Original Article

Potential non-biological therapeutic options for coronavirus disease-2019: Recent updates

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ABSTRACT

Coronavirus disease-2019 (COVID-19) has been spread across the world and reached to the pandemic level. It has proved as a serious threat to the humanity, therefore, understanding of the ongoing situation and the development of stringent strategies to cure the same is of prime concern. As the potential vaccines development is in continuation, various non-biological therapeutic agents which are being investigated against COVID-19 as a current strategy for symptomatic treatment should be uncovered. To date, various drugs that are approved by the USFDA for their therapeutic effects against rheumatoid arthritis, malaria, influenza A and B and AIDS viruses, pancreatitis, chronic hepatitis C, Middle East respiratory syndrome, inflammation, and immunosuppression are deliberately being used to treat COVID-19 infection. These drugs have shown promising results against this deadly virus. In addition to remdesivir and hydroxychloroquine, oral chlorine dioxide, fluvoxamine, methylprednisolone, losartan, dapagliflozin, and many more have been enrolled for clinical trial and currently recruiting the patients for the studies. This report highlights the potential non-biological therapeutic options used for the treatment of COVID-19, which is expected to help formulation and development scientists to come up with the new technologies of these molecules for better effect against this infectious disease.

Keywords: Coronavirus disease-2019, therapeutic options, hydroxychloroquine, remdesivir, non-biological therapeutic agents

BACKGROUND

Within a few days of the first report, coronavirus disease-2019 (COVID-19) had spread across the worldwide, reaching a pandemic level. It has proved as a serious threat to the humanity, therefore, understanding of the ongoing situation and the development of stringent strategies to cure the same is of prime concern. As the potential vaccines development is in continuation, various non-biological therapeutic agents which are being investigated against COVID-19 as a current strategy for symptomatic treatment should be uncovered.

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COVID-19 PATHOPHYSIOLOGY

The coronavirus (CoV) may travel from the lungs to the peripheral blood, and then, it may attack the organs that express the ACE2 receptor such as gastrointestinal tract, heart, renal, kidney, bladder, and lungs.[1,2] The CoV spike glycoprotein S (S1 and S2) can attach to ACE2 receptors expressed on the surface of human cells. S1 protein contains receptor binding domain which allows CoV to attach with ACE2 while S2 protein plays major role in fusion of cell membrane and virus.[3] After fusion virus enters into cell, the viral genome RNA is released into the cell cytoplasm and translated into two polyproteins (pp1a and pp1ab) and structural proteins after that form replication transcription complex which continuously replicate and synthesize subgenomic RNA. These are inserted into the membrane of endoplasmic reticulum or Golgi and a new genomic RNA is formed by a combination of genomic RNA and nucleocapsid protein that forms viral particle buds.[4] At last, virus

containing vesicles fused with the plasma membrane. Therefore, the virus infected patients show a high level of inflammatory cytokines such as interleukin (IL)-1β and IL-6, as well as IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, monocyte chemoattractant protein 1, MIP1α (23) interferon-γ, macrophage inflammatory protein-1β, platelet-derived growth factor, tumor necrosis factor-alpha, and vascular endothelial growth factor-A.[5,6] High level of pro-inflammatory cytokines leads to shock and tissue damage in kidney, liver, heart, and lung results acute respiratory distress syndrome (ARDS) and multiple organ failure.[2]

COVID-19 PANDEMIC CURRENT STATUS

The novel CoV is new identified β-CoV originated from Wuhan, China, in December 2019 which has rapidly spread across China and many other countries. Initially, the World Health Organization (WHO) named it as 2019-nCoV on January 12, 2020.[3] The WHO officially named this epidemic disease as COVID-19 and International Committee on Taxonomy of Viruses renamed it as severe acute respiratory syndrome CoV-2 on January 11, 2020.[7] Based on the crown-like shape of the outer fringe of envelope protein, they were termed as CoV.[8] CoVs are divided into four subfamilies including α, β, γ, and δ CoV among these α and β CoV are able to infect humans while γ and δ CoV infect birds.[2]The β CoV may cause more fatalities and disease, whereas δ CoV causes mild symptomatic infections.[8] The COVID-19 infection develops pneumonia, sore throat, fever, cough, fatigue, lung infection, muscle pain, breathing difficulty in the patients including lymphopenia, dyspnea, diarrhea, and hemoptysis and ARDS.[9] In the absence of any specific therapy for the treatment of COVID-19, thousands of people have been died worldwide.

RECENT ADVANCES IN NON-BIOLOGICAL THERAPEUTIC OPTIONS FOR COVID-19

Despite the initiatives taken by the leading global institutions and companies to develop vaccines for the prevention of COVID-19, several other investigations have shown immense clinical pertinence of various alternative therapeutic options. At present, several repurposing therapeutic options are being investigated for the treatment of COVID-19. Recent publications have brought attention to use various antiviral and antimalarial drugs for efficient treatment of COVID-19.[10,11] In table 1 we provide recent updates of therapeutic treatment options other than monoclonal antibodies based treatments and vaccines, for the beneficial effect against COVID-19. Utilization of these therapeutic options presently is the best strategy until a suitable vaccine is developed.

To date, various drugs that are approved by the USFDA for their therapeutic effect against rheumatoid arthritis, malaria, influenza A and B and AIDS viruses, pancreatitis, chronic hepatitis C, Middle East respiratory syndrome, inflammation, and immunosuppression are deliberately being used to treat COVID-19 infection. These have shown promising results against this deadly virus infection. In addition to remdesivir and hydroxychloroquine, oral chlorine dioxide,[12] fluvoxamine, methylprednisolone, losartan, dapagliflozin, and many more have been enrolled for clinical trial and currently recruiting the patients for the studies. Here, we summarize potential drugs used for the treatment of COVID-19. Due to the lack of specific vaccines against COVID-19, current treatment strategies focused on symptomatic treatment.

Table 1: Non biologics treatment options for COVID-19

Drugs	Drugs action	Anti-infective mechanism	Therapeutic indication	References
Remdesivir	Adenosine analogue	Viral protein inhibitor	Viral infection*	[2,7,8,13]
Chloroquine/ Hydroxychloroquine	9-Aminoquinolin	Increasing the endosomal pH required for virus-cell fusion	Malaria*	[8,11]
Galidesivir	Nucleoside RNA polymerase inhibitor	Inhibit the process of viral replication.	Viral infection	[8]
Oseltamivir	Viral fusion inhibitor	Inhibits the viral neuraminidase and blocks the release of viral particles from host cells.	Influenza A and B	[13,14]
Ganciclovir	Nucleoside analogue	Inhibits viral DNA polymerases	AIDS	[7]
Lopinavir/ritonavir	Protease inhibitor	Lopinavir is a protease inhibitor. Ritonavir inhibits metabolizing enzyme cytochrome P450 3A and increases lopinavir half-life.	HIV*	[7,13]
Tenofovir	HIV reverse transcriptase	Inhibit DNA synthesis.	HIV	[7]
Nelfinavir	Selective inhibitor of HIV protease	Inhibits replication of SARS-CoV-2.	HIV	[15]
Arbidol	Fusion inhibition	Blocks virus entry into the cell	Influenza virus	[2,16]
Nafamostat	Synthetic serine protease inhibitor	Prevent fusion of the envelope of the virus	Pancreatitis, influenza	[3]
Ribavirin	Nucleoside analogs	Destabilize viral RNA	Chronic hepatitis C*	[17]
Favipiravir	RNA dependent RNA polymerase inhibitors	Targets the viral RNA polymerase	Influenza*	[18]
Nitazoxanide	Broad-spectrum antiviral agent	Inhibiting expression of the viral N protein	Middle East respiratory syndrome	[19]
Diarylheptanoids	Papain like protease inhibitors	Inhibit papain like protease of SARS-CoV	Nutraceuticals	[20]
Thalidomide	Anti-inflammatory	Increase the secretion of interleukins, such as IL-12, and activate natural killer cells	Anti-inflammatory action	[14]
Methylprednisolone	Corticosteroid	Immunosuppressant and anti-inflammatory	Immunosuppressant	[14]
Pirfenidone	Immunosuppressant	Inhibiting IL-1β and IL-4	Inflammation	[14]

*Drugs are in clinical trial for the treatment of COVID-19. COVID-19: Coronavirus disease-2019, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, IL: Interleukin

CONCLUSION

The potential non-biological treatment options for COVID-19 have been highlighted here in this report. These treatment strategies focused on symptomatic treatment have currently been used as the best strategic option against COVID-19 as the development of a vaccine for its treatment is far from the reach of affected people. Therefore, highlighting these molecules could help formulation and development scientists to come up with the new technologies of these molecules for better effect against this infectious disease.

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