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Jeevan Ranjan Dash
Department of Pharmacology and Toxicology, CVSc and AH, OUAT, Bhubaneswar, India

Repurposed Drugs and Covid-19 Pandemic-What and Why?

Jeevan Ranjan Dash

ABSTRACT

New remedies for COVID-19 are the demand of time as we live in a phase beyond containment in this current pandemic. Its impractical to think of a quick relief immediately as drug development from a scratch is not an easy and quick process. Repurposing of drugs might be a method where drugs already tested safe to humans will be redeployed to curb a disease. Use of repurposed drugs alone may not be able to produce a clear and advantageous clinical result where a carefully combined cocktails could be a good alternative, as seen in treatment of HIV in the 1990s. But the most important question now is now, which combination? This article gives a detailed review on repurposed drugs under clinical trial for COVID-19 to find out a suitable cocktail.

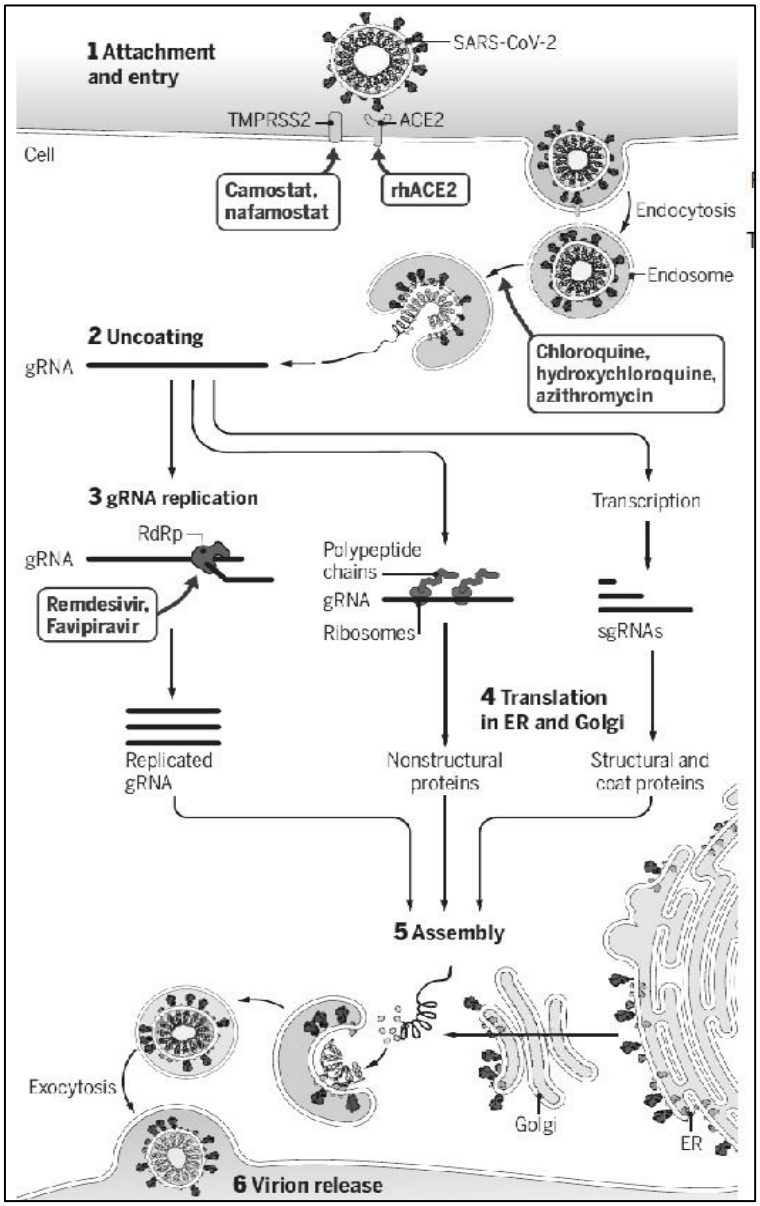
Keywords: Antiviral, COVID-19, Drug repurposing, SARS.

INTRODUCTION

COVID-19 disease is due to a group of viruses called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). In December 2019 it was first reported in Wuhan city, Hubei, China and has resulted in an ongoing pandemic [1]. COVID-19 spreads mainly by coughing or sneezing or talking or singing when infected people come in close contact and one inhales small droplets spread by an infected individual (may or may not be symptomatic) [2]. As per WHO recommendation a minimum social distance of 1 metre (3 ft) is required to prevent it's spread. Centre for Disease Control and Prevention, USA recommends a minimum of 2 metres (6 ft) distance. As reported by some researchers this virus can survive in aerosol up to 3 hours [3]. So far, no medication is approved yet treat this disease [4] which has created a havoc throughout the world though some vaccines are accorded. Many of the International centres and industries on vaccines and medicines in COVID 19 including government organisation is underway [5-6]. In March 2020, "Solidarity Trial" was initiated by WHO where four existing antiviral compounds having proven efficacy are accessed [7] and hydroxychloroquine suspended from assessment due to safety concerns. As of today, only some supportive therapy is practised for treatment of patients with symptoms of COVID-19. If a successful therapy would be available soon; patients would be greatly benefited. One of the many strategies to be followed is to repurpose approved drugs with proven efficacy against other diseases can be a quick solution to the problem. Again, it would be advantageous as detailed information on its pharmacology and toxicology on animal or human trials already existing which may enable fast clinical trial & regulatory approval.

Correspondence:
Dr. Jeevan Ranjan Dash
Department of Pharmacology and Toxicology, CVSc and AH, OUAT, Bhubaneswar, India
Email: jeevandash5@gmail.com

Cellular Pathway of Covid-19



Source: Guy *et al*., 2020 [8]

Figure 1: depicts different steps in the lifecycle of Coronavirus.

Entry into host cell by ACE2 and TMPRSS2 receptor

⇩

RNA replication and Transcription

⇩

Translation and Viral proteins protelysis

⇩

Virion assembly

⇩

Exocytosis and Release of new virus

Drugs In Phase III-IV of Clinical Trials for Covid 19 Infection

When a drug's trial is in Phase I & II it has a low success rate (<12%) to pass through all phases trial to get final approval [9]. If it reaches Phase III, success rate may be about 72%.

1. Remdesivir

Remdesivir is a drug which is active against SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) in animal models [10] is tested in laboratory against SARS-CoV-2 by Gilead Sciences in January 2020. Wuhan Institute of Virology applied for a Chinese patent on 21st January 2020 for treatment of COVID-19[11]. As recorded in Johns Hopkins ABX Guide, 2020 Remdesivir is considered to be the drug of choice in management of COVID-19. It is one of the four treatments under study in the international Solidarity trial [7]. US FDA mentioned, on 1st May 2020, that potential benefits of Remdesivir outweigh its potential risks in some specific

populations hospitalized with severe COVID-19 symptoms and it is reasonable [12]. As per the 'rolling review' of data on the use of Remdesivir in COVID-19 by European Medicines Agency (EMA, 2020) [13], GS-443902 is an active metabolite of Remdesivir that inhibit RNA-dependent RNA polymerase of virus and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production [14].

2. Favipiravir

It is used to treat influenza in Japan [15]. China started trial on Favipiravir against COVID-19 in 2020 February [16]. In China Favipiravir has been approved to be used in clinical trials of COVID-19[17]. Trials supposed to be approved in Japan [18]. China approved its selling in a hurry in February 2020. One of the most affected European country Italy approved experimental trial of flavipiravir against COVID-19 in March 2020 in three of its most affected regions though Italian Pharmaceutical Agency warned general public that the results in support of this drug is just preliminary. This particular drug is under multicentric clinical trials throughout the world including USA and London suggests its high efficacy in COVID-19 cases with few adverse effects. This drug produce its effect due to selective inhibition of viral RNA-dependent RNA polymerase [19] and its nontoxic to human as it does not inhibit RNA or DNA synthesis in mammalian cells [20].

3. Lopinavir/ritonavir (LPV/r)

lopinavir/ritonavir is one of the most sited combination for HIV first-line treatment approved by the US Department of Health and Human Services [21]. Lopinavir inhibit viral replication due to inhibition of enzyme protease. Ritonavir mostly boosts the action of lopinavir [22]. This combination of drugs is mostly safe, although hepatotoxicity is seen in some cases [23]. However, its effectiveness against COVID-19 is yet to be seen after its clinical trial.

4.rhACE2

rhACE2, or APN01 is a recombinant human ACE2 is under clinical trial against COVID-19. It prevents entry of the virus into the human cell–derived organoids [24]. It's phase-I trial on patients of acute lung injury and pulmonary arterial hypertension was very successful.

5. Camostat

Camostat and nafamostat [25] are two drugs which inhibit SARSCoV-2 replication in TMPRSS2-expressing human cells. Camostat acts by inhibition of TMPRSS2 [26]. Camostat is approved in japan for treatment of chronic pancreatitis and postoperative gastric reflux disorders though few serious adverse effects are recorded but its rare. Camostat successfully prevented SARS-CoV-2 infection in mouse model and its clinical trial is already started in Netherlands and Germany.

6. Chloroquine/hydroxychloroquine

Chloroquine, a proven immunomodulator prevent SARS-CoV-2 infection at entry and post-entry stages [25]. Antimalarial drug hydroxychloroquine also has promising result in-vitro (NIH Clinical Trials, 2020) [27].

7. Monoclonal antibodies

Trial on human antibodies that prevent the IL-6 (Interleukin -6) against COVID-19 virus was announced in March 2020 by The Feinstein Institute of Northwell Health. Since march 2020 China already approved the use of a humanoid antibody tocilizumab in cases with the coronavirus SARS-CoV-2 (www.reuters.com, 2020) [28]. Tocilizumab is an immunosuppressant mainly used in patients of atrophic arthritis (RA) and systemic juvenile idiopathic arthritis. A report published in 2020 by an Italian physician Paolo Ascierto suggested effectiveness of tocilizumab in three severe cases of COVID-19 in Italy (ANSA.it, 2020) [29]. Italian Pharmacological Agency (AIFA) expanded it's testing in five more hospitals (www.ilmessaggero.it, 2020) [30]. Sarilumab, another human monoclonal antibody used in rheumatoid arthritis (RA) is also under trial. It also acts by inhibition of IL-6 receptor.

CONCLUSION

World supposed to live with COVID-19 for a long period and several peaks likely to occur before herd immunity develops. In this emergent situation it's very difficult to rely on the results of rapid hypothesis generating studies and needs larger trials in later peaks to provide adequate information for approval of a cocktail of medicines for COVID-19. Since a long time, world wide spread of this pandemic created a havoc in many countries including the developed world too. Though many countries developed vaccines against the virus but this virus is fast mutating. It is the need of the hour for all involved in drug discovery to figure out a quicker and well justified medicines for registration-enabling trials.

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Conflict of Interest

No conflict of interest.

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