry, viral assembly and other host-immune response. The viral attachment with the host cell is mediated through the viral spike protein that interacts with the cell membrane protein angiotensin-converting enzyme 2 (ACE2) in order to enter human cells. The spike is a glycoprotein homotrimer composed of two subunits S1 and S2 that are about 150 kDa in size each, among which S1 contributes to receptor binding and S2 is required for the fusion and entry of the virus particle in the host cell (7).

Strategies for therapeutic and preventive intervention

Until now there is no approved antiviral drug or vaccines available for corona virus treatment or prevention. The pandemic situation has provided a thrust for exploring of a range of strategies for effectively combating with the virus in terms of drug and vaccine development including other therapeutic modalities (8).

Repurposing of Antivirals for COVID-19

Development of drugs involves a lengthy process from its laboratory synthesis to translation into clinical trials and obtaining regulatory approval for therapeutic use. Hence scientists and clinicians are trending on the practice of repurposing of molecules (9) that has already been in the developmental stage in order to find a fast-track treatment option in patients. These molecules interfere (10, 11) with several key proteins that affect the vital steps of pathogenesis such as viral polypeptide cleavage into functional protein (proteases 3CLpro and PLpro), host attachment (S protein, ACE2 receptor and transmembrane protein serine 2 TMPRSS2) and replication (RNA dependant RNA polymerase RdRp). Remdesivir (GS-5734), a broad-spectrum antiviral originally developed by Gilead as a treatment option for Ebola has been currently reported to prove beneficial in patients (12). Multicentric clinical trials are underway to test its safety and efficacy in COVID-19. The molecule is a prodrug of the parent adenosine analogue, GS-441524, both of which are metabolized into an active nucleoside triphosphate (NTP) by the host that competes with the ATP incorporation into the RNA, thus blocking RNA Polymerase and checking the viral replication machinery in host cell. The therapeutic efficacy of Remdesivir in SARS-CoV-2 infected rhesus macaque has been reported in a preclinical study at NIH (13) and currently in clinical trial.

FDA approved drug Kaletra, a combination of Ritonavir and Lopanivir, developed for treating HIV infection has been reported to inhibit protease activity in corona virus as studied *in vitro* and in animal (14). These two molecules have been registered in a randomized controlled clinical trial. Based on the past

knowledge and accumulated experience as treatment option in SARS and MERS outbreak, the combination raises hope for SARS-CoV-2 treatment as well.

Ribavirin, a guanosine analogue, used to treat several virus infections, including respiratory syncytial virus, hepatitis C virus, and some viral haemorrhagic fevers has been shown to target RNA-dependent RNA polymerase in a sequence analysis, modelling, and docking studies against SARS-CoV-2. This molecule had shown improved clinical outcome in MERS-CoV infected rhesus macaque with interferon-α 2b (15).

Use of Chloroquine Derivative

Chloroquine is a widely-used as an antimalarial and anti-inflammatory agent for the treatment of rheumatoid arthritis and lupus erythematosus. This drug that has been reported to elicit potential broad-spectrum antiviral drug activity by increasing endosomal pH required for virus cell fusion with host cell, as well as interfering with the glycosylation of cellular receptors of SARS-CoV (16). The combined antiviral and anti-inflammatory properties make it a potential candidate for treatment of SARS-CoV-2 pneumonia. However, the less toxic derivative hydroxychloroquine (HCQ) (17) has received FDA approval recently for use on compassionate basis at optimal doses. Studies reveal that HCQ also acts efficiently to attenuate the production of cytokines and other pro-inflammatory factors in critically ill patients. A study by Raoult (et al) found that treatment with hydroxychloroquine and azithromycin resulted in a rapid decline in the nasopharyngeal viral load in COVID patients (18). Clinical trials to explore the efficacy of hydroxychloquine as single agent and in combination with azithromycin, monoclonal antibodies (mAbs), interferons, antivirals and other agents are underway (https://clinicaltrials.gov/) (Fig.1).

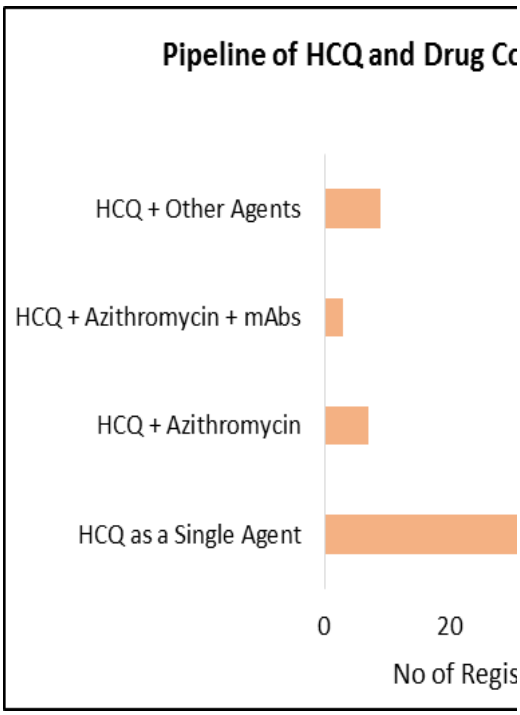

Figure 1: The number of registered trials of Hydroxychloroquine (HCQ) as a single agent and in combination with other drugs in Clinical Trial (Data obtained from https://clinicaltrials.gov/)

Use of Monoclonal antibodies

Monoclonal antibodies find wide application in therapeutic intervention of many diseases. In case of viral disease these antibodies generally target the vulnerable sites on viral surface proteins and bring about activation of the immune system. The CoV spike (S) protein plays the most important roles in viral attachment, fusion and entry by binding strongly to host angiotensin-converting enzyme 2 (ACE2) receptors. Hence it serves as a target for development of antibodies, entry inhibitors as well as vaccines. Several known SARS-CoV RBD-specific monoclonal antibodies are tested for cross reactivity in SARS-CoV-2 (19). It is found that they do not have appreciable binding to SARS-CoV-2, suggesting that antibody cross-reactivity may be limited between the two Receptor binding Domains (RBDs). A report by Tian et al has re- vealed that a SARS-CoV-specific human mono- clonal antibody, CR3022, could binds potently with SARS CoV2 Receptor binding Domain. In- terestingly, the epitope of CR3022 does not overlap with the ACE2 binding site within 2019- nCoV RBD (20). These results suggest that CR3022 may have the potential to be developed as candidate therapeutics alone or in combina- tion with other neutralizing antibodies, for the

prevention and treatment of 2019-nCoV infec- tions. However development of MAbs for novel pathogens require sufficient time to translate into clinical practice.

Convalescent plasma therapy

Convalescent plasma therapy has been one in- vestigational treatment option that is being ex- plored for COVID-19 currently (6). It refers to the administration of convalescent plasma col- lected from individuals who have recovered from COVID-19 that contains immunoglobins against the SARS-CoV-2. In order to ensure a high neutralization antibody titre, the covalescent plasma needs to be collected within two weeks after recovery of the patient. This kind of empirical therapy has been reported to be effective during 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1 influenza virus pandemic, and the 2012 MERS-CoV outbreak. The FDA has issued guidance on the recommended use of this therapy to healthcare professionals based on the public health necessity and emergency treatment. It is important to study the safety and efficacy of COVID-19 convalescent plasma in well designed-clinical trials.

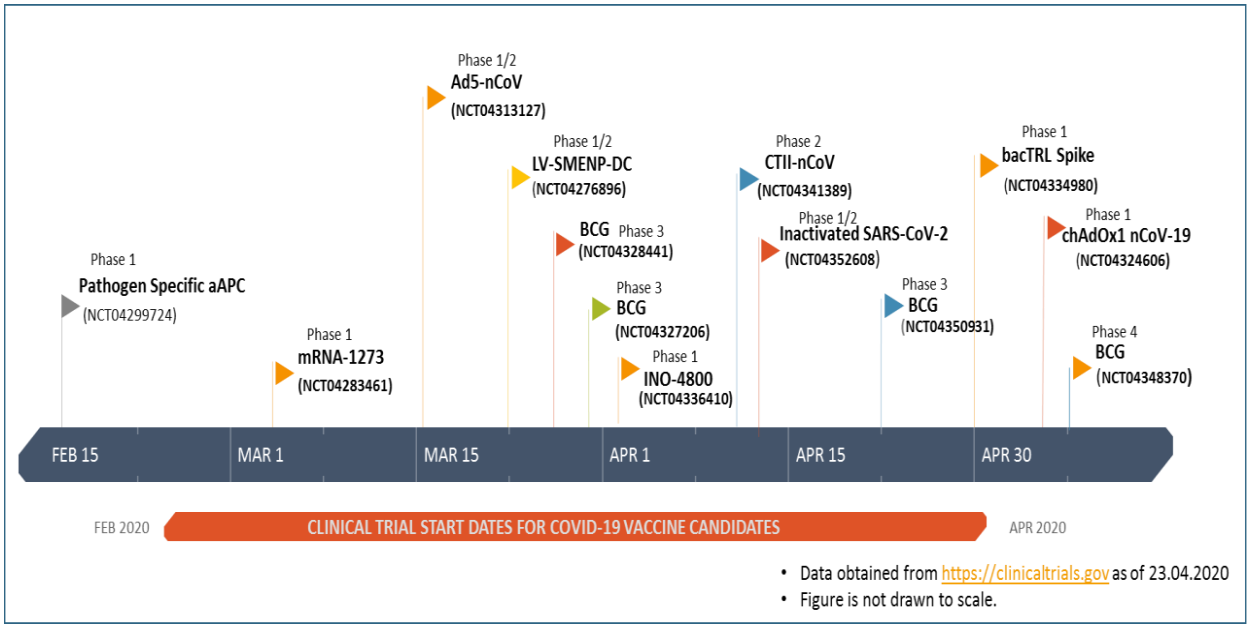

Figure 2: The Vaccine pipeline of COVID-19

Vaccine Development

The discovery of the genetic sequence of coronavirus has given a head start to several institution and biotech companies for vaccine development. This process is being supported by the Coalition for Epidemic Preparedness Innovations (CEPI) and other global health authorities. Vaccines based on several technologies have entered into clinical trial (21) (Fig 2). The mRNA-1273 vaccine from Moderna is a novel lipid nanoparticle encapsulated mRNA-based (22) vaccine that encodes the prefusion stabilized form of the Spike protein as the antigen to elicit neutralising antibody response. Ad5-nCoV (23) is an adenovirus based vaccine that has been developed by CanSino Biologicals while INO-4800 (24) is a DNA vaccine developed by Inovio, both of which encodes for the S protein. The two other vaccines developed by Shenzhen Geno-Immune Medical Institute the LV-SMENP-DC (25) and Pathogen specific aAPC (26) are similarly in phase 1 trial. In the former a lentiviral vector system is used to express viral proteins and immune modulatory genes to modify dendritic cells (DCs) and activate T cells, while the latter uses a lentivirus modification to artificial antigen presenting cells (aAPCs) to generate immune protection. CTII-nCoV, bacTRL Spike, chAdOx1 nCoV-19 and inactivated SARS-CoV-2 are some other vaccine candidates (27-30) in clinical trial.

Interestingly vaccine development pipeline shows a diversity in technology platforms including live attenuated virus and inactivated virus approaches, use of adjuvants, nucleic acid (DNA and RNA), virus-like particle, peptide, viral vector (replicating and non-replicating) and recombinant protein. This has a great implication to target a diverse population in a way that given vaccine might be effective in a certain population while another one might be effective in a different population. Currently studies (31) has been undertaken to explore the protective effect of the century old BCG vaccine in COVID-19. However, there is lacking evidence of mechanism of immune protection induced by this vaccine. Initial results indicate that it acts in a non-specific manner.

Conclusion

Viruses are constantly on the process of mutation which a natural part of their life cycle. Hence it is imperative to design antivirals, or use combination of several neutralising antibodies that can provide a broad range of coverage by recognising different epitopes on viral surface. The current pipeline of therapeutics and vaccination technologies foresees the possibility of identification of several potential agents for combatting with SARS-CoV-2. Preclinical studies by choosing appropriate animal model are a necessity for any new chemical entity or a biological before being considered for intervention in humans. However, the state of emergency demands using fast track models for prompt response through adaptive development and innovative regulatory process. Under these circumstances it is necessary to design robust multicentre clinical trials to assess the safety and efficacy of these vaccines, drugs and other therapeutic options. Funding agencies, therapeutics/vaccine developers, global regulatory bodies and policymakers need to extend their support to accelerate the process from developmental stage to manufacturing and scale-up process. Such a paradigm shift might enable us see light at the end of a dark tunnel.

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