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Prospect for Covid-19 Investigational Drugs: The Timeline

(Prospect for Covid-19 Therapeutics)

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Abstract:- An outbreak of Coronavirus disease-2019 (COVID-19), firstly reported in Wuhan, China in December 2019, and eventually turned into pandemic, is continuing to put a lot of burden on the health sectors worldwide. Thus, finding a fast and effective therapy is crucial to discontinue the current human-to-human transmission and to treat serious cases. Several active pre-clinical and clinical studies are going on towards these goals, while existing drugs are being used alone and in combination to treat symptoms in COVID-19 patients. Here, bearing in mind the timeline and various stages of drug development, and considering the extremely-low probability that any new biological target or molecule identified as potentially relevant to the SARS-CoV-2 will result in an approved new medicine, a brief look at those basic studies and clinical trials of the investigational drugs and projected success of COVID-19 therapeutics based on the unprecedented rapidity of the processes being witnessed were emphasized. Despite the current explosion in such studies, from an expert opinion, it is believed that concerted and efficient development plans may ultimately yield a fast and effective medicine for the disease or we may live with the disease (COVID-19).

Keywords:- *SARS-Cov-2, COVID-19, Clinical Trials, Therapeutics, Drug Development.*

I. INTRODUCTION

A severe acute respiratory disease known as coronavirus -2 (SARS-CoV-2) which started in China (Yao et al., 2020) has caused several deaths and continues to pose a major public health threat to the world [2]. Some basic symptoms include cough, pyrexia, and acute respiratory distress syndromes [3]. Several active researches are ongoing to understand the nature of the disease and to develop more efficient methods of testing and treating. By August 2022, 222 vaccine candidates and 300 potential therapies for COVID-19 disease were at various stages of preclinical or clinical studies. The rapid crystallization of SARS-CoV-2 proteins has encouraged structure-assisted drug design. So far, there are several SARS-CoV-2 related structures available on the protein data bank (https://www.rcsb.org/) and such number continues to grow exponentially. Several existing drugs have been identified as potential candidates for treatment of COVID-19 and these include anti-viral drug [4], anti-asthmatic drug, (zafirlukast), anti-malarial drug (chloroquine and hydroxychloroquine), cardiac glycoside (dgitoxin), two anthracyclines (zorubicin and aclarubicin), a tetracycline derivative (rolitetracycline), a cephalosporin (cefoperazone) and several other drugs (itrazol, fazadinium, troglitazone, gliquidone, Idarubicin, Oxacillin) [5].

While active studies are ongoing toward the discovery of new effective drugs for treatment of COVID-19, it is imperative to bear in mind that the development of new therapeutics is a complex process with thousands of molecules being screened each year but only few make it at the approval stage [6]. Typically, it takes about ten years (from concept stage to the market) to develop a drug at an estimated cost of about $2.5 billion [7]. Interestingly, because of the present health and economic threats posed by COVID-19 pandemic, we are witnessing an unprecedented acceleration of the process with few clinical drugs already showing effectiveness in treating the symptoms of serious COVID-19 cases.

II. METHOD

In this study, a careful look at the time it will take to create a novel drug to serve as treatment for COVID-19 was presented by discussing each of the different drug production stages. On the other hand, published papers were obtained on drugs that are undergoing clinical trials, and those that have completed clinical trials from multiple journals. In each of those papers, the case study and the number of people who are undergoing/ have undergone different clinical trials were taken into consideration. Multiple papers were downloaded and filtered based on the inclusion and exclusion criterion. COVID-19 research related papers without clinical trials were rejected. The outcome of each trial in terms of success and failure, sex ratio, age group, and location were considered. A comprehensive report on each accepted paper along with unbiased expert opinion was presented. The entire paper is therefore divided into two stages. The procedure in developing a new drug with key emphasis on the stages and time frame were initially discussed. It is noted that the total time can however be reduced with the aid of a computational approach. This was followed by the presentation of the efforts made my clinical researchers to obtain a treatment plan for people with COVID-19 through the use of already approved drugs for illnesses that have signs and symptoms in common with the disease. Drugs considered in these clinical trials were drugs for influenza, respiratory related diseases, etc.

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III. OVERVIEW OF DRUG DEVELOPMENT STAGES

Drug discovery and development is a time-consuming and laborious process associated with many failures and much uncertainty. Nevertheless, in the case of COVID-19, expedited processes are being executed, and this is likely to reduce the overall timeline of discovering medicine for the disease. However, it is important to bear in mind that regulatory agencies such as FDA can apply canonical procedure of rigorous assessment of therapeutics before approval to be used in the human body. To familiarize readers with these processes, the various stages of the development of novel drugs briefly summarized below.

A. Preclinical Testing.

The goal of a preclinical drug testing program is to deliver a handful of clinical candidate molecules that show sufficient evidence of biologic activity against a target relevant to a disease as well as sufficient safety and drug-like properties enough to proceed into clinical trials. At this stage, an investigation of the pharmacodynamics and pharmacokinetics properties of a drug, as well as its absorption, distribution, metabolism, elimination (ADME), and persistence of pharmacological effects are carried out [8]. Using high-throughput screening techniques, many compounds are evaluated and top lead compounds are subjected to in-depth assessment at many doses against many assays [9]. This process takes about three and a half years on average.

B. Investigational New Drug (IND)

Pharmaceutical company files an IND with the FDA to begin the testing of drug candidate in humans. The IND becomes effective if the FDA does not disapprove the drug within 30 days. Details on IND include: the results of previous experiments; the chemical structure of the compound; mechanism of action; any toxicity found in the animal studies. These studies ensure the safety of pharmacology, genetic toxicology, acute and sub-chronic toxicology, ADME studies, reproductive and developmental toxicity [10].

C. Phase I Clinical Trials.

Phase I studies are usually the first tests of a drug under development on healthy volunteers. About 20 to 100 volunteers are recruited [7]. The tests determine safety profile, including the safe dosage range, and ADME, as well as the duration of its action. Phase I trials last about a year (Akhondzadeh, 2016).

D. Phase II Clinical Trials.

These are slightly larger studies that are done on patients with the disease for which the drug is intended. This phase is usually designed to identify effective dosages, short-term side effects and administration methods. The trials generally involve 100 to 300 patients on a volunteer basis. They are done to assess the drug's effectiveness and last about 2 years.

E. Phase III Clinical Trials

This stage takes into consideration a large randomized trials that are submitted to the FDA to seek approval of a drug. This phase examines the effectiveness as well as the safety (adverse events) of the new drug and is designed to confirm the preliminary evidence accumulated in Phase II [8]. Phase III clinical trials usually take into consideration 1,000 to 3,000 patients. During this phase, patients are usually for possible side effects, often derived from what was observed in the previous phase. While on the new drug or the placebo (the "sugar pill" that is given to a percentage of patients in a trial study), patients are free to report any other side effects that occur. Phase III takes about 3 years [12].

F. Filing investigational New Drug Application (NDA)

After the Phase III Clinical Trials, the drug manufacturer analyzes all the data from the studies and files an NDA with the FDA (provided that such data conform to the safety and efficacy standard of the drug). The NDA contains all the data collected on the drug. The average NDA review time for new drugs approved in 1992 was close to 30 months [12].

G. Marketing the Drug

The concluding stage in the drug development process is known to be marketing. Upon approval of the drug by regulatory authorities, the drug manufacturers must submit authorization applications in each country or places where they want to sell the drug.

H. Phase IV Studies

This phase is referred to as “post-marketing surveillance”. Phase IV is an organized collection of data from patients who are taking a drug that has already received approval by the FDA. These trials normally include additional drug-drug interaction [8]. In this Phase, patients are expected to check boxes on a list (as in phase III studies) or they may just report other symptoms associated with the drug (Figure 1).

Although there are other routes that can expedite the process (referred to as fast-tracking), this is the usual path for a drug from invention to marketplace in the U.S. [13].

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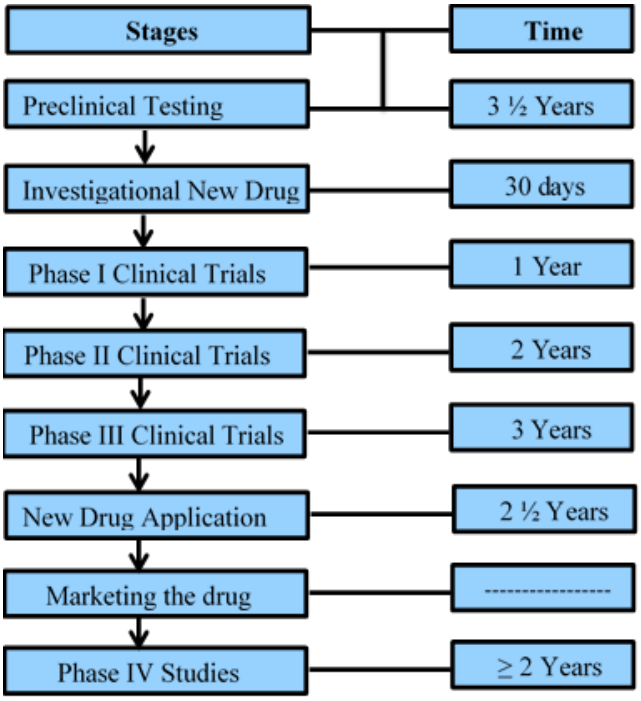

Fig. 1 Stages of drug development along with estimated time

IV. STATUS OF SOME COVID-19 THERAPEUTICS IN CLINICAL USE

There are several ongoing pre-clinical and clinical studies which mainly focus on efficacy and safety of existing drugs for repurposing use to treat COVID-19 patients. It is noteworthy that despite the large number of the ongoing basic and clinical studies, very few drugs will make it to the marketplace due to the rigorous nature of the drug development process, which ensures that the desired efficacy and safety of drug candidates are met before approval to be used in human body. The prospect of COVID-19 drug discovery and development is depicted in Figure 2. Thousands of molecules are being identified through basic and pre-clinical studies to have therapeutic potentialities for COVID-19, however, due to the rigor inherent to the endeavor, extremely low fraction of them proceed to the clinical trial stages. Sadly, many of them will be withdrawn from further clinical trials due to toxicity and/or efficacy concerns, and very few will gain approval. Hence, to facilitate the rapid development of the discovered COVID-19 drug candidates, concerted and directional research plans are needed.

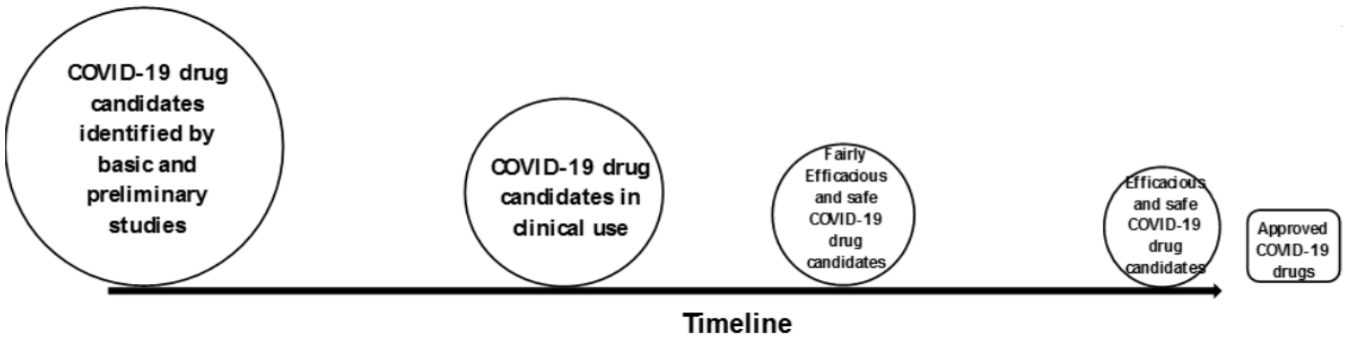

Fig. 2 Prospect and timeline for COVID-19 drug discovery and development

A. Remdesivir

Remdesivir is a nucleoside analogue pro-drug known to have inhibitory effects on severe acute respiratory infections. The clinical trial of remdesivir as a COVID-19 therapeutic took place in ten hospitals in Hubei, China on laboratory-confirmed SARS-CoV-2 infected patients. A phase III randomized, double-blind, placebo-controlled trial was performed during the studies. The hospitalized patients were enrolled and randomly assigned to a treatment group (158 remdesivir group and 79 inactive drugs group). Adverse events were reported in 102 of the patients on remdesivir compared to the 50 placebo. Statistically, the ratio of adverse events in remdesivir and placebo recipients was 12% to 5% respectively [14]. Consequently, remdesivir was stopped early because of adverse events, and was concluded that remdesivir does not show statistically significant clinical benefits on COVID-19 patients [15]. In one study, a total of 1063 patients were randomized, and preliminary results from the 1059 patients (538 assigned to remdesivir, and 521 to placebo) revealed that 21.1% of remdesivir group and 27.0% in the placebo group demonstrated adverse events, suggesting the superiority of remdesivir to placebo in shortening the time to recovery in hospitalized adults with evidence of lower respiratory tract problem [15].

B. Hydroxychloroquine, Chloroquine and Azithromycin

Hydroxychloroquine and azithromycin have been found to be efficient treatment for COVID-19 symptoms.

In a study conducted in The Méditerranée Infection University Hospital Institute in Marseille on a total of 20 COVID-19 adult patients, each patient received 600mg of hydroxychloroquine daily, and their viral load in nasopharyngeal swabs were tested daily. Azithromycin was then added to the treatment based on their clinical presentation.

It is recorded that patients who participated in taking the hydroxychloroquine responded well to the treatment and showed a reduced time to clinical recovery as well as the promotion of the absorption of pneumonia [16]. The potential shortcomings of this study may arise from the fact that children were not included, low sample size, and lack of variety of subjects from different geographical settings. A combination of Hydroxychloroquine and azithromycin was

shown to be efficacious in a preliminary clinical trial [17]. To gain chemistry-based insights, the pharmacological activity of chloroquine and hydroxychloroquine was compared. Hydroxychloroquine was known to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro. The loading dose of hydroxychloroquine sulfate was 400 mg twice daily given orally, followed by a maintenance dose of 200 mg twice daily for four days, showed a potency three times higher than 500 mg of chloroquine phosphate given twice daily for five days. However, due to weak methodology, these studies have been biased and not so robust [18]. On the other hand, in another randomized investigation on 30 patients in China, hydroxychloroquine showed no advantage over standard treatment and observational examination [16].

C. Favipiravir versus Arbidol

An approved antiviral drug for influenza in Japan called Favipiravir, could not efficiently be used as treatment for COVID-19 given the drug's proven efficacy as post-exposure prophylaxis for mice exposed to Ebola virus [19]. Although favipiravir was not found to significantly improve clinical recovery rate for patients in a randomized clinical trial, the drug was shown to reduce the incidence of fever, cough, except for some antiviral-associated adverse effects [3]. On the other hand, arbidol, another anti-influenza drug that targets the viral hemagglutinin (HA), also reported to inhibit a wide array of viruses by interfering with multiple steps of the virus replication cycle, has been used in clinical trial against SARS-CoV-2. This drug which is a derivative of indole has been licensed for some years ago in Russia and China against influenza. It is suggested that arbidol interferes with SARS-CoV-2 binding to the human ACE-2, and blocks the viral-host interaction [20].

D. Lopinavir–Ritonavir

Lopinavir is an approved drug as an inhibitor of the human immunodeficiency virus (HIV) type 1 aspartate protease. The enzyme 3CLpro plays a crucial role in processing the viral RNA5 6. As Lopinavir is a protease inhibitor, it may inhibit the action of 3CLpro, thereby disrupting the process of viral replication and release from host cells [21] Lopinavir has antiviral activity against SARS-CoV-2 in vitro [20]. This drug has also been evaluated in a study comprising a total of 199 laboratory-confirmed COVID-19 patients from which 100 patients were placed in a standard-care group whereas 99 patients were given a combination of lopinavir–ritonavir. Symptomatically, gastrointestinal adverse events were more common in the lopinavir–ritonavir group, whereas more serious adverse events were common in the standard-care group. In a randomized controlled examination, there was no relationship between treatment of patients with serious COVID-19 with lopinavir–ritonavir and decrease in SARS-CoV-2 viral burden or noteworthy clinical advantage [22].

E. Nafamostat and Camostat

The SARS-CoV-2 spike protein is inserted into the viral envelope and mediates viral entry into human cells. The spike protein depends on the cellular enzyme transmembrane protease serine 2 (TMPRSS2) for activation upon cleavage. Camostat acts as an antagonist to the serine protease TMPRSS2 in vitro to block the entry of SARS-CoV-2 into the cell. While nafamostat inhibits viral cell entry with efficiency approximately 15-fold higher than that of camostat, both are known to block the entry of SARS-CoV-2 into cells. In Japan and the USA, both drugs are currently at phase II and phase II/III clinical trials, respectively. Both nafamostat and camostat are approved for use against human pancreatitis [13].

F. Ivermectin

Ivermectin is a lipophilic macrolide used as a broad-spectrum anti-parasitic drug with an established safety profile for human use [23]. Ivermectin binds glutamate-gated chloride ion channels in parasites, leading to paralysis or death of the parasite. Studies revealed a potential role for IMPα/β1 during infection in signal-dependent nucleocytoplasmic shutting of the severe acute respiratory disease (SARS-CoV) Nucleocapsid protein [24]. Thus, ivermectin's nuclear transport inhibitory activity may be effective against SARS-CoV-2, being closely related SARS-CoV. Ivermectin inhibits the replication of SARS-CoV-2 in vitro [3].

V. PROSPECTS FOR COVID-19 THERAPEUTICS AND CONCLUDING REMARKS

Herein, an overview of the drug discovery along with its development processes was presented to familiarize the readers with the canonical routes from concept through approval of a drug, to the marketplace. The status of some drugs used to treat COVID-19 were briefly discussed. Currently, antiviral drug Veklury (remdesivir) has been approved for adults with COVID-19 and few others have been found to be efficacious and free of adverse events, the current trends of rigorous testing and exploration of every potential lead suggest a promising future for COVID-19 drug discovery. However, despite the explosion in both basic and clinical investigations, it is recommended that concerted and efficient development plans be made that could ultimately yield a fast and effective medicine for the disease through collective research. Generally, to remain in good health (COVID-19 free) we must keep following the health protocols.

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