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Mini Review

COVID-19 treatments | A glance at the most recent reported drugs, which may close to the operational phase

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Abstract

Due to the increasing spread of the Coronavirus 2019 (COVID-19), the competition for the most successful possible solution has become very popular among different countries. Therefore, addressing the issue of which is the next most likely candidate to enter the global market; It is a question that sooner or later every country must answer. This study was planned based on the latest published information on drugs that are currently undergoing the fourth clinical phase of the estuary, has tried to cover the common concern, which means that recent reports indicate the importance of which of the existing or newly synthesized drugs in the control of this disease? The findings suggest that the introduced chemical structures are evidence of measurable success on a laboratory scale, but there are no reliable reports of the high potency of these drugs to control or treat COVID-19 in long term. In conclusion, FDA approved most of these drugs permanently or under a specific condition. This means that scientists had to get along with trial and error these days to overcome the probable upcoming catastrophe.

Keywords: Coronavirus, COVID-19, Treatments, Laboratory Experiments, Trial and Error, FDA

Introduction

The COVID-19 disease is one of the most tragic events of the recent century that has affected the whole world. Research and clinical studies have begun to find a suitable solution from the first days of the pandemic outbreak, but no definitive treatment solution has been proposed yet. So far, various drugs for the control of this disease have been introduced and marketed, including Hydroxychloroquine,[1-3] Favipiravir,[4,5] Remdesivir,[6-10] Steroids: Dexamethasone,[11,12] Plasma therapy,[13-15] etc. However, no accurate pieces of proof have demonstrated the long term of their effectiveness in a large number of populations for COVID-19 exclusively.[16,17] It may be due to the relatively short time that has passed since the outbreak of this disease followed by our knowledge that is being updated day by day.[18] This study has presented five new drugs which are in phase four of the external clinical trials for COVID-19 and related conditions. These drugs might be the next alternatives for those existed ones that were purchased all by one country in advance. In this review, extensive investigations in PubMed, Scopus, and Google Scholar have been performed using keywords including Budesonide, Lenalidomide, Linagliptin, Acetylcysteine, and Gamolenic acid. Accordingly, the most important research papers about this subject based on the quality and level of pieces of evidence have been collected, categorized, and discussed.

Budesonide (NCT04374474 | Sponsored by Lawson Health Research Institute)

Budesonide is a glucocorticoid consisting of two epimers 22R and 22S. This drug can be used to treat pulmonary and intestinal inflammations such as asthma, COPD, Crohn's disease, and ulcerative colitis.[19,20] Short-term effects of corticosteroids include decreased permeability of blood vessels and capillaries, as well as reduced leukocyte migration to the site of inflammation.[21] Binding corticosteroids to glucocorticoid receptors causes a series of changes in gene expression, which in turn triggers multiple

effects in the downstream region over hours to days.[21] Glucocorticoids inhibit neutrophil apoptosis and demargination. They also reduce the formation of arachidonic acid derivatives by inhibiting phospholipids A2. It also inhibits NF-Kappa B and other inflammatory factors in the transcription process. Ultimately, it promotes anti-inflammatory genes such as interleukin-10.[21] Low-dose corticosteroids have anti-inflammatory effects, while high-dose corticosteroids suppress the immune system.[21] Long-term use of these compounds leads to binding to mineralocorticoid receptors, which in turn increases sodium levels and decreases potassium amounts.[21] Budesonide was granted FDA approval on 14 February 1994.[22]

Lenalidomide (NCT04361643 | Sponsored by Hospital Universitario Getafe)

Lenalidomide is a derivative of thalidomide that was marketed under the brand name CC-5013 by the Celgene Company in 2004. Initially, this drug was used to treat multiple myeloma,[23,24] but later showed its effectiveness on hematological disorders, including myelodysplastic syndromes.[25] The mechanism of action of this drug is not fully explained. Thus, it can be stated that in vitro, lenalidomide inhibits the expression of cyclooxygenase-2 (Cox-2), while these interactions are not true for cyclooxygenase-1 (Cox-1). In vitro, by inhibiting bone marrow stromal cell support, it directly or indirectly induces tumor cell apoptosis by anti-angiogenic, anti-osteoclastogenic effects, and also immunomodulatory activity.[26-29] Lenalidomide was approved by the FDA on December 27, 2005.

Linagliptin (NCT04341935 | Sponsored by University of Miami)

Linagliptin is one of the DPP-4 inhibitors introduced by Boehringer Ingelheim for the treatment of type 2 diabetes.[30] This type of inhibitor differs from other types of DPP-4 inhibitors in several ways. It exhibits non-linear pharmacokinetic properties, is not destroyed by the renal system, and ultimately depends on the concentration of bound protein.[31] Regarding the mechanism of this drug, it can be said that it is a reversible inhibitor for DPP-4. The inhibition of this enzyme reduces the breakdown of GLP-1 and Glucose-dependent insulinotropic peptide (GIP).[30,31] These two factors in turn stimulate the release of insulin from pancreatic beta cells and at the same time inhibit the release of glucagon from pancreatic beta cells as well.[30] Altogether, these effects lead to decreased glycogen breakdown in the liver and increased insulin release in response to glucose.[30,31] Linagliptin was approved by the FDA on May 2, 2011.[30]

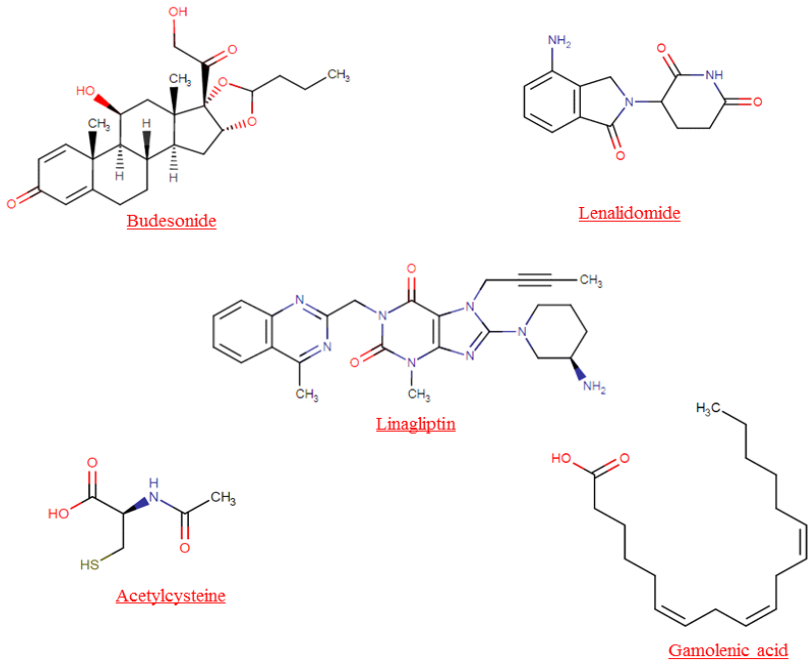

Figure 1. Chemical structure of proposed drugs (Information collected from drugbank.ca)

Table 1. Summary of mentioned chemical structures in addition to the identifications

Names	Identifications				Phase
	Accession Number	Group	Molecular Weight	Chemical Formula	
	Title		Purpose	Status	Ref.
Budesonide	DB01222	Approved	Average: 430.5339	C25H34O6	4
Olfactory Retraining Therapy and Budesonide Nasal Rinse for Anosmia Treatment in Patients Post-CoVID 19. A Randomized Controlled Trial			Treatment	Active Not Recruiting	68
Lenalidomide	DB00480	Approved	Average: 259.2606	C13H13N3O3	4
Double-blind Randomized Controlled Clinical Trial of Low-dose Lenalidomide in the Treatment of COVID-19 Disease.			Treatment	Active Not Recruiting	69
Linagliptin	DB08882	Approved	Average: 472.5422	C25H28N8O2	4
Effects of DPP4 Inhibition on COVID-19 Patients With Type 2 Diabetes.			Treatment	Active Not Recruiting	70
Acetylcysteine	DB06151	Approved, Investigational	Average: 163.195	C5H9NO3S	4
Determination of Efficacy of N-Acetylcysteine in Preventing Those With Mild or Moderate COVID-19 From Progressing to Severe Disease.			Treatment	Active Not Recruiting	71
Gamolenic acid	DB13854	Approved, Investigational	Average: 278.4296	C18H30O2	4
Anti-inflammatory / Antioxidant Oral Nutrition Supplementation on the Cytokine Storm and Progression of COVID-19: A Randomized Controlled Trial.			Supportive Care	Active Not Recruiting	72

Acetylcysteine (NCT04419025 | Sponsored by Cambridge Health Alliance)

Acetylcysteine, also known as N-acetylcysteine, N-acetyl L-cysteine, or NAC, was originally used as a mucolytic agent in acetaminophen-induced poisoning.[32] It is a derivative of cysteine with the acetyl group attached to the cysteine amine agent.[33] The NAC is basically a kind of precursor that is converted to cysteine by the enzyme aminoacylase-1 (ACY-1) in the gut and then absorbed at the same site.[34,35] Cysteine is one of the main constituents of glutathione; therefore, the administration and use of acetylcysteine lead to the restoration of glutathione stores. It can also be used as a general antioxidant to reduce the effects of diseases caused by Reactive Oxygen Species (ROS).[36-38] For example, acetylcysteine is commonly used for people who suffered from kidney problems to prevent the acceleration of acute renal failure.[39] In addition, it has been shown that this drug can be useful for mild to moderate brain damages as long as it is used after an injury to reduce neuronal loss and cognitive and neurological signs.[40,41] It is now widely used to treat HIV;[42] secondly, the use of this drug in diseases such as chronic obstructive pulmonary disease [43] and contrast-induced nephropathy has been reported.[44,45] Acetylcysteine has been considered as a successful drug in the treatment of various neuropsychiatric [46-48] and neurodegenerative disorders [49-51] such as cocaine, cannabis, and smoking addictions, Alzheimer's and Parkinson's diseases, autism, compulsive and grooming disorders, schizophrenia, depression, and bipolar disorder. Recent data have shown that acetylcysteine prevents muscle weakness and is a factor in increasing strength in endurance or athletic performance.[52]

Gamolenic acid (NCT04323228 | Sponsored by King Saud University)

Gamolenic acid or gamma-linolenic acid (GLA) is an essential fatty acid (EFA) consisting of 18 carbon atoms with three double bonds commonly found in human milk or other plant sources.[53] Gamolenic acid is more or less produced by the body as a metabolite of delta 6-desaturase. By converting this substance to Dihomo-gamma-linolenic acid, the precursor monoenoic prostaglandins, including PGE1, are biosynthesized.[54] Due to the fact that Gamolenic acid is naturally found in abundance in the fatty acid fractions of some plants seed oil such as evening primrose oil, and Borage oil [55] (concentration of about 7 to 14%).[54] Evening primrose oil has been studied for clinical use for menopausal syndrome,[56] diabetic nephropathy,[57] and chest pain.[58] Gamolenic acid might be found in over-the-counter dietary supplements and also in fungal sources,[59] which is introduced in the

form of triglycerides. Different clinical signs of Gamoleic acid have been examined including rheumatoid arthritis, atopic eczema,[60] acute respiratory distress syndrome,[61] asthma,[62] premenstrual syndrome,[63] cardiovascular disease,[64] ulcerative colitis,[65] ADHD, cancer, osteoporosis, diabetic neuropathy,[66] and insomnia.[67]

Conclusion

In conclusion, much of the existing treatment methods have resulted out from an understanding of the previous two outbreaks, particularly the SARS-CoV outbreak which shares similarities with the novel strain of the Coronavirus. However, to generate treatments with high efficacy, the unique features of SARS-CoV-2 must be understood to a greater extent, especially its spike protein. Besides these, different serotypes are being identified in different countries with a slight variation which may respond to a different host response, pathogenesis, and symptoms in different regions. On the other side, it is clear that the drugs currently proposed may not be a definitive treatment for COVID-19. In general, what seemed quite certain was the effort of each country to find a formulation to control this global pandemic. This article briefly tried to suggest some drugs that have the potential to be replaced by current treatments in the near future and to address them reasonably.

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