

**TREATMENT APPROACHES TO COVID-19 INFECTION: AN OVERVIEW**

Nalawade Rohit Deepak, Ransing Pratik Sunil and Kolhe Rohini C.
 Rasiklal M. Dhariwal Institute of Pharmaceutical Education and Research
 Chinchwad, Pune, Maharashtra, India

Abstract

COVID-19 disease spread worldwide and creates pandemic situation. In starting period of pandemic situation COVID-19 not have any specific or treatment to stop the further spread of viral infection. For treatment purpose various drugs like higher generation antiviral drug, Interleukin 6 inhibitor, and higher antibiotics are preferred which not properly treat infection but reduces the mortality of COVID-19 infection. Those drugs either used singly or in combination for affectivity purpose but increases the lifesaving chances. As antiviral Remdesivir and Flavipiravir used this used for mild to moderate COVID-19 infection patients. Both drug act with in short period of time as well as shows short recovery period but not used long term because of resistance and adverse effects. During antiviral drug treatment azithromycin which is higher generation antibiotic preferred to increase effectiveness of antiviral drug. Combination has much effectivity against the infection but not clinically proven. For severe condition of COVID-19 infection IL-6 inhibitor used which used as long-term treatment. Mainly tocilizumab preferred which act by reducing cytokinin level and inflammatory responses. In this review, we aim to highlight drugs which used for treatment of COVID-19 infection and their effectivity and recovery period which based on conducted clinical trials and evidences.

Keywords: Antiviral Drugs, IL-6 Inhibitor, Vaccination, 2-Deoxy-D-Glucose.

Introduction: ^[1] ^[2]

Nowadays novel corona virus produces pandemic situation worldwide. This novel corona virus directly attacks on the human immune system and excite it. Due to excitation, body inflammation increases as well as body secretion also increases like production of cough in respiratory system. COVID-19 not has any particular specific treatment. So, WHO gives permission to some drugs which act as lifesaving in this pandemic situation? These WHO granted drug not properly treat COVID-19 infection but these reduce the infection much time and save the life. These drugs used after the permission of WHO after that doctor used these drugs in prescription. Approved drugs are antiviral drugs such as Remdesivir, Flavipiravir, Ribavirin, Lopinavir etc. Interleukin-6 inhibitor also granted. Doctors prescribes drugs to patient according to their severity in antiviral drugs Remdesivir and flavipiravir both shows shorten recovery time so, these two drugs are act as first line treatment in COVID-19. As severity increases then combination treatment used which is combination of antiviral drugs and interferons. In severe condition this combination therapy mainly preferred because it provides immune modulating action so, it can improve immune system. If immune start improving then it produces the antibodies against COVID-19 infection and fight against them.

What is COVID-19?: ^[3] ^[4] ^[5]

It is novel SARS CoV-2 viruses contain fresh lineage of beta-corona virus. Corona virus contains strains which effectively participate in spreading and stuck in host body with the help of these strains, first attack on the immune system of host and used host's genetic material for further replication and development. Virus also shows their mutation with time period. Airborne droplets are the main reason of spreading of virus and these spread from infected people. Virus initially shows the flu like symptoms so; at early phase detection is quite difficult which further attack on immune system. In incubation period of virus in host's body, virus shows their symptoms within five days such as sore in throat and fever but it very mild. As incubation period increases then virus attack on the respiratory system of host and over stimulate it which leads to cause stimulation of mucus cell so, cough overproduction can happen. These overproduced coughs further decrease the oxygen level of body then external oxygen supply needed to that infected person or patient. If treatment occur in proper ways, then patient recover from infection within two months.

Treatment❖ **Antiviral drugs****1. Remdesivir:** ^[6] ^[7]

It is antiviral, an RNA polymerase inhibitor. It is prod rug after administration it undergo metabolism and converted to C-adenosine nucleoside triphosphate which actively act on RNA and stop their polymerisation from DNA. It leads to cause blocking of viral RNA synthesis.

Remdesivir able to kill virus by blocking RNA synthesis but it also shows effect on healthy cells so, treatment conducted under investigation of well experienced doctor. Remdesivir only used for adults not in children. Dose regimen of remdesivir is single 200 mg loading dose with 100 mg daily infusion. Drug have half-life more than 35 hrs, so, due to long half-life they accumulate in



Cover Page

DOI: <http://ijmer.in.doi./2021/10.06.50>



body and starts showing adverse effect on body organ such as impairment of hepatic and kidney function. Also majorly act on glomerular filtration rate, virus shows resistance after prolonged treatment of Remdesivir.

2. Flavipiravir:^[8]

It is also RNA polymerase inhibitor stops the RNA polymerisation from DNA and inhibits synthesis of viral RNA and breaks the further spreading of viral infection. It comes under the purine nucleotide class. Initially flavipiravir in inactivated form; after metabolism it converted to active form then attack on RNA polymerase. It provides fast relief from pyrexia and cough.

Dose regimen of flavipiravir depends on severity for treatment two doses required daily. The loading dose of flavipiravir is 24,00 -3,000 mg dose every 12hr. which followed by 1,200-1,800 mg dose every 12hr. It is short acting drug with faster recovery rate but shows serious adverse effect than other drugs. Flavipiravir shows adverse effect such as hyperuricemia, teratogenicity so, avoid during pregnancy as well as breast feeding.

3. Chloroquine or hydroxychloroquine:^{[9][10]}

Chloroquine or hydroxychloroquine is an approved antimalarial drug which also be used for autoimmune disease also. But it acts as antiviral drug during COVID-19 treatment. It not acts genetic material it simply prevents the entry of virus inside the cell as well as post entry stages. Drugs show their antiviral action by inhibiting phosphatidylinositol-binding clathrin and clathrin mediated endocytosis which leads to cause prevention of nanoparticle uptake towards macrophages. Also additionally acting on endocytic vesicles fusion and prevent acidification of lysosomes.

The dose regimen of chloroquine or hydroxychloroquine in COVID-19 treatment is 600 mg twice a daily for 10 days. In some condition, chloroquine or hydroxychloroquine given with combination of azithromycin but this combination not have any clinical efficacy so, it not shows improvement in treatment. Overdose of drugs leads to cause adverse effect on cardiac system such as QT prolongation, Torsade de pointes and arrhythmia as well as azithromycin combination also increase the cardiac load. Also shows hypoglycaemia, retinopathy and bone marrow suppression after long term therapy. It shows interaction with CYP-450 inhibitors and P-glycoprotein inhibitor. Also avoid co administration with remdesivir because both can decrease antiviral action of each other.

4. Ribavirin and interferon:^[11]

It is guanosine analogue drug which act directly on RNA and stop their capping, polymerisation, and mutagenesis; indirectly shows blocking action on inosine monophosphate dehydrogenase and produce immunomodulatory effect. It having narrow therapeutic effect and 100 times less fold effective than remdesivir and flavipiravir.

Ribavirin not effective much singly but in combination with interferon alpha-2b; it shows affectivity against virulence clearance. In combination treatment virulence clearance increases due to interferon which is cytokinin effectively eliminate virus infected cells. Further study of ribavirin with combination interferon and lopinavir/ritonavir are under trial. It shows interaction with anticoagulants as well as nucleoside reverse transcriptase inhibitor (zidovudine). Avoid in pregnancy because have teratogenic effect.

5. Lopinavir/Ritonavir:^{[11][12]}

Lopinavir shows the inhibitory action on aspartate protease enzyme which mainly used in treatment of HIV. Lopinavir act on protease 3CL^{PRO} which only found in HIV virus not in corona virus. Lopinavir safe and widely used for HIV patients but not shows much effective role in COVID-19 treatment.

When lopinavir given in combination with another protease inhibitor such as ritonavir, which act as CYP450 3A inhibitor and increase the half-life of lopinavir. Dose regimen ration of combination is 400 mg lopinavir and 100 mg ritonavir given orally every 12 hrs. For 10 days. This combination is uncertain to treat COVID-19 infection but it indirectly reduces the hypoxia and increasing lifesaving chances but there is no evidence about efficacy of lopinavir/ritonavir combination. Overuse of combination can produce the hyper inflammatory response, hepatotoxicity as well as QT prolongation. Also show interaction with CYP-450 inhibitors.

❖ Interleukin-6 inhibitor:

• Tocilizumab:^[1]

Some cases of COVID-19 treatment show inflammation associated with organ failure which caused due to increase level of cytokinin in body so, intensive care as well as medication required to reduce inflammation. Here, tocilizumab mainly preferred for treatment which humanized monoclonal antibody and bound both membrane receptor and soluble receptor of IL-6. Only preferred in severe COVID-19 condition and shows concentration dependent action.



Cover Page

DOI: <http://ijmer.in.doi./2021/10.06.50>



Dose regimen of tocilizumab is 70 to 800 mg per dose in one or two dose forms. Also used at low doses such as 40 to 200 mg with repeated dose after 24-48 hrs.

Dose administration done via intravenous infusion. Tocilizumab is very sensitive drug so; treatment should conduct under investigation of experienced person. Higher dose can produce the immunosuppression which leads to cause thrombocytopenia and neutropenia.

Other IL-6 inhibitor used in treatment which is siltuximab with one or two dose 11 mg/kg and sarilumab with dose of 400 mg.

❖ Consecutive treatment in COVID-19

I. Dexamethasone:^[13]

Dexamethasone is a synthetic corticosteroid medicine showing the anti-inflammatory as well as immunosuppressant action. It shows their action by preventing spreading of viral infection in body. Dexamethasone effectively works against infection and decrease mortality up to one third.

Dexamethasone administered via oral and intravenous route with 6 mg once a daily for ten days. In some cases, acute respiratory distress syndrome (ARDS) caused during COVID-19 infection so, these ARDS effectively treated by dexamethasone also reduces their mortality.

II. Azithromycin:^[14]

Azithromycin is used to treat infections caused by certain bacteria in throat. Azithromycin shows both antiviral and anti-inflammatory properties which used in treatment of covid-19 infection. It clinically not approved as effective in combination. It shows antiviral property by binding to 50 subunits of the bacterial ribosome thus inhibiting translation of mRNA so, it effectively used as consecutive treatment in COVID-19.

Azithromycin not effective singly as much as in combination. Mainly azithromycin preferred in combination with treatment of chloroquine/hydroxychloroquine. Here dose regimen should use as 500 mg tablet per day with continuous 5 days in adults. In combination treatment, azithromycin helpful to decrease mortality period as well as reduces recovery time period. In initial stage of COVID-19 infection shows symptoms like throat sore, fever that also be reduced by azithromycin.

III. Ivermectin:^[15]

It is approved by FDA for use as an anti-parasitic drug and is known to have nematocidal, insecticidal, and properties. Also shows safety efficacy at higher doses. Antiviral activity of ivermectin act through inhibition of nuclear import of proteins of virus as well as of host. Also, transmembrane receptor CD147 affected by ivermectin.

One more action of ivermectin is, that directly act on genomic material of virus so inhibit transcription and translation process which leads to cause death of viral cell and stop further infection. Currently performed clinical trial said that, ivermectin used at dose 600-1200 µg/kg for 5 days effectively treat infection. This dose used at early-stage patient which shows mild symptoms of COVID-19 after dosing that patient not needs hospitalization.

IV. Doxycycline:^[16]

Doxycycline (DOX) is a broad-spectrum synthetic derivative of tetracycline, a bacteriostatic antibiotic drug. Its works by inhibiting (Translation) protein synthesis by acting on 30 s subunit at A site. It blocks the further addition of new amino acid which leads to cause inhibiting peptide chain formation. Doxycycline also inhibits metalloproteinase (MMPs) which prevents viral entry into host cells and effectively attenuate viral-mediated acute respiratory distress syndrome (ARDS). DOX inhibits the critical inflammatory mediator of the senescence-associated secretory phenotype (SASP) which responsible for most serious complications of viral infection.

Dose regimen of doxycycline is 100 mg twice a daily or daily via oral or IV route. But due to their anti-inflammatory action there is chance to develop cytokine storm which adversely effects on immune system. DOX is inexpensive and widely available, it is safe and attractive option for treating COVID-19.

V. Multivitamins:^[17]

In viral infection of COVID-19, increase the demand for several micronutrients such as vitamin A, B, C, D, zinc, and selenium. Dietary supplementation of micronutrients poses key role in immune function can optimize the modulation of the body's immune response, reducing the risk of infections. Zinc supplement needed immune cell development. An antioxidant, vitamin C



Cover Page

DOI: <http://ijmer.in.doi./2021/10.06.50>

prevents damage of biomolecules such as nucleic acids, proteins, lipids and carbohydrates from exposure Viral infection. Currently performed clinical trials on multivitamin said that, daily 200 mg dose of vitamin with combination therapy can effectively treat infection. But dose of vitamins varies with age.

Such multivitamins have ability to improve fighting capacity of white blood cell against viral infection so, automatically immune get improve. Due their fighting ability they also used in Combination therapy to bust up immune and recover time period. Those vitamins overdose can shows effects like constipation, nausea, diarrhoea it should be taken under instructions of physician.

❖ Herbal supplementary treatment in COVID-19:^[18]

i. **Echinaceapurpurea:**

It mainly found in Europe and North America which called as purple coneflower in common language. It shows their action on virus induced diseases. The antiviral action shown because virus induced cells membrane are very sensitive to E. Purpurea and easily broken down it leads to stop further spread. E. Purpurea has another immunomodulatory activity which cans helps to increase the release of IL-10, IL-6 and TNF-alpha by macrophages. Those increases cytokines to develop immunity activity of cells. So, E. purpurea used as supplementation in COVID-19 treatment. Overuse of E. purpurea leads to cause hypercytokinemia which knows as CRS. But there is no clinical evidence of safety profile and efficacy of E. purpurea in COVID-19 treatment.

ii. **Curcumin:**

It obtained from rhizomatous plant *Curcuma longa* belongs to family Zingiberaceae. In some case of COVID-19 infectious patients seen the hypertensive symptoms which treated by curcumin which used as supplement medication in treatment. It helps to reduce blood pressure by acting on angiotensin II receptor type 1 (AT-1) which leads to cause decrease the binding of angiotensin II to AT-1 receptors. By blocking angiotensin II blood vessels get relax and reduce blood pressure. But overuse of curcumin shows cytokine storm which caused to production of proinflammatory cytokines and that may cause worst effect on COVID-19 infectious patients.

iii. **Xanthorrhizol:**

It is herbal plant widely found in south Asian countries which biological name is *Curcuma xanthorrhiza* Roxb. belongs to family Zingiberaceae.

The main category of Xanthirrhizol is immunosuppressive action which shown by inhibiting production of proinflammatory cytokines and TNF-alpha. Further it promotes the anti-inflammatory cytokines which helps to decrease excessive body secretion during COVID-19 infection such as mucus secretion. It leads to prevent cytokine storm and increases the lifesaving chances of patients. But there may be chances of causing adverse effect.

❖ Preventive treatment:

• **Vaccination:^{[19][20]}**

As we know, prevention is better than cure for same purpose vaccination worked. Vaccination prevents from novel corona virus infection by developing artificial antibodies within body. Those produced antibodies build up immune system and develops the disease resistant antibodies.

In India, Covaxin, Covisheild, Sputnik V which used under emergency condition after approval of WHO. It is two dose vaccination and dose interval between these doses also be set because intervals can helpful to increase effectivity of vaccine.

❖ Anti-covid drug:

• **2-Deoxy-D-Glucose (2-DG):^{[21][22][23]}**

2-DG is first anticovid drug discovered by Institute of Nuclear Medicine and Allied Science (INMAS) and Defence Research and Development Organisation (DRDO) with collaboration of Dr Reddy's Laboratory (DRL). It is generic molecule and analogue of glucose. 2DG helps in faster recovery and reduces the dependency of oxygen. Now drug worked under clinical trial at phase II but due to their effectivity result Drug Controller General of India (DCGI) give approval for emergency use of 2-DG as an additional therapy for moderate to severe COVID infected patients.

It is orally administered water-soluble drug which directly accumulated in virus infected cells and stop their further viral synthesis and energy production. It leads to cause stop the growth of virus infected cells death of cell happened. Drug shown their action in three days of treatment so, indirectly reducing the hospital stay of COVID-19 infected patients.



Cover Page

DOI: <http://ijmer.in.doi./2021/10.06.50>



Conclusion:

Pandemic situation of COVID-19 is a threatening to the world so far. Severity remains same because of imperfect treatment for COVID-19 infection. Antiviral drug helpful in clearance of virulence collaborated drugs like azithromycin, ivermectin, vitamins. C helps to improve effectiveness and recovery period. With treatment some preventive action should be required such as wearing masks, using sanitizer, checking oxygen level etc. these not directly but indirectly helpful for fast recovery. Now many more worldwide companies are trying their best to discover proper treatment or drug against infection. Vaccination is another route preferred to prevent COVID-19 infection also many more drugs worked under clinical trials.

Abbreviations

- COVID-19: Corona Virus Disease 19.
- WHO: World Health Organization.
- IL-10: Interleukin-10.
- IL-6: Interleukin-6.
- TNF-alpha: Tissue Necrosis Factor- alpha.
- AT-1: Angiotensin Receptor Type 1.
- SARS-CoV 2: Serve Acute Respiratory. Syndrome Corona Virus 2.
- RNA: Ribose Nucleic Acid.
- DNA: Deoxyribose Nucleic Acid.
- DOX: Doxycycline.
- 2-DG: 2-Deoxy-D-Glucose.
- DRDO: Defence Research & Development Organisation.

References

1. Xie P, Ma W, Tang H and Liu D (2020) Severe COVID-19: A Review of Recent Progress with a Look Toward the Future. *Front. Public Health* 8:189. doi: 10.3389/fpubh.2020.00189.
2. Corona virus Disease (COVID-19) Treatment Guidelines. (2021, May 27). Retrieved from COVID-19 Treatment Guidelines (nih.gov)
3. COVID-19 (Corona virus) Drugs: Are there any that work? (2021, April 27). Retrieved from COVID-19 (corona virus) drugs: Are there any that work? - Mayo Clinic
4. Lauren M. S. What is corona virus? (2021, May 19). Retrieved from What Is Corona virus? | Johns Hopkins Medicine
5. ET Explains: Everything you need to know about corona virus. (2020, April 21). Retrieved from What is Corona virus | Corona virus causes, prevention, symptoms and cure | corona virusIndia news (indiatimes.com)
6. Beige J. Tomashek K. Dodd L. et. al. Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med* 2020; 383: 1813-1826.
7. WHO recommends against the use of remdesivir in COVID-19 patients? (2020, November 20). Retrieved from WHO recommends against the use of remdesivir in COVID-19 patients
8. Hassanipour, S., Arab-Zozani, M., Amani, B. et al. The efficacy and safety of Favipiravir in treatment of COVID-19: a systematic review and meta-analysis of clinical trials. *Sci Rep* 11, 11022 (2021). <https://doi.org/10.1038/s41598-021-90551-6>
9. Chloroquine or Hydroxychloroquine with or Without Azithromycin. (2020, October 09). Retrieved from Chloroquine or Hydroxychloroquine | COVID-19 Treatment Guidelines (nih.gov)
10. Treatment For COVID-19. (2021, April 22) Retrieved from Treatments for COVID-19 - Harvard Health.
11. Barati, F., Pouresmaeli, M., Ekrami, E. et al. Potential Drugs and Remedies for the Treatment of COVID-19: a Critical Review. *Biol Proced Online* 22, 15 (2020). <https://doi.org/10.1186/s12575-020-00129-1>
12. Lopinavir and Ritonavir. (2021, January 15). Retrieved from Lopinavir and Ritonavir: MedlinePlus Drug Information
13. Corona virus Disease (COVID-19): Dexamethasone. (2020, June 25). Retrieved from Corona virus disease (COVID-19): Dexamethasone (who.int)
14. Principle Trial Collaborative Group. Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. *THE LANCET* (2021); Vol. 397(10279): P1063-1074.
15. COVID-19 treatment guidelines: ivermectin. (2021, February 11). Retrieved from Ivermectin | COVID-19 Treatment Guidelines (nih.gov)
16. Doxycycline to Azithral: Are tablets prescribed for COVID-19 treatment effective? (2021, May 17). Retrieved from Doxycycline to Azithral: Are tablets prescribed for COVID-19 treatment effective? | The News Minute
17. COVID-19 Prevention: Does taking Zinc multivitamin tablet keep you safe from corona virus? (2020, June 28). Retrieved from COVID-19 <https://www.indiatvnews.com/fyi/covid-19-prevention-taking-zincovit-daily-immunity-for-coronavirus-prevention-629923>



Cover Page

DOI: <http://ijmer.in.doi./2021/10.06.50>



INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY EDUCATIONAL RESEARCH

ISSN:2277-7881; IMPACT FACTOR :7.816 (2021); IC VALUE:5.16; ISI VALUE:2.286

Peer Reviewed and Refereed Journal: VOLUME:10, ISSUE:6(3), June:2021

Online Copy of Article Publication Available: www.ijmer.in

Digital certificate of publication:<http://ijmer.in/pdf/e-Certificate%20of%20Publication-IJMER.pdf>

Scopus Review ID: A2B96D3ACF3FEA2A

Article Received: 10th June - Publication Date:30th June 2021

18. Rhea Veda Nugraha, HastonoRidwansyah, Mohammad Ghozali, Astrid FeinisaKhairani, NurAtik, "Traditional Herbal Medicine Candidates as Complementary Treatments for COVID-19: A Review of Their Mechanisms, Pros and Cons", Evidence-Based Complementary and Alternative Medicine, vol. 2020, Article ID 2560645, 12 pages, 2020. <https://doi.org/10.1155/2020/2560645>
19. Benefits of Getting a COVID-19 Vaccine. (2021, April 12). Retrieved from Benefits of Getting a COVID-19 Vaccine | CDC
20. COVID-19 Vaccines-WHO. (2021, April 19). Retrieved from COVID-19 vaccines (who.int)
21. Explainer: What is 2-DG, India's new anti-Covid drug? How does it work? (2021, May 17). Retrieved from Explainer: What is 2-DG, India's new anti-Covid drug? How does it work? (msn.com)
22. Corona virus treatment: Everything we know about DRDO's COVID medicine, 2-deoxy-D-glucose. (2021, May 17). Retrieved from Corona virus | 2-DG Anti Covid Drug: DRDO launches anti-COVID medicine, 2-deoxy-D-glucose, know all about how it works (indiatimes.com)
23. Pawelczyk A. Zaprutko L. Anti-COVID drugs: repurposing existing drugs or search for new complex entities, strategies and perspectives. Future Medicinal Journal (2020); vol. 12 (19). <https://doi.org/10.4155/fmc-2020-0204>.

Filename: 10
Directory: C:\Users\DELL\Documents
Template: C:\Users\DELL\AppData\Roaming\Microsoft\Templates\Normal.dotm
Title:
Subject:
Author: Windows User
Keywords:
Comments:
Creation Date: 12/21/2020 11:11:00 AM
Change Number: 39
Last Saved On: 6/14/2021 10:19:00 PM
Last Saved By: Murali Korada
Total Editing Time: 104 Minutes
Last Printed On: 7/1/2021 4:41:00 PM
As of Last Complete Printing
Number of Pages: 6
Number of Words: 3,850 (approx.)
Number of Characters: 21,949 (approx.)