AIJR Preprints
Section: Coronavirus
Article Id: 177, Version: 1, 2020
URL: https://preprints.aijr.org/index.php/ap/preprint/view/177
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NOT PEER-REVIEWED

Version 1: Received: 21 July 2020 / Approved: 26 July 2020 / Online: 26 July 2020

An Overview on Drug Evolution and Trials on Pandemic COVID-19 Infection

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ABSTRACT

The disease caused by severe acute respiratory syndrome (SARS-CoV2) is highly pathogenic and communicable infection, progressed in Wuhan city of China and then around the world. The Genomic investigations shows that phylogenetically SARS-CoV2 resembles the other SARS-like bat viruses, therefore bats were also considered as the possible potential reservoir for SARS-CoV2. COVID-19 pandemic has presented considerable challenges to public health care system at global scale. Novel COVID-19 virus is member of corona Viridae family. Drug evolution and alternative therapy has come in the focus prominently in the treatment of COVID-19 infection. Although, clinical trials, also be in faster rate in all over the world. A number of drugs which were previously used against SARS-CoV-2 infection such as Remdesevir, Lopinavir, Ritonavir, Interferon beta-1b and Ribavirin, but they are being tested in randomised trials and show less prominent effects. In the review we summarized the latest research progress nationally and internationally on treatment and clinical trials of COVID-19 pandemics.

Keywords: COVID-19, Plasma Therapy, Clinical Trial.

1. Introduction

World pandemic threat COVID-19 seriousness is crucial to the human life and for reducing distortion of livelihood. International Committee on Taxonomy of Viruses (ICTV) labelled SARS-CoV-2 (SARS-Severe Acute Response Syndrome) virus induced corona virus disease. COVID-19 was outbreak from Wuhan, China from 2020 January[1]. Similar kind of outbreak was happened previously with different pathogens named SARS-CoV in 2003 and Middle East Respiratory Syndrome Coronavirus-MERS-CoV (Since 2015, centred on Arabian Peninsula)[2]. However, SARS-CoV-2 virus promoting respiratory problems and ease of spreading (through air droplets) will make severe life threats than the other, hence COVID-19 is belonging to Corona Viridae family and size is 65-125 nm diameters approximately. After outbreak from china, according to the worldometer.info, on 26th July 2020, approximately 16,205,467 peoples have been affected with COVID-19, 648,476 peoples death occurs and 9,914,060 peoples recovered, still it continuous on. An overall good sign has been mortality rate (6%) worldwide. The affected patients are increasing in the rate of multiplication; thus, world governments should make consensus to eradicate the COVID-19 as much earlier, which will be helpful to save the poor population globally[3].WHO is gathering daily international multilingual scientific findings and knowledge on COVID-19 [4].

How to Cite:

Varshney *et al.* "An Overview on Drug Evolution and Trials on Pandemic COVID-19 Infection". *AIJR Preprints*, 177, version 1, 2020.

2.Drug Evolution

2.1 Hydroxychloroquine: Chloroquine has been used worldwide for more than 70 years. However, it is also a part of WHO model of essential list. The efficacy and safety of Hydroxychloroquine for the treatment of SARS-CoV-2 (new virus causing COVID-19) pneumonia, still remain not known[5]. More than a billion Indians currently stand at the precipice of a massive increase in cases of Coronavirus disease 2019 (COVID-19). India had shown a staggered course of severe acute respiratory syndrome Coronavirus (SARS-CoV-2) transmissions, with 1397 cases diagnosed between Jan 31, and April 1 of 2020. However, there has been a recent surge in cases, with numbers rising to 1,387,481 as of 26th July 2020 [6]. The Indian Council of Medical Research (ICMR), under the Ministry of Health and Family Welfare, recommended chemoprophylaxis with Hydroxychloroquine (400 mg twice on day 1, then 400 mg once a week thereafter) for asymptomatic healthcare workers treating patients with suspected or confirmed COVID-19, and for asymptomatic household contacts of confirmed cases caused by COVID-19 [7].

2.2 Remdesivir Remdesivir (Antiviral) is a Prodrug of a nucleotide analogue that is intracellular metabolized to an analogue of Adenosine Triphosphate that inhibits viral RNA polymerases. By June 2020, several potential post infection therapies including Remdesevir, Favipiravir and Topinavir used in international solidarity trial. Remdesivir has broad spectrum activity against members of several virus families, including Filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERSCoV]) and exhibited prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses [8].

2.3 Other Promising Drugs used against COVID-19 infection

Currently, there are no FDA approved treatments for COVID-19, although lots of drugs (Table 1) are being tested against COVID-19 infection [9].

Table 1: List of promising drugs against COVID-19 infection

List of drugs	Category
Baricitinib	Janus kinas inhibitor
Bemcentinib	AXL kinase inhibitor
Bevacizumab	VEGF inhibitor
Colchicin	Anti-inflammatory
Eidd-2801	Oral antiviral
Favipiravir	Antiviral
Fingolimod	Against multiple sclerosis
Azithromycin	Antibiotics
Lvermectin	Anti-Parasitic
Leronlimab	CCR5 antagonist
Lopinavir and Ritonavir	Anti-HIV
Methylprednisolone	Glucocorticoids
Remdesivir and Umifenovir	Antiviral
Sarilumab	Il-6 receptor antagonist
Tocilizumab	Il-6 receptor antagonist

2.4 Developing COVID-19 Vaccines at Pandemic Speed

Vaccine development is a lengthy, expensive process, Attrition is high, and it typically takes multiple candidates volunteers and many years to produce a licensed vaccine for human beings. Because of the cost and high failure rates, developers typically follow a linear sequence of steps, with multiple pauses for data analysis or manufacture in process checks. To developing a vaccine quickly requires a new pandemic paradigm with a fast start and many steps executed in parallel before confirming a successful outcome of another step, hence resulting in elevated financial risk. For platforms with respective experience in humans, phase 1 clinical trials may be able to proceed in parallel steps with testing in animal models [10, 11]. According to WHO guidelines, Participation in Solidarity Trial in March 2020 provides simplified procedures to enable even overloaded hospitals to participate, with no paperwork required. As of April 21 2020, over 100 countries are advised to working together to find effective therapeutics as soon as possible, via the trial. The greater the number of participating countries, the faster results will be generated [12]. Conservative estimated of time needed to prove a safe and effective vaccine is about early 2021. As per survey on 25th July 2020 by MarketWatch,com, Some leading pharmaceutical industries which are working on coronavirus treatments [13]. However, seven Indian pharmaceutical companies like Bharat Biotech, Serum Institute, Zydus Cadila, Panacea Biotech, Indian Immunologicals, Mynvax and Biological E, are in race to develop COVID-19 vaccine. Bharat biotech has received approval to conduct phase 1 and 2 clinical trials for vaccine candidate (Covaxin) that as on July 2020, started human clinical trials. Leading vaccine major serum institute of India and Astra Zeneca oxford undergoing phase 3 clinical trials and will started human trials in India in Aug 2020 [14].

Table.2 List of Pharmaceutical Companies Working on Coronavirus Treatment

Companies	Type	Stage	name
Amagen And Adaptive Biotechnologies	Antibody Treatment	Preclinical	AdCOVID
BioNTech and Pfizer	m RNA Vaccine	Phase 1/2	BNT162 Program
Cytodyn	Treatment	Phase 2 and Phase 2b/3 Clinical Trial	Leronlimab
Gilead sciences	Treatment	Emergency and Authorization	Remdesivir
Heat Biological	Vaccine	Preclinical	No name yet
Inovio Pharmaceuticals	DNA based vaccine	Phase-1 Clinical Trial	INO-4800
Johnson and johnson	Vaccine	Phase-1 Clinical Trial	No name yet
Moderna	RNA-based Vaccine	Phase-1 Clinical Trial	m RNA-1273
Novavax	Vaccine	Phase-1 Clinical Trial	NVX-CoV2373
Regeneron	Prevention and Treatment	Phase-1 Clinical Trial	REGN-COV2
Regeneron Pharmaceuticals	Treatment	Phase 2/3 Clinical Trials	Kevzara
Roche	Treatment	Phase 3 Clinical Trial	Actemra
Sanofi	vaccine	Preclinical	No name yet
Takeda pharmaceuticals	Antibody Treatment	Preclinical	TAK-888
Vaxart	Vaccine	Preclinical	No name yet
Vir Biotechnology	Vaccine	Preclinical	VIR-2703

2.5 Plasma Therapy

According to the therapeutic studies, Convalescent plasma or immunoglobulin, have been used to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with corticosteroids (Methyl Prednisolone). Moreover, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma [15]. In 2014, the use of convalescent plasma collected from recovered patients from Ebola virus disease, was recommended by World Health Organization (WHO) as an empirical treatment during outbreaks. A protocol for the convalescent plasma used in the treatment of Middle East respiratory syndrome Coronavirus [16]. The following steps were taken Donors for Convalescent Plasma Transfusion, Plasma Preparation Procedure and Quality Control, Serology Test and Real-Time RT-PCR, Detection of SARS-CoV-2 and Other Pathogens, Treatment (with antibiotics, antifungal, glucocorticoids, oxygen support), Data Collection [17]. Using data from March 31 (2020), which according to some data of JHU indicates 330 infections in India, it was founded that, among 11 quarantine scenarios, with 50% effective quarantine, 1,387,481 citizens in India would become infected, while 10% effective quarantine would result in 521 million infections. These grim numbers suggest that solutions other than social distancing are urgently needed to combat the epidemic and to minimize the loss of life [18].

2.6 Anti-cytokine therapeutics

Baricitinib (Antiviral agent) was used in April 2020, for first clinical trial and show anti-cytokine effects. However, Ruxolinitib and Acalabrutinib were used as IL-1 and IL-6 inhibitors. Tocilizumab is IL-6, Janus kinase and TNF inhibitor which inhibit the inflammation and decrease entry of SARS-CoV-2, shown remarkable effects in anti-cytokine therapeutics [19].

3. Randomized Clinical Trials during Disease Outbreaks

Conducting trials of novel interventions during infectious disease emergencies, such as the ongoing COVID-19 pandemic, is increasingly recognized as important for determining the efficacy of potential vaccines and therapies. Clinical trials to evaluate investigational interventions are being implemented as part of the broader efforts to control the spread of an infectious disease and to improve patient outcomes. In such circumstances, however, it can be challenging to acquire the necessary evidence about the effects of the interventions to inform future patient care and public health planning, in part because of the unpredictable size, geographic location, and duration of outbreaks [20]. A number of clinical trials and study have the important role to overcome infectious disease. Controlled **PREVAIL** (Partnership for Research on Ebola Virus in Liberia) II trial for the triple monoclonal antibody cocktail **ZMapp**, which helped in investigation of a large Ebola outbreak in the Democratic Republic of Congo (DRC) in 2018, investigators used ZMapp rather than the standard of- care treatment as the control against which to compare other Ebola therapeutics in the randomized Another trial used, **PALM** trial (Investigational Therapeutics for the Treatment of People with Ebola Virus Disease). There is an obvious need to balance the importance of publishing the results of all completed clinical trials against the potential adverse consequences. Thus, new approaches to clinical trials are welcome to enable reliable evaluations of vaccines and treatments for outbreak pathogens [21-23].

5. Drug design and laboratory testing

New chemical entities (NCEs) are the compounds that emerge from the process of drug discovery to a specific vaccine or antiviral therapeutic agents which having promising effects for activity against a

biological target related to COVID-19 infection. However, in addition drug development must establish the related physicochemical parameters which are directly related to stability, solubility and optimization of NCE [24].

6. Conclusion

In this review we obtained the relevant information from articles, online recourses and focused much on therapies drug development and vaccines development currently being used against COVID-19. As the knowledge on SARS-CoV-2/COVID-19 pandemic is still evolving. As per WHO guideline avoid the contact with sick person and also avoid the market or public place as per possible. There are no anti corona virus vaccine to prevent or treatment but some supporting therapy work. We summarized the current trends related to decreases the effect of SARS-CoV-2, drugs evolutions and trials struggle to find out the promising results. World's leading Pharmaceutical Companies are developing new vaccines to decrease the infections caused by COVID-19. New drugs and therapies in progressive stage globally and trying to decrease the effect of corona virus infections and COVID-19 outbreaks. However new drug entities (NCE) also in progressive stage.

7. Declarations

7.1 Competing Interest

The authors declare that they have no competing interest.

7.2 Authors' contribution

All authors wrote and revised the paper. All authors read and approved the final manuscript.

7.3 Acknowledgement

The authors acknowledge the Raj Kumar Goel Institute of Technology (Pharmacy), Ghaziabad for the supportive cooperation**.**

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