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Drug repurposing in COVID-19: A review with past, present and future

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ABSTRACT

The coronavirus SARS-CoV-2 which causes the COVID-19 disease is a global public health emergency. Coronavirus are single-stranded positive-sense RNA viruses and their genome size is approximately 30 kb, which encodes some important structural proteins. The interaction between viral Spike protein and ACE2 on the host cell surface is of significant interest since it initiates the infection process. This review will focus on the effectiveness of reuse of currently used drugs against COVID-19, including clinical trials, molecular docking, and computational modelling approach.

Methods: A systematic search in Pubmed, MEDLINE, EMBASE was conducted from from January 2020 to July 2021.

Applying computational, clinical and experimental approaches, numerous drugs such as remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, tocilizumab have been repurposed and have shown promising protection against SARS-CoV2 both in vitro and in clinical conditions. Although there is only one repurposed drug approved by the U.S. Food and Drug Administration (FDA) to treat coronavirus disease 2019 (COVID-19), i.e, Remdesivir. However, the FDA withdrew the authorization of the drugs Hydroxychloroquine and chloroquine,that are not effective for COVID-19 and can also cause serious heart problems. Molecular coupling would be the ideal technique to identify such therapeutic agents against COVID19.

1. Introduction

The COVID-19 pandemic situation is constantly evolving worldwide. Globally, as of July 14, 2021, there have been 187,519,798 confirmed cases of COVID-19, including 4,049,372 deaths, reported to WHO [1]. Severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002–03, Middle Eastern respiratory syndrome coronavirus (MERS-CoV) in 2012 and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in 2019–20 are large, (genus beta-coronavirus; subgenus sarbecoronavirus) 27–32 kb RNA with typical corona-shaped glycoprotein peaks (peplomers) [2]. Very high recombination rates lead to constant transcription errors and RNA-dependent RNA polymerase (RDRP) jumps in coronaviruses [3] give them the opportunity to become various zoonotic pathogens such as SARSCoV2. The overall genome sequence of SARS-CoV2 showed a 79.5% similarity to SARS-CoV and, interestingly, 96.2% similarity to the bat coronavirus RaTG13. The mechanisms of SARS-CoV2 infection are not yet clear, however it is genetically similar to SARS-CoV and other coronaviruses [2,3].

Outbreaks of COVID-19, pose challenges for therapeutic/drug treatments in the clinical setting with very little time available for novel drug discovery. Furthermore, development of a vaccine for any disease, including COVID-19, is time taking process and in accelerated mode also it would take 18–20 months to introduce it as a ready-to-use product. Therefore, there is a need for an utmost search for effective therapeutic agents to treat COVID-19 [2]. Drug reuse, is also known as drug repurposing, defined as the search for new indications for existing drugs. It is believed that 75% of known drugs could be repurposed for various diseases. The advantage of drug repurposing is that we have a range of pre-clinical (pharmacological, toxicological, etc), and clinical efficacy and safety data already available, as the candidate drug has already undergone through the prior drug development.

2. Methodology

The investigator reviewed the various. Literature search was performed in WHO reports, PubMed, Scopus, Science Direct, Nature, JAMA, BMJ and THE LANCET journals using following terms: repurposing of drugs, repurposing of drugs in COVID, COVID-19 and Dug and vaccines in coronaviruses to find articles published from January 2020 to June 2021. Some of the information pertaining to India is taken from the

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Ministry of Health, Government of India. No language limits or study design filters were applied. Drugs not related with coronaviruses, directly or indirectly, were excluded from the studies.

3. Discussions

In cases such as the current global pandemic, where the medical scenario is unexpected and the need for treatment is high, drug repurposing presents a convenient alternative in the search for effective therapeutic agents. As the approach uses compounds with known biochemical and physiologic effects, clinical testing can begin with Phase III or IV studies, potentially offering cost and time savings. In comparison to novel drug development, drug repurposing could be an economical medical treatments for COVID-19.

3.1. Reused drugs that act through RNA genome

SARS-CoV2 replication is directly dependent on the enzyme RNA-dependent RNA polymerase (RDRP). Interestingly, the potential protease and polymerase targets for SARS-CoV2 and SARS CoV are highly conserved with an overall identity of 96% and 97%. Hence, these blockers developed against SARS can act as good therapeutic candidates for binding protease or polymerase sites against SARS-CoV2 [4].

3.2. RNA mutagens: remdesivir, favipiravir and ribavirin

3.2.1. Remdesivir

Use of remdesivir in SARS-CoV2 infection, is considered to be a possible candidate drug for reuse against COVID-19. Remdesivir is a nucleotide analog (adenosine), which is fused with the replicating genome of the virus and forms its triphosphate form which further compete with adenosine triphosphate (ATP) to act as a substrate for RDRP. Remdesivir adds three more nucleotides before terminating the growing RNA strand. The three additional nucleotides can protect the 3′-5 ′ viral exonuclease clearance inhibitor activity [5]. Ineffective against Ebola, Remdesivir has shown its efficacy against SARS-CoV2 in preclinical as well as clinical cases [6]. Several clinical trials have been conducted to test efficacy of remdesivir in COVID-19. However, the results were conflicting. A study treated a cohort of 53 patients with severe COVID-19 with compassionate use of remdesivir for 10 days, 200 mg intravenously on day 1 and 100 mg for the next 9 day. The results show that after the first dose of remdesivir, 68% of patients showed clinical improvements in oxygen support [7]. Another study in Italy administered remdesivir for compassionate use to 10 days to a cohort of 35 severe COVID -19 patients in both the ICU and infectious disease ward, and the results indicate that remdesivir benefits patients outside the ICU [8]. The FDA has approved remdesivir (Veklury) to treat COVID-19 in adults and children who are age 12 and older. Remdesivir may be prescribed for people who are hospitalized with COVID-19. It's given through a needle in the skin (intravenously).

3.2.2. Favipiravir

Favipiravir has similar mechanism of incorporation of ATP and GTP into RdRp, however it is not as effective as remdesivir [9]. In an open-label, non-randomized controlled study, the effects of favipiravir and ritonavir-lopinavir on Treatment with SARS-CoV-2 was compared. The favipiravir group showed a significantly shorter virus spread time, better chest images and fewer adverse reactions [10].

3.2.3. Ribavirin

Ribavirin used for the treatment of hepatitis C. The mechanism of ribavirin is similar to that of favipiravir [9]. A phase 2, randomized, open-label study evaluated the Efficacy of a combination of IFN-β-1b, lopinavir/ritonavir and ribavirin in the treatment of SARS-CoV-2 infected patients. The study demonstrated that triple therapy was superior to using lopinavir/ritonavir alone in the treatment of patients with mild or moderate SARS-CoV-2 infection [11].

3.3. Repurposed drugs that work through protease inhibitors

Protease Inhibitors used in HIV-1 therapy have been shown to be effective in SARS-CoV. In-silico and in-vitro approaches were used to validate the inhibition of SARS-CoV2 protease from HIV-1 protease inhibitors [12]. Examples are saquinavir, amprenavir, indinavir, nelfnavir, ritonavir and lopinavir, few of them are being repurposed against SARS-CoV2.

Since CoV replication and gene expression processes require the proteolytic processing of polypeptides into non-structural proteins, it is suggested to use protease inhibitors to block these processes. Examples of this category are darunavir and ritonavir - lopinavir. Ritonavir - lopinavir combination is used as AIDS drug that inhibits the HIV protease. A retrospective study including 120 patients shows that early administration of ritonavir - lopinavir could reduce the time to onset of the virus detachment in SARS-COV-2 [13]. A controlled study involving 47 patients with COVID-19 infection indicated that a combination of ritonavir - lopinavir and adjuvant drugs significantly reduced the number of days for clearance compared to adjuvant drugs alone [14]. In a retrospective cohort study, 50 patients were split into ritonavir lopinavir group and arbidol group and compared to the ritonavir-lopinavir group, viral clearance is faster in patients in the arbidol group [15].

Darunavir is also a protease inhibitor originally used for HIV. Worsening of respiratory function caused by SARS was reported by Riva et al. [16] in three HIV positive patients infected with SARS - CoV - 2. Darunavir is rapidly absorbed through oral administration and approximately 95% of the drug bound to plasma proteins and is metabolized exclusively by CYP3A4. Therefore, the co-administrating small doses of ritonavir (CYP3A4 inhibitor) increase the bioavailability of darunavir.

3.4. Virus entry blockers: chloroquine, hydroxychloroquine, arbidol

SARS - CoV - 2 enters the human cell by binding to receptors on the plasma membrane. Therefore, interfering with this process would block virus entry and therefore has the potential to fight virus infection. Examples of the drug in this category are arbidol and potentially chloroquine and hydroxychloroquine, angiotensin receptor blocker (ARB), statins.

Chloroquine has been used as an antimalarial drug for many years. The antiviral mechanism of chloroquin is not entirely clear. There are studies that suggest that it interrupts the binding of the virus to the receptor by interfering with the human cell membrane receptor angiotensin converting enzyme 2 (ACE2) [17]. Gao et al. [18] reported that clinical trials have shown that chloroquine worked better than control treatment to improve clinical outcomes for COVID-19 infected patients. However, the study did not give any details of clinical trials. A controlled study in a cohort of 22 patients showed that compared to ritonavir--treatment with lopinavir, chloroquine phosphate significantly reduced the duration of the disease [19]. However, large scale studies are still needed to determine the efficacy of chloroquine.

Hydroxychloroquine is the hydroxylated form of chloroquine and therefore they share similar antiviral mechanisms. Some studies have found hydroxychloroquine to be effective for mild treatment with COVID-19 [20]. In a study with a cohort of 80 mildly infected patients showed that combination therapy with hydroxychloroquine and azithromycin can improve the situation of the infected patients [21]. However, another study claimed it did not see clinical improvement when the same drugs and doses were used to treat 11 severely COVID -19 infected patients [22]. Another recent observational study of 181 SARS - CoV - 2 patients who need oxygen, but not intensive care, does not support the efficacy of hydroxychloroquine [23]. The FDA recently raised the issue of safety concerns caused by chloroquine and hydroxychloroquine, including severe heart rhythm problems, blood and

lymphatic system disorders, kidney damage and liver problems, and has warned against the use of these drugs outside the hospital setting.

Arbidol, is a powerful broad-spectrum antiviral agent against a broad range of enclosed and non-enveloped viruses. Arbidol and arbidol mesylate have been reported to act directly on viral replication of SARS-CoV at an early stage in vitro [24]. Arbidol's antiviral mechanism against influenza A and B involves inhibition of viral fusion by hindering the hemagglutinin membrane fusion mechanism, thus blocking the entry of the virus into the cell [25]. Treating COVID-19 patients with arbidol leads to a reduction in mortality rate and an increase in recovery rate [26].

Statins, lipid-lowering drugs, have shown immunomodulatory properties to prevent acute lung injury in various experimental and clinical conditions, therefore, it can be used as a repurposed drug for COVID-19. The spike proteins of the virus adhere to the cell surface of ACE2 expressed in the epithelial cells of the oral mucosa, lungs, intestines, blood vessels and kidneys. ACE2 activity has been shown to be upregulated with the use of atorvastatin [27]. Statins, which are immunomodulators, have been hypothesized to act against MERS coronaviruses [28].

3.5. Cytokine storm inhibition

Cytokine storm is a crucial factor leading to acute respiratory distress syndrome and multi-organ failure which would suddenly aggravate the disease and eventually lead to death. Therefore, cytokine storm inhibition is an important step in the treatment of COVID-19. Drugs in this category include interleukin 6 (IL-6) inhibitors (tocilizumab) and CD24Fc [29]. Tocilizumab, a drug used against rheumatoid arthritis and cytokine release syndrome/systemic inflammatory response syndrome [30]. The condition of some COVID patients get worsen because of an overreaction of the body's immune response (a cytokine storm) to the viral infection. When this happens, the body overproduces interleukin-6 (IL-6), a protein involved in inflammation in lung cells. Tocilizumab blocks the action of IL-6, and thereby dampens the exaggerated immune system response. Observational studies in patients with severe or critical COVID-19 infection showed that the use of tocilizumab immediately improved clinical outcomes. Repeated treatment and dosing is recommended for patients with elevated levels of IL-6 [31]. However, two cases have been reported with adverse effects and the clinician's justification is required when using tocilizumab [32]. The FDA has granted emergency use authorization (EUA) for tocilizumab (Actemra) for the treatment of hospitalized adults and children ages 2 years and older who are receiving systemic corticosteroids such as dexamethasone, and who require supplemental oxygen, mechanical ventilation, or a heart-lung bypass machine.

Dexamethasone is the first-line treatment for immune-related complications. The metabolic side effects of dexamethasone include a slight increase in blood glucose level, ocular hypertension and cataracts, neuropsychological side effects such as changes in mood and behavior, and osteoporosis [33] mainly associated with long-term high doses. WHO has added dexamethasone to COVID 19 treatment guidelines [34].

3.6. Other potential agents for the treatment of COVID-19

Nitazoxanide is a broad-spectrum anthelmintic and antiviral prodrug that is metabolized to an active compound tizoxanide. It had shown inhibitory potential against low concentration SARS-CoV2 in Vero E6 cells [35].

Ivermectin, a broad-spectrum anti-parasitic agent has also been shown to be effective against some viral infections. Recently, this drug was studied against SARS-CoV2. In March 2021, the FDA issued a statement that ivermectin should not be used to treat or prevent COVID-19. There are risks associated with using ivermectin, even for approved uses. For example, ivermectin can interact with other medications, such as blood thinners, and increase the risk of bleeding. The NIH currently does not have enough data to recommend for or against using ivermectin for COVID-19 [36].

3.7. In silico approach

A Fluoroquinolone antibiotic, Prulifloxacin and Tegobuvir, (a new non-nucleoside RNA replication inhibitor of the human coronavirus), Nelfinavir (a protease inhibitor that inhibits the cleavage of gag-pol polyprotein) and Bictegravir (HIV-1 integrase inhibitor) have binding sites to protease proteins which has been demonstrated well with bio-informatics analysis. These would be considered as potential candidates for repurposing against COVID-19 in the future [37,38].

Elbasvir, drug for the treatment of hepatitis C showed multiple binding sites on RDRP, papain-like proteinase and helicase of SARS-CoV2 using coupling simulations and computational models [39]. Recently it is suggested that IL-6 production can be potential reassignment agents against COVID-19 in the future with sufficient evidence from in vitro and in vivo studies [40].

3.7.1. Protein structure-based drug design

Significant efforts have been put into the computational works for prioritizing previous FDA-approved drugs for repurposing to treat COVID-19. These studies are mainly based on the choice of protein targets, anchor sites on protein targets, drug/molecule databases and virtual detection algorithms. SARS - CoV - 2 major proteases of type 3C (3CLpro or Mpro), as the first SARS - CoV - 2 protein whose crystal structure becomes the target of most molecular docking drug screening studies [41]. Molecular dynamic simulation were used by binding free energy calculations to validate higher coupling molecules and other targets include RdRp, spike protein (S) and human-human protein interface ACE2 spike (S) [42].

Furthermore, several studies have investigated relatively new targets, such as the cellular transmembrane protease serine 2 (TMPRSS2) and SARS -Envelope Protein (E) of CoV-2. Shi et al. [43] developed a novel molecular coupling-based web server that facilitates drug detection based on protein structure. Since the structure of RdRp has recently been established, we anticipate that more inhibitors for this target protein could be proposed.

Docking simulation for antibody processing: Park et al. [44] proposed that the human antibody CR3022 may have a high affinity for the SARS-CoV-2 spike protein and, therefore, may be a potential treatment for COVID-19. Multiple In Silico Studies Have Been Performed to Design Multi-epitope Vaccines against SARS - CoV - 2[45]. There are various databases and computational tools available for drug repurposing which include e-Drug3D, Drug Predict, Drug Bank, Promiscuous, Mantra2.0, PharmDB, DRAR-CPI, repoDB, Repurpose DB, DeSigN, Cmap, DPDR-CPI etc [46].

3.7.2. Drug repurposing for COVID-19 in indian perspectives

Unavailability of complete data regarding dose and duration of therapy, safety, efficacy, and adverse reactions of drugs restricts the clinical recommendation for COVID-19. Remdesivir and favipiravir have emerged as promising treatment but more clinical evidence is required for use in Indian populations. In India, favipiravir (FabiFlu-Glenmark, Favivir-Hetero Drugs Ltd)., and Remdesivir (JUBI-R- Jubilant Life-Sciences, Covifor-Hetero, Redyx- Dr. Reddy's Laboratories Ltd., etc.) have received marketing authorization from DCGI [47]. Scientists are also concerned that the emergency authorizations are influencing other countries' decisions. One of the drugs approved for COVID-19 in India is itolizumab, which is used to treat the autoimmune condition psoriasis. This has now been approved for emergency use in Cuba, partly on the basis of Indian data and approval, according to Cuban media. DCGI has approved itolizumab for treating moderate to severe acute respiratory distress in people with COVID-19 [48].

4. Conclusions

We have carried out a comprehensive and systematic search of the literature. It is worth noting that there are no drugs that have passed clinical trials and have been approved by the FDA for COVID-19 till date. Lack of conclusive results from randomized clinical trials indicates absence of appropriate treatment of COVID-19. Previously developed or used as treatments for severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), HIV/AIDS, and malaria, have been researched as potential COVID-19 treatments, with some moving into clinical trials. Applying computational, clinical and experimental approaches, numerous drugs such as remdesivir, favipiravir, ribavirin, lopinavir, ritonavir, tocilizumab have been repurposed and have shown promising protection against SARS-CoV2 both in vitro and in clinical conditions. The spike protein needs be investigated as a target for the SARS-CoV-2. Some drugs are in the early stage of research such as Ivermectin for use against COVID-19. Molecular coupling would be the central technique to identify likely therapeutic agents against COVID19 patients. In future, these drugs could be the potential drug therapy against this deadly disease.

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Competing interest

The authors have declared that no competing interest exists.

Declaration of competing interest

The authors declare no conflict of interest.

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