

## Review Article

### THERAPEUTIC STRATEGIES FOR COVID-19

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**Publication history: Received on 10/08/2020, Accepted on 31/08/2020, Published online 02/09/2020**

#### ABSTRACT

The explosive and unprecedented nature of corona virus without any explicit method of control has put the whole world into crisis causing millions of life and sending billions to self-isolation. With a proven vaccine to take at least a year from being fully tested for safety and efficacy, only approach for the development of effective medication has been therapeutic repurposing of existing drugs. Drug repurposing is the process of clinical research of swift selection and establishing the safety and efficacy of existing drugs that are approved for other ailments to be used for people with COVID-19 infection. This review deals with various therapeutic strategies that are aimed for the treatment of COVID-19.

Keyword: Corona virus, COVID-19, Therapeutics.

#### INTRODUCTION

COVID-19 (Coronavirus disease 2019) is caused by an infection of the SARS-CoV-2 virus which belongs to the family of viruses called coronavirus. This family also comprises viruses like SARS-CoV which caused severe acute respiratory syndrome (SARS) in 2002 and MERS-CoV which caused Middle East respiratory syndrome (MERS) in 2012 [1-2]. Like the other coronaviruses, the SARS-CoV-2 virus primarily causes respiratory tract infections, and the severity of the COVID-19 disease can range from mild to fatal. Serious illness from the infection is caused by the onset of pneumonia and acute respiratory distress syndrome (ARDS) [3-4].

The outbreak of the novel SARS-CoV-2 pathogen and corresponding COVID-19 have had an enormous impact on both global health and the daily lives of billions of people worldwide. Current clinical management includes infection prevention, control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. With a proven vaccine to take at least a year from being fully tested for safety and efficacy, only approach for the development of effective medication has been therapeutic repurposing of existing drugs. Drug repurposing is the process of clinical research of swift selection and establishing the safety and efficacy of existing drugs that are approved for other ailments to be used for people with COVID-19 infection [5].

**CURRENT THERAPEUTIC APPROACH**

There are more than one hundred vaccines in preclinical development by pharmaceutical companies and research centers. More than seventy of these are being tracked by the World Health Organization (WHO). Out of 120 vaccine candidates under consideration for potential therapies, vaccine developed by Imperial College London has entered human trial phase after showing safe and effective response in animal study [6]. This vaccine has been prepared using synthetic RNA strands mimicking the virus which once injected into muscle self-amplifies generating number of copies of itself and instructs body's own cells to make copies of a spike protein found outside of virus which triggers immune system to recognize and fight coronavirus. The World Health Organization (WHO), European Medicines Agency (EMA), US Food and Drug Administration (FDA), and the Chinese government and pharmaceutical companies are coordinating with academic and industry researchers for the rapid development of antiviral drugs, vaccines and post-infection medications [7]. The International Clinical Trials Registry Platform of the WHO confirmed 536 clinical studies of drug therapies for COVID-19 infections along with various existing antiviral drugs for repurposing against COVID-19 are under clinical research [8-10]. The WHO has embarked on an ambitious global "mega trial" called SOLIDARITY in which confirmed cases of COVID-19 are randomized to standard care or one of four active treatment arms (remdesivir, chloroquine or hydroxychloroquine, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon beta-1a) [11].

The antiviral drug remdesivir gained emergency use authorization (EUA) from the FDA on 1 May 2020 based on preliminary data showing a faster time to recovery of hospitalized patients with severe disease [12]. As the present review focuses on therapies only, the details of drug candidates have been summarized below [13]:

**a. Hydroxychloroquine/chloroquine**

Drug class: Antiparasitic/anti-rheumatic

Existing disease approval: Malaria/ Rheumatoid arthritis

Trial sponsors: CEPI/WHO/INSERM

Location: GSCT/ Europe

[CEPI: Coalition for epidemic preparedness Innovations, INSERM: Institut national de la santé et de la recherche médicale, GSCT: Global solidarity clinical trial]

**b. Remdesivir:**

Drug class: Antiviral- Protease Inhibitor

Existing disease approval: Investigational (failed clinical trial against Ebola in 2014)

Trial sponsors: Gilead/WHO/INSERM

Location: GSCT

**c. Favipiravir: (First approved coronavirus drug in China)**

Drug class: Antiviral- inhibits RNA dependent RNA polymerase

Existing disease approval: Influenza

Trial sponsors: The national medical products administration in China, Fujifilm (China)

Location: China

**d. Lopinavir/ritonavir**

Drug class: Antiviral- Protease inhibitors

Existing disease approval: HIV AIDS

Trial sponsors: CEPI, WHO, UK Oxford, INSERM

Location: GSCT

**e. Sarilumab**

Drug Class: Monoclonal body against human interleukin-6 receptor

Existing disease approval: Rheumatoid arthritis

Trial sponsors: Regeneron-Sanofi

Location: Multiple countries

**f. Tocilizumab**

Drug Class: Monoclonal body against human interleukin-6 receptor

Existing disease approval: Immunosuppressant, Rheumatoid arthritis

Trial sponsors: Genentech-Hoffman-La Roche

Location: Multiple countries

**g. EIDD-2801 (New drug)**

Drug class: interferes SARS-CoV-2 reproduction mechanism

Existing disease approval: Investigational

Trial sponsors: Ridgeback Biotherapeutics, USA

Location: United States of America

Status: Human trial pending

Various drugs that were previously used/tested for the treatment of SARS, MERS, HIV/AIDS, malaria and antiviral agents are now investigated for COVID-19 treatments, and some are under clinical trials. Some antibiotics such as teicoplanin, oritavancin, dalbavancin, monensin and azithromycin are being repurposed for COVID-19 treatment [14-15]. Ivermectin, an antiparasitic drug is also recently repurposed for COVID-19 therapy [16]. Several immunomodulatory agents traditionally used for non-infectious indications demonstrate in vitro activity or possess mechanisms purported to inhibit SARS-CoV-2, including baricitinib, bemsentinib, dasatinib, and cyclosporine [17]. Clinical studies are in preparation to determine the effectiveness of a Janus kinase (JAK) inhibitor called baricitinib (used for the treatment of rheumatoid arthritis) in the treatment of COVID-19 patients. Bemcentinib, An AXL kinase inhibitor called has been fast-tracked in a UK Phase II clinical trial to study its effectiveness in the treatment of hospitalized patients with COVID-19. Bemcentinib has previously been studied in cancer patients and is safe and well-tolerated. It has also been reported to exhibit potent antiviral activity in preclinical models against several enveloped viruses, including Ebola and Zika virus, and recent data have expanded this to include SARS-CoV-2 [18]. Nitazoxanide, traditionally an antihelminthic agent, has demonstrated in vitro antiviral activity against MERS and SARS-CoV-2 [19-20]. Camostat mesylate, an approved agent in Japan for the treatment of pancreatitis, prevents nCoV cell entry in vitro through inhibition of the host serine protease, TMPRSS2 [21].

Bevacizumab, a VEGF inhibitor used in certain types of cancer is being studied as a treatment for acute lung injury (ALI) and acute respiratory distress syndrome in critically ill patients with COVID-19 pneumonia at the Qilu Hospital of Shandong University in Jinan, China [22].

Methylprednisolone, a widely used glucocorticoid is being studied for safety and effectiveness in the treatment of novel coronavirus pneumonia in several hospitals in the Hubei province of China [23]. Dexamethasone indicated for use in rheumatoid arthritis and asthma has also been under study for potential activity against coronavirus. Colchicine, an old anti-inflammatory drug is being studied to prevent complications of COVID-19 in high-risk patients [24]. Colchicine has long been used in the treatment of gout. Fingolimod, used in the treatment of relapsing forms of multiple sclerosis is being studied as a treatment for COVID-19 at the First Affiliated Hospital of Fujian Medical University in Fuzhou, China [25]. Ivermectin, an anti-parasitic drug is effective against the SARS-CoV-2 virus in an in-vitro laboratory study by researchers at Monash University in Melbourne, Australia. Further clinical trials need to be completed to confirm the effectiveness of the drug in humans with COVID-19 [26]. Leronlimab, a CCR5 antagonist has shown promise in calming the 'cytokine storm' in a small number of critically ill COVID-19 patients hospitalized in the New York area [27]. Umifenovir, an antiviral drug (used for the treatment of influenza) is being studied in China and other countries as a treatment for COVID-19 [18].

## CONCLUSION

The explosive and unprecedented nature of COVID-19 pandemic presents the greatest global health crises of this generation. The development of concomitant therapeutic even in the middle of this pandemic has been the prime challenge. Till time, there is no therapeutic method of control for COVID-19 and the best way of preventing infection has been to avoid the exposure.

## Acknowledgment

We would like to acknowledge and pay gratitude to all the doctors, pharmacists, scientist and researchers who are continuously putting their effort into the development of rational therapeutic approaches to tackle the COVID-19 crisis.

## REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2014;395: 470-73. [https://doi.org/10.1016/S0140-6736\(20\)30185-9](https://doi.org/10.1016/S0140-6736(20)30185-9)
2. Holshue ML et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020; 382: 929-36. <https://doi.org/10.1056/NEJMoa2001191>
3. Li Q et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med* 2020; 382: 1199-207. <https://doi.org/10.1056/NEJMoa2001316>
4. Zhang L, Liu Y. Potential interventions for novel coronavirus in China: a systemic review. *J Med Virol* 2020; 92(5): 479-90. <https://doi.org/10.1002/jmv.25707>
5. Pushpakom S et al. Drug repurposing: progress, challenges and recommendations. *Nat Rev Drug Discov* 2019; 18: 41-58. <https://doi.org/10.1038/nrd.2018.168>
6. Corona virus: Human trial for new vaccine begins in UK. <https://www.bbc.com/news/health-53061288> (Assessed on 26th July, 2020)
7. Dhama Ket al. COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics and therapeutics. *Human Vaccine and Immunotherapeutics* 2020; 16(6): 1-7. <https://doi.org/10.1080/21645515.2020.1735227>
8. Maguire J, Guérin PJ. A living systematic review protocol for COVID-19 clinical trial registrations. *Wellcome Open Research* 2020; 5(60): 1-9. <https://doi.org/10.12688/wellcomeopenres.15821.1>
9. Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat. Rev. Drug Discov.* 2020; 19: 149-50. <https://doi.org/10.1038/d41573-020-00016-0>
10. Harrison C. Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology* 2020; 38(4): 379–81. <https://doi.org/10.1038/d41587-020-00003-1>

11. WHO Solidarity Clinical trials for COVID-19 treatments <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments> (accessed on 9 Aug, 2020)
12. Coronavirus: US authorizes use of anti-viral drug Remdesivir. Published on 1st may, 2020. <https://www.bbc.com/news/world-us-canada-52511270> (accessed on 9 Aug, 2020)
13. Katakam P, Adiki SK, Assaleh FH, Ahmed MM. An update on therapeutic repurposing strategies for COVID-19. *Indo Global J. Pharm. Sci.* 2020; 10(1): 12-8. <http://doi.org/10.35652/IGJPS.2020.10102>
14. Coronavirus: Scientists could repurpose drugs to treat infection. *Medical News Today*. 28 February 2020 <https://www.medicalnewstoday.com/articles/coronavirus-existing-drugs-could-be-repurposed-to-treat-infection> (Accessed on 9 Aug, 2020)
15. Existing drugs may offer a first-line treatment for coronavirus outbreak. <https://medicdialogues.in/medicine/news/existing-drugs-may-offer-a-first-line-treatment-for-coronavirus-outbreak-63467> (Accessed on 9 Aug, 2020)
16. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020; 178: Article ID- 104787. <https://doi.org/10.1016/j.antiviral.2020.104787>
17. Li G, Clercq ED. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov.* 2020; 19(3): 149-50. <https://doi.org/10.1038/d41573-020-00016-0>
18. COVID-19: Prevention and Investigational Treatment. <https://www.drugs.com/condition/covid-19.html> (Accessed on 9th Aug, 2020)
19. Wang M. et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res.* 2020;30(3):269-71. <https://doi.org/10.1038/s41422-020-0282-0>
20. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *J Infect Public Health* 2016; 9(3): 227-30. <https://doi.org/10.1016/j.jiph.2016.04.001>
21. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *Clinical review and education* 2020; 223(18): 1824-36. <https://doi.org/10.1001/jama.2020.6019>
22. Clinical trial on “Bevacizumab in severe or critical patients with COVID-19 Pneumonia (BEST-CP).” <https://clinicaltrials.gov/ct2/show/NCT04275414> (Assessed on 26th july, 2020)
23. Veronese N. et. al. Use of Corticosteroids in Coronavirus Disease 2019 Pneumonia: A Systematic Review of the Literature. *Frontiers in Medicine* 2020; 7(170). <http://doi:10.3389/fmed.2020.00170>
24. Clinical trial on “Colchicine coronavirus SARS-CoV2 Trial (COLCORONA).” <https://clinicaltrials.gov/ct2/show/NCT04322682> (Assessed on 26th june, 2020)
25. Clinical trial on “Fingolimod in COVID-19.” <https://clinicaltrials.gov/ct2/show/NCT04280588> (Assessed on 26th june, 2020)
26. Lab experiments show anti-parasitic drug, Ivermectin, eliminates SARS-CoV-2 in cells in 48 hours. <https://www.monash.edu/news/articles/coronavirus-fight-possible-covid-19-drug-identified-by-scientists> (Assessed on 26th july, 2020)
27. CytoDyn begins leronlimab treatment in coronavirus trial. <https://www.clinicaltrialsarena.com/news/cytodyn-leronlimab-dosing-covid-19/> (Assessed on 26th july, 2020)

Paper cited as: **Himal Barakoti, Rabindra Kumar Rokaya. THERAPEUTIC STRATEGIES FOR COVID-19. INTERNATIONAL JOURNAL OF PHARMACOLOGY AND THERAPEUTICS.. 2020; 10(1): 7-11.**