

## DRUG REPOSITIONING IN THE TREATMENT OF COVID-19

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### ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2, also known as 2019-NCOV), occurred as a worldwide with high death and disease rates. However, at present there are no specific drugs for the cure of 2019-ncov/SARS-cov-2. Clinicians are left with general supportive care and often available treatment options. Drug repositioning commonly called as drug repurposing and it is otherwise called as drug re-profiling. It is the practice of renewing a drug for use in another disease. An antiviral medication used to treat and prevent the viral diseases (including HIV), and antimalarial drugs are found to show activity against the SARS-cov-2. We aimed to review the evidence supporting the repurposed drugs in the cure of coronaviruses and to discuss their potential in SARS-CoV-2.

### INTRODUCTION

In November 2019 an unexplained disease outbreak was observed in the Chinese city Wuhan. The reason for the disease is found to be novel coronal virus, hence the disease now termed as NCOVID-19. It is quick in spreading to different nations, which threatens many lives. In the 21<sup>th</sup> century, the major cause of disaster is 2019-novel coronavirus (ncov).<sup>[1]</sup>

Coronaviruses were recognized in the mid-1960s and are identified to infect human beings and a variety of animals (including birds and mammals). Since 2002, two coronaviruses effecting animals have developed and caused

diseases in humans: Severe Acute Respiratory Syndrome (SARS-cov) recognized in southern China in 2003, and in 2012 Middle East Respiratory Syndrome (MERS-cov), discovered in Saudi Arabia. Collectively, they lead to greater than 1600 deaths.<sup>[2]</sup>

Another pathogenic human coronavirus, that is NCOVID-19 (or SARS-cov-2), as the cause of coronavirus infection in 2019 which is was found in Wuhan, China. These virus is also belongs to the family that caused two other outbreaks before in 2003 and 2012. However the new coronavirus may be immense virulent. In

mid-April, the number of total confirmed cases of COVID-19, had exceeded 25, 00,000, and the sum total count of deaths due to nCOV-2 is established to be more than 1,74,000. [3]

The cases of covid-19 confirmed is greater than combined total cases of SARS and MERS, this proves that how fast it was spreading and dangerous: 'he infection mainly transmitted from Coronaviruses (covs) infected persons to other people. It mainly attack on the respiratory tract of mammals, including humans, and which leads to mild to severe respiratory tract infections.

Some studies shows that the males are more vulnerable to this disease than the females, the reason behind this may be due to the high proportions of smoking habits in men than women. In one research study reveals that the genetic difference in female may also because of lower amount of cases [4]

The symptoms of the syndrome are flu like infection, fever greater than 101°F, acute onset of continuous cough (with or without sputum), hoarseness, nasal excretion or blocking, shortness of breath, sore throat, wheezing, sneezing. Diagnostic data supporting of pneumonia, acute respiratory distress syndrome and the viral test which confirms the presence of coronavirus Sudden Outbreaks of emerged infections present healthcare professionals with the unique challenge in the choice of proper treatments within the less time available for drug analysis and development.

However, there are no powerful medicines against 2019-ncov now. To control the infection there is a vital requirement for the development of effective prevention and therapeutic approaches for 2019-ncov outburst. The yearly amount of new medicines approved by the U.S. FDA has continued to be unvarying and limited. a study recently evaluated that drug agencies consumed ₹300 crore in 2015, up from ₹75 crores in 2003, in the establishment of an FDA-licensed chemical new drug entity [3]

In the absence of any known efficient therapy and because of the situation of a “public-health emergency”, many drugs have been tried

recently in the treatment for COVID-19 for the remission of this pandemic clinicians look after the repurposing of some drugs which are having anti-viral activity. Concept of Repurposing of the drugs was not new. It is the reuse of a drug which is used to cure one disease for another treatment.

Naturally, for the Given development times and manufacturing necessities for fresh products, re-profiling of current drugs is likely the only way out for pandemics due to evolving viruses.it could significantly reduce the time and moderate the charge contrast to a new remedy finding and randomized clinical trials As there is no distinct antiviral therapy that is endorsed for COVID-19. As of now effected persons should receive supportive care to aid in relieve of symptoms. For the purpose of viral shredding the antiviral drugs are recommended which are already marketed for the other purpose. Hence, this repurposing of drugs are essential for both the stoppage of further transmission of disease and as a preventive treatment.

Pre-exposure prophylaxis and after exposure protection (PEP) with antibacterial medications are beneficial in reducing sickness prior to possible exposure or afterwards exposure to a heterogeneity of microorganisms that are pathogenic, and lessen the danger of peripheral spread of infection.it is recommend that to start after exposure medication as immediately as possible after a possible exposure to SARS-CoV-2 [5].

#### ANTI-MALARIAL DRUGS

Chloroquine and hydroxylchloroquine (HCQ) belong to these class. The structure and mechanism of action of these drugs are exactly same except an additional hydroxy moiety in one terminal in HCQ. Both are weak bases hence they can change the ph of acidic intracellular organelles containing endosomes/lysosomes, crucial for the membrane fusion [6].

The mechanism of action of these drugs on COVID19 IS Not clearly known, but they changes the ph of endosomes and believed to

prevent viral entry, transport and post-entry events Inhibits infection of cells by SARS-cov-2 *in vitro*, It is been on the opinion that both the agents could be productive tools against SARS-cov-1 and SARS-cov-2 <sup>[7,8]</sup>

### HYDROXYCHLOROQUINE

The hydroxylchloroquine, is an antimalarial drug and also used as ant rheumatic drug, for the prevention and therapeutic purpose of disease. It has wide range of safe therapeutic concentration with different available tolerable doses. Remarkably, the HCQ displays antiviral action against coronaviruses *in vitro*, and in particular, SARS-cov-2. It is used as Prophylaxis at approved doses which helps in preventing SARS-cov-2 disease and improve viral shedding. Therefore it was also approved by the FDA to be tested as a remedy for COVID-19.

Hydroxylchloroquine is available as an oral tablet of 200 mg. It must be monitored as it Worsens skin ailments such as psoriasis or porphyria. This drug also causes heart disease, vision problems that can be permanent when used in high doses but lesser risk of eye toxicity with HCQ, as compared to Chloroquine. The antibiotic azithromycin, sometimes used in union with hydroxylchloroquine to stop the coronavirus.

### CHLOROQUINE

Chloroquine role in the treatment of patients with novel COVID-19 has been increasing to more for the reason that the drug had anti-viral and anti-inflammatory activities. Chloroquine increases endosome ph and interferes with the glycosylation of cellular receptor of SARS-cov and thereby it has the potential to block viral infection. Therefore viral replication is reduced with highly effective by this drug to which can be effortlessly achievable with standard dosing due to its advantageous diffusion in tissues including the lung <sup>[5]</sup>. Chloroquine drug at amount of 500 mg twice per day for 10 days for patients identified as cases of SARS-CoV-2 pneumonia without any contraindication <sup>[9]</sup>. it is also recommended the usage of chloroquine in people having severe COVID-19 infection admitted in the ICU.<sup>[10]</sup> There are some other

capable drugs for treating 2019-nCoV infection like selamectin & mefloquine hydrochloride.<sup>[11]</sup>

### ANTIVIRAL DRUGS

Antiviral agents administered swiftly after symptom onset can lessen infectiousness to others by decreasing viral shedding in the respiratory secretions of patients and aim at prophylactic treatment of contacts could ease their risk of developing into infected.<sup>[7]</sup> . The 90% of Effective Concentration value of chloroquine contra verse the 2019-nCoV in Vero E6 cells was 6.90  $\mu$ M, which can be clinically possible as revealed in the plasma of rheumatoid arthritis patients who received the dose of 500 mg administration.

### REMDESIVIR.

Remdesivir has been newly established as a capable antiviral drug contraverses a wide range of RNA viruses (together with SARS/MERS-CoV5) infection in artificially cultured cells. It was clinical developed for the remedy of Ebola virus infection which is currently under study. It is an adenosine analogue, which integrates into growing viral RNA chains and end results in pre-mature termination. Data revealed that EC<sub>90</sub> value of remdesivir against 2019-nCoV in Vero E6 cells was 1.76  $\mu$ M, proposing its working concentration is plausible to be achieved in Non-Human Primates models.

### LOPINAVIR / RITONAVIR

Another antiviral-drug candidate is a amalgamation of the HIV protease inhibitors that are lopinavir and ritonavir. Lopinavir, which works against the viral protease has moderate antiviral activity against SARS-CoV-2. In sync with ritonavir, which boosts drug bioavailability, consequently Obstructs viral cellular entry. <sup>[12]</sup> It is Effective against SARS-cov-1 both *in vitro* and human studies, but there was a conflict regarding the effectiveness of lopinavir/ritonavir in covid 19 patients inspite of its use it could cause significant liver damage. It is recommend using lopinavir 400mg/Ritonavir 100 mg BID or Chloroquine 500 mg orally per day or Hydroxylchloroquine 400 mg orally per day for 7–10 days, in moderate to severe case of COVID-19.<sup>[13]</sup> These

drugs along with the immunomodulator interferon beta-1b is more useful in early stage of disease.

### **RIBAVIRIN**

Ribavirin belongs to a guanosine analog that inhibits the replication of RNA and DNA viruses and mRNA capping. The ribavirin is widespread available at low budget with potential to significant influence in the management of nCoV infections.<sup>[14]</sup> this compound is extensively used in early stages to manage SARS-COV2 infection, inhibited CPE completely at 500–5,000 µg/ml at virus loads of 100–10,000 PFU per well. The concentration range observed is much greater than concentrations that inhibit other viruses in calculation, the CPE inhibitory concentrations achieved were exceeding the cytotoxic concentration range against Vero cells in one study analysis.<sup>[15]</sup> It is probable that ribavirin would be further efficient in combination with interferon.

### **FAVILAVIR**

The NMPA of China has accepted the utilization of Favilavir, an anti-viral drug, for the management of coronavirus. The treatment has apparently shown efficiency in curing the disease with little amount of side effects in a clinical evaluation involving 70 ill persons. This scientific experiment is being done in Shenzhen, Guangdong province.

### **OSELTAMIVIR**

Oseltamivir has been suggested by World Health Organization for people at elevated risk of infection before or after exposure to pandemic influenza. the proposed dose for the oseltamivir is 150mg BID for 5 days given per oral.<sup>[16]</sup>

### **Other antiviral drugs**

atazanavir seems to be effective in the management of COVID-19 by exhibiting overall high binding affinities amongst analysed antivirals for six proteins of SARS-CoV-2<sup>[17]</sup> HIV protease inhibitor (darunavir and the promoting agent cobicistat), viral RNA synthesis inhibitor (remdesivir, favipiravir, emtricitabine/

tenofovir alafenamide or ribavirin) are also under evaluation

### **INTERFERONS**

In SARS-cov infection, use of interferon is a suitable starting point the activity against coronavirus of interferon is by directly acting on infected cells or by controlling an immune response. Interferon cooperate with specific surface cell receptors, directing to production of interferon- accelerated gene products. SARS-CoV-2 is possibly more sensitive to interferon than the other coronaviruses. At early stages of the infection Interferon treatment should be performed to enhance antiviral therapy and elude adverse events. Investigation on interferon-based COVID-19 treatment is warranted. IFN-I might be a safe and efficient treatment against SARS-CoV-2.<sup>[18]</sup>

#### **Interferon β1**

The IFNβ subtype seems to be the most suitable for COVID-19 treatment. IFNβ is an extra potent inhibitor of coronaviruses than IFNα. A combination of IFNβ with lopinavir/ritonavir against MERS-CoV enhanced respiratory function however did not considerably decrease virus replication or pulmonary pathology severity. The protective activity of IFNβ1 in the lung, Reveals that the IFNβ1 to be most relevant interferon to treat coronavirus infections. Blood Plasma levels of interferon's given through the subcutaneous route are generally little with correspondingly short half-lives.<sup>[18]</sup>

#### **Interferon α**

The recommendations for the therapeutic affect against COVID-19 suggest to administer 5 million U of IFNα by vapour inhalation twice a day to the patients, in combination with ribavirin. Combination of IFNα with ribavirin suspended mortality without diminishing it on the long course Conventional clinical doses for interferon α range from 3 to 5 million IU three times a week to 5 million IU daily. It has also been proposed that interferon was efficient in patients only if they lacked comorbidities.<sup>[18]</sup>

#### **TOCILIZUMAB**

Actemra, (the brand name of tocilizumab) used to treat inflammation in arthritis patients it is

now approved by FDA to treat coronavirus. Tocilizumab inhibits the Interleukin 6 (IL-6) which drive some diseases including COVID-19. Yet, no experimental study has demonstrated the influences of Tocilizumab on COVID-19 and more studies are certainly required on drug safety and efficacy on corona virus.<sup>[19]</sup>

### **IVERMECTIN**

Another drug which is approved by FDA acts against parasites, that is Ivermectin. This drug manifest broad range of anti-viral activity in vitro, it also has the ability to inhibit the nCoV-2 in vitro. Its nuclear transport inhibitory activity against SARS-CoV-2 works excellently, as a result has a capacity for repurposing. Ivermectin is extensively available drug, by reason of its addition on the World Health Organization record of essential medications. It has a recognized safety profile for human beings to use A single usage able to influence ~5000-fold drop in virus at 48h in cell culture. A 99.8% fall in cell-linked viral RNA (suggestive of unreleased and unpackaged virions) was detected with Ivermectin treatment.<sup>[20]</sup>

### **Other classes of drugs**

Certain immunosuppressant drugs (rapamycin and everolimus) and a drug (tiotropium bromide) for asthma and chronic obstructive pulmonary disease (COPD) were identified as effective for SARS-CoV-2.

The application of these drugs for treatment and prophylaxis has several prerequisites. The supply of drugs must be adequate, the safety of treatment must be very important, and costs should preferably be low. Some research federations are functioning on the development of vaccines to prevent and treat the 2019-ncov/SARS-cov-2, yet vaccine for SARS-CoV-2 is currently not discovered. Prevention is the best method of restriction

### **CONCLUSION**

COVID-19 is a pandemic which is triggered by corona virus. It mainly effects the respiratory system as of now there is no specific treatment for the disease. To cure the infection in this limited period of time, the repurposing of available drugs is best possible way. In this we

concluded some of the drugs which can effectively work in the cure of COVID-19.

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### **CONFLICT OF INTEREST**

No conflict of interest

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