Trials of treatments for COVID-19: Review of drugs are tested.

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Abstract
Coronavirus disease (COVID-19) drug development process is the research processing to develop a preventative vaccine or therapeutic prescription drug that would alleviate the severity of 2019-2020 (COVID-19). Several hundred of special scientific research centers, research groups, and health organizations were developing and trying huge numbers of vaccine candidates and potential drugs for COVID-19 disease in various stages of preclinical or clinical research. Some clinical trials were in progress worldwide to find potential therapies against COVID-19.

Introduction
World Health Organization reported that viral diseases continue to emerge and represent a serious issue to public health. In the last twenty years, several viral epidemics such as the human severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 to 2003, and H1N1 influenza in 2009, have been recorded, then the middle rast respiratory syndrome coronavirus (MERS-CoV) was recorded in Saudi Arabia in 2012 [1]. Coronavirus disease 2019 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2,3]. The disease (COVID-19) was first known in December 2019 in Wuhan (China), and then has spread globally, resulting pandemic case in 2019 and 2020 coronavirus [4]. The CoVs became the main pathogens of emerging respiratory disease spread. They are a large family of single-stranded RNA viruses (+ssRNA) that could be identified and isolated in various animal species [5]. These viruses can pass the barriers and can attack humans, to cause illness ranging from the common cold to more severe diseases, like, MERS and SARS. Actually, the CoVs have probably originated from bats and transfer by moving into other mammalian hosts the Himalayan palm civet for SARS-CoV, and the dromedary camel for MERS-CoV, then transfer to humans as a host.
The dynamics of SARS-Cov-2 are not well known, but there is an estimation that it could be have an animal origin [6]. The researchers around the world are worked hard to find treatments for lowering or preventing the spread of the new coronavirus attack to find effective drugs. Recently, more than several hundreds of clinical trials of COVID-19 treatments or vaccines that are either ongoing or recruiting patients [7]. Every day a new trial of treatment is added, as the case count in the research centers around the world. The known drugs that first developed decades ago are being tested. we take a look at several of the treatments that scientific researchers hope will help for fighting COVID-19 everywhere.

**Drug development**

Drug development has important role to discover a new infectious disease vaccine or therapeutic drug for needs and the new drug been identified through the process of drug discovery [8]. It includes laboratory research on microorganisms and animals, filing for regulatory status, such as via the U.S. Food and Drug Administration (FDA), for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug [9,10]. The entire process – from concept through preclinical testing in the laboratory to clinical trial development, including Phase I-III trials to approved vaccine or drug typically takes more than a decade [8-10]. Development of a COVID-19 vaccine or therapeutic antiviral drug begins with matching a chemical concept to the potential prophylactic mechanism of the future vaccine or antiviral activity in vivo [9,10]. Figure 1 shows the drug discovery cycle process.

![Drug Discovery Cycle](image)

**Figure 1. The drug discovery cycle process.**
Antiviral EIDD-2801

EIDD-2801 is the isopropylester prodrug of N\(^4\)-hydroxycytidine [11,12] With improved oral bioavailability in non human primates, it is hydrolyzed in vivo, and distributes into tissues where it becomes the active 5’-triphosphate form [12]. The active drug incorporates into the genome of RNA viruses, leading to an accumulation of mutations known as viral error catastrophe [13]. Recent studies have shown EIDD-2801 inhibits replication of human and bat coronaviruses, including SARS-CoV-2, in mice and human airway epithelial cells [11]. EIDD-2801 has shown promise in test-tube experiments with human lung and airway cells [11]. The drug might even be more efficient at blocking the novel coronavirus, SARS-CoV-2, a drug being tested against COVID-19 in clinical trials that began in March 2020. EIDD-2801 introduces genetic mutations into the virus’s RNA. As the RNA makes its copies, so many damaging mutations accumulate that the virus could be an able to attack cells [14]. The drug also can work anti several RNA viruses, and it could be a multipurpose antiviral [14].

The synthesis of the isopropylester prodrug of N\(^4\)-hydroxycytidine could be followed steps in ref. [15,16].
Remdesivir is an antiviral medication

Remdesivir

Remdesivir is a broad-spectrum antiviral medication developed by the American biopharmaceutical company Gilead Sciences [17]. In beginning of 2020, remdesivir is being started to study as a possible treatment for COVID-19 [18]. Earlier studies demonstrated remdesivir's antiviral activity against several RNA viruses including SARS coronavirus and Middle East respiratory syndrome-related coronavirus [17]. Patient takes remdesivir by injecting into a vein [19]. Remdesivi is a nucleotide analog as an adenosine analog, which inserts into viral RNA chains, that interfering with viral replication and cause their premature termination [20]. Remdesivir was originally developed to treat Ebola virus disease and Marburg virus disease but was ineffective for these viral infections [17]. Remdesivir can be synthesized in multiple steps from ribose derivatives. The synthesis routes of remdesivir invented by Chun and coauthors from Gilead Sciences [21].
Japan flu drug

![Favipiravir](image.png)

Favipiravir is a pyrazinecarboxamide derivative, sold under the brand name Avigan, is an antiviral medication used for treatment influenza in Japan, in addition to treat some of other viral infections [22]. It is being developed and manufactured by Toyama Chemical (Fujifilm group) and was approved for medical use in Japan in 2014 [23]. In 2016 Tokyo-based Fujifim has licensed the active pharmaceutical ingredient for the flu drug Avigan to Zhejiang Hisun Pharmaceuticals co. of China. The mechanism of its actions is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase [25].

In February 2020, favipiravir was being studied in China for experimental treatment of the emergent COVID-19 [26,27]. Trials are also being planned in Japan [28]. Favipiravir was first synthesized from an inexpensive and commercially available starting material, 2-aminopyrazine [29].

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine have been confirmed by FDA (U.S. Food and Drug Administration) for the treatment of malaria, lupus and rheumatoid arthritis, but preliminary research in human and primate cells suggests that the medicines could effectively treat COVID-19.
- Chloroquine

[Chemical structure of Chloroquine]

Chloroquine is a medication primarily used to prevent and treat malaria in areas where malaria remains sensitive to its effects [30]. Chloroquine was discovered in 1934 by Hans Andersag [31,32]. Chloroquine has antiviral effects [33]. It increases late endosomal and lysosomal pH, resulting in impaired release of the virus from the endosome or lysosome – release of the virus requires a low pH. The virus is therefore unable to release its genetic material into the cell and replicate [34,35]. Chloroquine also seems to act as a zinc ionophore that allows extracellular zinc to enter the cell and inhibit viral RNA-dependent RNA polymerase [36,37]. In April 2020, chloroquine has limited evidence to use it in treating COVID-19 [38]. Chloroquine had been also proposed as a drug for SARS treatment, with in vitro tests inhibiting the SARS-CoV virus [39,40]. In October 2004, a group of researchers published results on chloroquine, which acts as an effective inhibitor of the replication of the severe acute respiratory syndrome coronavirus (SARS-CoV) in vitro [41]. Chloroquine was being considered in 2003, in pre-clinical models as a potential medicine against chikungunya fever [33]. Chloroquine was synthesized by reacting 4,7-dichloroquinoline with 4-diethylamino-1-methylbutylamine at 180 °C [42-45].
- Hydroxychloroquine

Hydroxychloroquine (HCQ), sold under the brand name Plaquenil, is a medication used to prevent and treat malaria. Also it uses for treatment of rheumatoid arthritis, lupus, and porphyria cutanea tarda [46]. Hydroxychloroquine increases lysosomal pH in antigen-presenting cells [47]. In inflammatory conditions, it blocks toll-like receptors on plasmacytoid dendritic cells [48]. Hydroxychloroquine is being studied as a treatment for coronavirus disease 2019 (COVID-19) [49]. The publication status of one non-randomized trial, which claimed hydroxychloroquine benefits for COVID-19 is ambiguous [50].

The preparation of several basic side chains containing an N-alkylethanolamino group and their condensation with 4,7-dichloroquinoline leads to hydroxychloroquine target. Hydroxychloroquine, 7-chloro-4-[4-ethyl(2-hydroxyethyl)amino]-1-methylbutylamino] quinoline is made by a scheme similar to that of making chloroquine. Reacting 1-chloro-4-pentanone with 2-ethylaminoethanol gives the corresponding aminoketone which undergoes reductive amination in conditions analogous, making 4-[ethyl(2-hydroxyethyl)amino]-1-methylbutylamihene. The latter is reacting with 4,7-dichloroquinoline makes the desired hydroxychloroquine [45,51]. Also one invention provides a process for the preparation of hydroxychloroquine by the reaction of 4,7-dichloroquinoline with N'-ethyl-N'-β-hydroxyethyl-1,4-pentadiamine under high pressure [52].

A failed Ebola drug
One of the drugs, REGN-EB3, is a cocktail of three monoclonal antibodies (REGN3470/3471/3479) [53] against Ebola made by Regeneron Pharmaceuticals. Regeneron compared the research it's now doing on a treatment for COVID-19 to the steps it took in designing, developing and
testing REGN-EB3 [54]. Monoclonal antibodies are antibodies that are made by identical immune cells that are all clones of a unique parent cell. Monoclonal antibodies can have monovalent affinity, in that they bind to the same epitope [55].

The second Ebola drug, mAB114, is derived from a single antibody recovered from the blood of a person who survived Ebola in the Democratic Republic of Congo in 1995, and was developed by Institute of Allergy and Infectious Diseases [56, 57]. The mAb114 is a neutralizing antibody [56], it binds to a protein on the surface of the virus that is required to infect cells. Specifically, mAb114 neutralizes infection by binding to a region of the virus envelope glycoprotein that, in the absence of mAb114, would interact with virus's cell receptor protein [57]. The monoclonal antibody (mab114) was administered to participants have covid-19. Results were encouraging with (35.1%) [58].

**An HIV drug combination**

Lopinavir/ritonavir (LPV/r), sold under the brand name Kaletra is a fixed dose combination medication for the treatment and prevention of HIV/AIDS [59].

Lopinavir and Ritonavir were originally developed as an inhibitor of HIV protease, one of a family of pseudo-C2-symmetric small molecule inhibitor [59]. In 2020 lopinavir/ritonavir was found not to work in severe COVID-19. In the trial the medication was started within about two weeks after the start of symptoms [60].
Synthesis of ritonavir and lopinavir, a short synthesis of hydroxyethylene dipeptide isostere, a core unit of the HIV-protease inhibitors ritonavir and lopinavir, its C-3 epimer and C2 symmetric diamino diol is described. The crucial aspects of the synthesis are self-cross metathesis and exploitation of C2-symmetric of the metathesis product to obtain the required skeleton [61].

An immunosuppressant and an arthritis drug

Tocilizumab

Tocilizumab, also known as atlizumab, is an immunosuppressive drug, mainly for the treatment of rheumatoid arthritis and systemic juvenile idiopathic arthritis, a severe form of arthritis in children [62]. It was developed by Hoffmann–La Roche and Chugai. It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R). Interleukin 6 (IL-6) is a cytokine that plays an important role in immune response and is implicated in the pathogenesis of many diseases, such as autoimmune diseases, multiple myeloma and prostate cancer [63]. Tocilizumab permitted to treat coronavirus disease 2019 (COVID-19) of inflammation in patients in China, but there is no evidence whether this treatment is effective [64]. In Australia (ASCIA) considered tocilizumab drug to be as an off-label medicine with COVID-19 related acute respiratory distress syndrome [65].
A blood pressure drug

Losartan

Losartan, sold under the trade name Cozaar, is a medication mainly used to treat high blood pressure [66]. It is also used for diabetic kidney disease, heart failure, and left ventricular enlargement [67]. Losartan is a selective, competitive angiotensin II receptor type 1 (AT1) antagonist, reducing the end organ responses to angiotensin II. All of the physiological effects of angiotensin II, including release of aldosterone, are antagonized in the presence of losartan. Reduction in blood pressure occurs independently of the status of the renin–angiotensin system [68]. A hypothesis emerged in an opinion commentary published in March 2020, that AT1R blockers such as losartan may work to mitigate the symptoms of COVID-19 (SARS-CoV-2) infection [69].

The preparation of Losartan and its potassium salt, which comprises reacting 4′-Bromomethyl-2-biphenylcarbonitrile with 2-Butyl-4-Chloro-5-Formylimidazole in the presence of a base and a phase transfer catalyst to produce a cyano aldehyde; reacting the formed cyano aldehyde with sodium azide in the presence of tributyl tin chloride to produce aldehyde tetrazole; reducing the formed aldehyde tetrazole with sodium borohydride to produce Losartan [70].

Conclusion

Coronavirus disease (COVID-19) drug development researches are still under trials of process. These drugs are included vaccine or therapeutic prescription drug. To date there is no approved specific drug to cure patients infected by SARS-CoV-2. A large number of local and international special scientific
research centers are working hard to test vaccine candidates and potential drugs for COVID-19 disease in various stages of preclinical or clinical research. We have believe and hope in science.

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