Review Article

An overview on chloroquine and its role in COVID-19

Divya Dhawal Bhandari*, Tejinder Kaur

Department of Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Punjab, India

Correspondence:
Divya Dhawal Bhandari, Department of Pharmaceutical Chemistry, University Institute of Pharmaceutical Sciences, Chandigarh University, Gharuan, Punjab, India.
E-mail: nainagumber@gmail.com

How to cite this article: Bhandari DD, Kaur T. An overview on chloroquine and its role in COVID-19. Pharmaspire 2020;12(2):134-138.

Source of Support: Nil,
Conflicts of Interest: None declared.

ABSTRACT

Objective: The current COVID-19 pandemic acting as a great challenge in front of all of us and there is a need to deal with this by searching any suitable treatment thereof. Current situation demands research into new drugs or repurposing of existing drugs. **Materials and Methods:** Chloroquine, an antimalarial drug, has been found effective as repurposing in the treatment of various disorders such as cancer, skin infections, and neurological disorders. Chloroquine or hydroxychloroquine (HCQ) also bind directly to nucleic acids at molecular level thus blocking TLR9 signaling at the intracellular level by inhibiting TLR–ligand interactions. It is important to further determine the mode of action of HCQ and chloroquine, along with safe and efficacious use at prescribed dose. **Results:** Chloroquine and its derivative HCQ has been found effective in treating Coronavirus-19 (COVID-19) by inhibiting replication of SARS-CoV-2 *in vitro*. A group of Chinese researchers found that chloroquine is effective at EC_{90} of 6.9 μM using Vero E6 cells infected by SARS-CoV-2 at MOI 0.05. **Conclusion:** The chloroquine or HCQ is considered as the need of present situation to fight with COVID-19. More research is required in this field to find out the exact mechanism of chloroquine action in treatment of COVID-19 and to rule out its dose and dose regimen. Thus, chloroquine can be considered as effective drug for the treatment of novel coronavirus but lot more work is required in this direction.

Keywords: ACE receptors, chloroquine, COVID-19, hydroxychloroquine, virus

INTRODUCTION

In the emerging era of viruses and diseases, there is an unmet need for the development of newer therapeutics or the use of existing drugs in the treatment of other related diseases or disorders by altering structure activity relationship of existing drugs. This process is defined as "repurposing" of drugs and has been shown to be frequently successful.[1-3]

Hydroxychloroquine (HCQ) and chloroquine have been used from the last 50 years to treat systemic lupus erythematosus (SLE) and other rheumatic diseases. These drugs are well tolerated and rarely need any discontinuation or report any adverse systemic reaction.[4] Both these drugs are also used as antimalarials for the treatment of rheumatic disorders from past, so many decades. However, with the advancement of time, HCQ has overcome chloroquine as antimalarial therapy. In general, antimalarials are well tolerated and rarely show any adverse systemic reaction. However, usually two general types of side effects are usually encountered. The first type includes gastrointestinal intolerance, aquagenic pruritus, and other cutaneous manifestations. These usually disappear by the reduction of dose and rarely require withdrawal of treatment. The second type of side effect is rare but severe which includes retinal, neuromuscular, and cardiac impairments.[5]

Chloroquine and HCQ are originally used to treat or prevent malaria but they have been successfully used to treat several infectious such as HIV, Q fever, Whipple's disease, fungal infections, rheumatological (SLE, antiphospholipid antibody syndrome, rheumatoid arthritis, and Sjögren's syndrome), and other immunological diseases. They have been also found to possess anti-inflammatory, immunomodulating, anti-infective, antithrombotic, and metabolic effects. Their potential

Access this article online	
Website: www.isfcppharmaspire.com	**P-ISSN:** 2321-4732 **E-ISSN:** XXXX-XXXX

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

© 2020 Pharmaspire | Published by SPER Publications

as antitumoral agents is also an important biological effect primarily due to their strong antiproliferative, antimutagenic, and inhibiting autophagy capacities. Thus, acting as a new choice of treatment for various tumors along with radiotherapy and chemotherapy. Hence, the repurposing of chloroquine and HCQ is currently being examined for neurological diseases such as neurosarcoidosis, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to corticosteroids, and primary progressive multiple sclerosis. The clinical trials are going on testing these drugs in non-neoplastic and neoplastic diseases. However, their use is also safe even during pregnancy due to their good tolerability.[6]

MECHANISM OF ACTION

The mechanism of action of HCQ and chloroquine remains under continuous study in modern molecular medicine[7,8] using advanced tools in computational biology,[9] synthetic biology,[10-12] immunology,[13,14] structural biology,[15,16] and "big data"-driven public health science.[17,18] HCQ and chloroquine occur in the form of weak bases and have characteristic "deep" volume of distribution and a half-life period of 50 days. These drugs cause interference in lysosomal activity and autophagy. These drugs are found to interact with membrane stability and modify the signaling pathways and transcriptional activity resulting in the inhibition of cytokine production. Chloroquine through cathepsin signaling can initiate lysosome induced apoptosis thus causing cell death, that is, anti-tumor effect. HCQ strongly binds to melanin and can deposit in melanin-containing tissues such as the skin and the eyes, thus explaining tissue-specific mechanism.[19]

Evidence suggests that HCQ can delay or prevent organ damage,[20] including bone destruction,[21] in autoimmunity, and that this drug has antithrombotic effects.[22]

One mechanism explaining cellular level anti-inflammatory effects is by impairment of antigen presentation through the lysosomal pathway. Lysosomes contain hydrolytic enzymes and help other vesicles to digest material from outside the cell (through the endocytosis or phagocytosis pathway). Lysosomes are not only involved in recycling[23] but also in antigen processing and MHC Class II presentation thus helping in immune activation.[24] Chloroquine or HCQ also bind directly to nucleic acids at molecular level thus blocking TLR9 signaling at the intracellular level by inhibiting TLR–ligand interactions. It is important to further determine the mode of action of HCQ and chloroquine, along with safe and efficacious use at prescribed dose.

CHLOROQUINE AND ITS DERIVATIVES

HCQ and chloroquine belong to a class of drugs known as 4-aminoquinolines [Figure 1]. Quinolines, in turn, are derived from quinine, which was first isolated in 1820 from cinchona tree bark. These drugs are rapidly and completely absorbed from the gut and excreted 70% as such in the urine.[25] They usually get concentrated in liver, spleen, kidney, lungs, leukocytes, and also in melanin containing tissues. Quinine is a basic amine and is usually found in the form of salt.

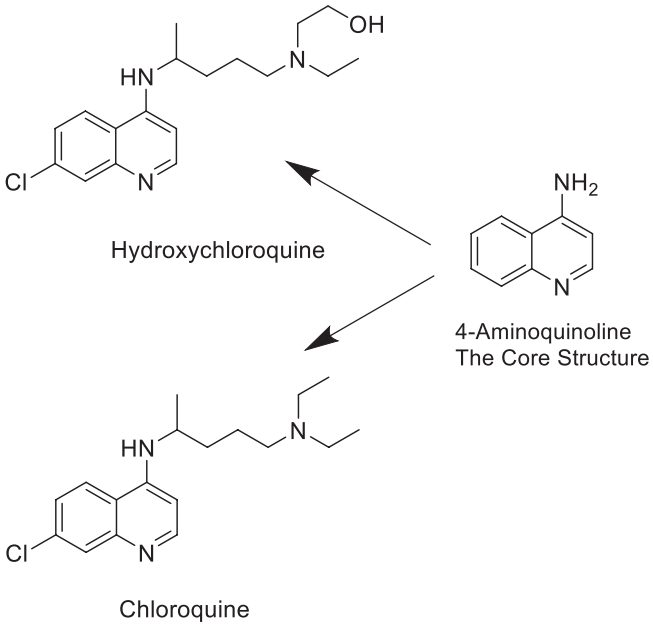


Figure 1: Chloroquine and Hydroxychloroquine from quinoline core

Various preparations include the hydrochloride, dihydrochloride, sulfate, bisulfate, and gluconate. In US, quinine sulfate is commercially available in 324-mg tablets under the brand name qualaquin. HCQ is administered as a sulfate, whereas chloroquine is administered as a phosphate salt.[19] Both HCQ and chloroquine occur as enantiomers (R and S isomers).

SYNTHETIC STRATEGIES TO CHLOROQUINE

Chloroquine, 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline can be synthesized by the reaction of 4,7-dichloroquinoline (1) with 4-ethylamino-1-methylbutylamine (2) at 180°C [Scheme 1].[26-28]

Another method consists of reacting 3-chloroaniline (3) with ethoxymethylenmalonic ester (4) to form (3-choroanilino)-methylenemalonic ester (5), which undergoes high-temperature heterocyclization to form 7-chloro-4-hydroxyquinolin-3-carboxylic acid (6). Hydrolyzation of this with sodium hydroxide gives 7-chloro-4-hydroxyquinolin-3-decarboxylic acid (7), which on further decarboxylation at 250–27°C, forming 7-chloro-4-hydroxyquinoline (8). Treatment of (8) with phosphorus oxychloride gives chloroquine [Scheme 2].[29,30]

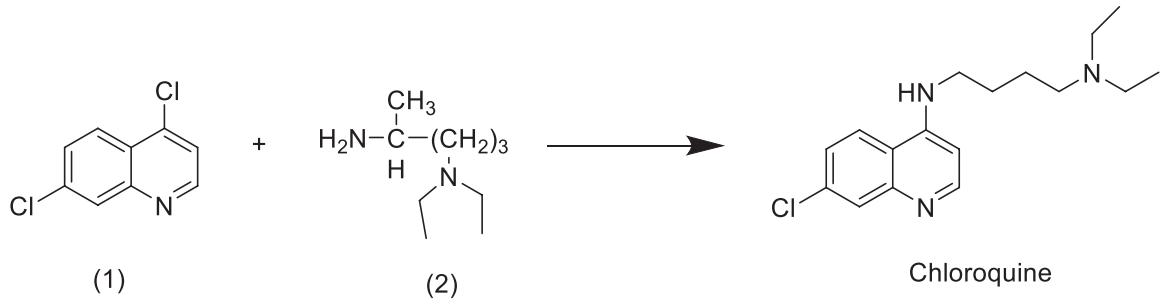
The third method consists of reacting 3-chloroaniline (3) with the ethyl ester of formylacetic acid (9) to make enamine (10), which on further heating cyclizes to 7-chloro-4-hydroxyquinoline (8). Treatment of (8) with phosphorus oxychloride gives chloroquine [Scheme 3].[31]

WHAT IS COVID-19?

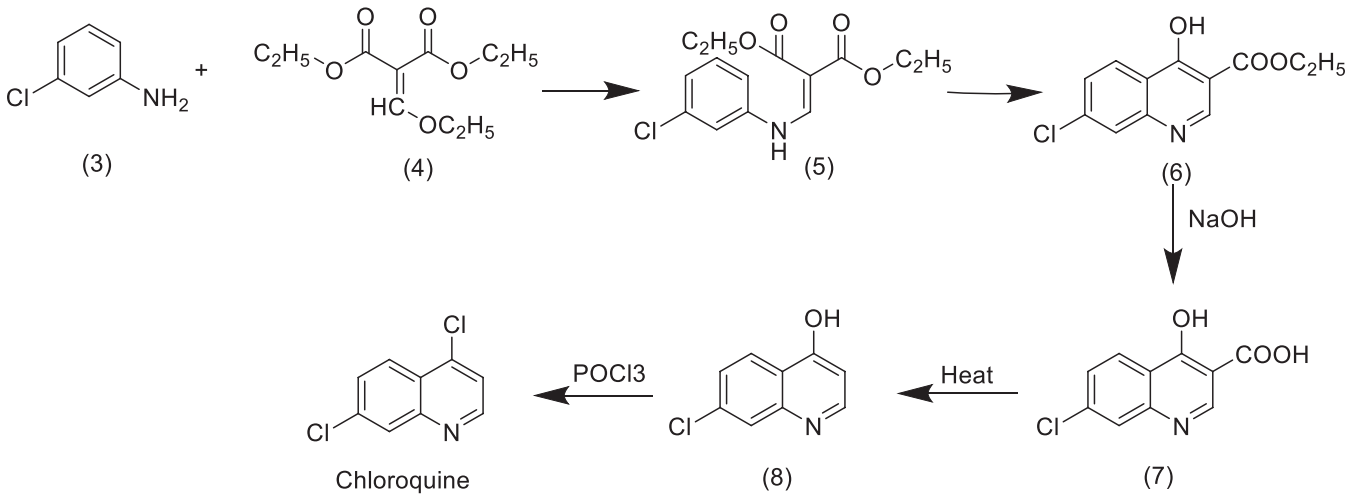
Nomenclature

Infection: Coronavirus disease 2019 or COVID-19.

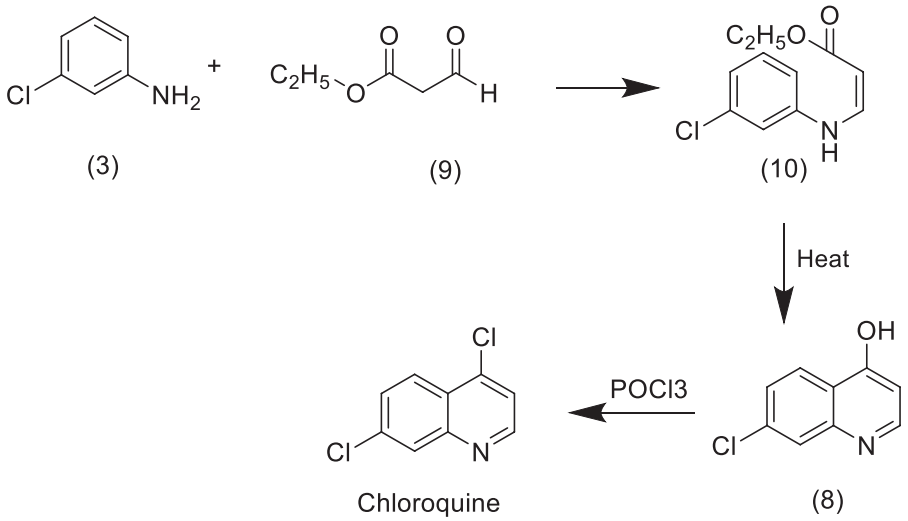
Virus: SARS-CoV-2, 2019 Novel Coronavirus.



Scheme 1: Synthesis of chloroquine



Scheme 2: Synthesis of chloroquine from ethoxymethylenmalonic ester



Scheme 3: Synthesis of chloroquine from ethyl ester of formylacetic acid

Biology

It is 30 kbp, +ssRNA enveloped coronavirus. It is likely to be a zoonotic infection whose source or reservoir is unclear (Bats/Pangolins). It is spread primarily person to person or can be by asymptomatic carriers. The viral particles enter into lungs through droplet nuclei, that is, airborne. The virus binds to ACE2 receptors on type 2 pneumocytes. However, the ACE effect is unclear. Other routes of infection are contact and enteric.

Epidemiology

- Its attack rate is 30–40%
- R_0 = 2–4
- Case fatality rate (CFR) = 2.3%
- Incubation time = 3–14 days (15 days max)
- Viral shedding = Median 20 days (Max 37 days)
- Breakdown of disease severity

- 80% Non-severe (mild pneumonia)
- 15% Severe (Hypoxia, Respiratory Distress)
- 5% Critical (Respiratory Failure)

- Disease Clusters: Conferences, Gatherings, Cruise Ships etc.
- Strategies: Handwashing, social distancing, avoid face and nose touch, and quarantine.

Diagnosis

Symptoms

- 50–80% cough
- 45% febrile on presentation
- 20–40% dyspnea
- 15% URI symptoms
- 10% GI symptoms.

Labs

- CBC: Leukopenia and lymphopenia
- BMP: Increased BUN
- LFT: Increased AST/ALT/Tbili
- ↑D-dimer, ↑CRP, ↑ LDH
- ↑ IL-6, ↑ Ferritin
- ↓Procalcitonin
- CXR: Hazy bilateral, peripheral opacities
- CT: Ground glass opacities, crazy paving, and consolidation
- POCUS: Numerous B-lines, pleural line thickening, consolidations with air bronchogram.

Isolation

- Phone call is best isolation
- Place patient in mask, single room, and limit visitors
- Move ventilator controls and IV pumps outside room if possible.

Precautions

- Contact either airborne or droplet
- N95 masks must be fit tested, wear eye protection
- PPE should be donned/doffed with trained observer
- Hand hygiene: 20+s with soap/water or alcohol containing hand gel.

Treatment

- Isolate and send PCR test early.
- GOC discussion/triage.
- Fluid sparing resuscitation and empiric antibiotics.
- Intubate early under controlled conditions: RSI, no bagging, and VL have suction and capnography connected to avoid circuit breaks.
- Avoid NIPPV unless individualized reasons exist along with helmet mask, avoid nebulizer, and bronchoscopy.
- Mechanical ventilation for ARDS.
- Consider using POCUS to screen cardiomyopathy.
- Investigational therapies such as remdesivir, HCQ, chloroquine, tocilizumab, lopinavir/ritonavir, oseltamivir, and corticosteroids.

Prognosis

Age and comobidities are significant predictors of poor clinical outcome.

ROLE OF CHLOROQUINE IN THE TREATMENT OF COVID-19

A group of Chinese researchers found that chloroquine is effective at EC_{90} of 6.9 μM using Vero E6 cells infected by SARS-CoV-2 at Multiplicity of Infection (MOI) 0.05. Studies demonstrated that chloroquine is highly effective in reducing replication of virus at a dose which is easy to maintain as it can penetrate tissues easily. It is assumed that chloroquine increases endosomial pH and thus interferes with glycosylation of the cell surface receptors of SARS-CoV-2. Thus, immunomodulation effect of this drug enhances to bring about antiviral effect.[32]

One of the studies reports the use of chloroquine phosphate in the treatment of COVID-19 associated pneumonia as highly efficacious and safe in a dose of 500 mg twice a day for 10 days.[33] The Dutch center of disease control suggested the regimen in adults which include 600 mg chloroquine base, followed by 300 mg after 12 h on day 1 then 300 mg * 2/die on 2–5 days.[34] Italian society of infectious and tropical diseases suggested use of chloroquine 500 mg * 2/die or HCQ 200 mg die for 10 days varying from 5–20 days.[35]

CONCLUSION

The chloroquine or HCQ is considered as the need of present situation to fight with COVID-19. More research is required in this field to find out the exact mechanism of chloroquine action in treatment of COVID-19 and to rule out its dose and dose regimen. Thus, chloroquine can be considered as effective drug for the treatment of novel coronavirus but lot more work is required in this direction. Along with chloroquine, other drugs can be considered as "repurposing" in this field.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

REFERENCES

1. Savarino A, Boelerat JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infection: An old drug on todays's disease? Lancet Infect Dis 2003;3:722-7.
2. Colson P, Rolain JM, Raoult, D. Chloroquine for the 2019 novel coronavirus SARS CoV-2. Int J Antimicrob Agents 2020;55:1-2.
3. Vesterinen HM, Connick P, Irvine CM, Sena ES, Egan KJ, Carmichael GG, *et al*. Drug repurposing: A systematic approach to evaluate candidate oral neuroprotective interventions for secondary progressive multiple sclerosis. PLoS One 2015;10:1-18.
4. Nathalie CC, Dunogué B, Leroux G, Nathalie M, Jallouli M, Le Guern V, *et al*. A critical review of the effects of hydroxychloroquine and chloroquine on the eye. Clin Rev Allergy Immunol 2015;49:317-26.

5. Costedoat N, Hulot JS, Amoura Z. Cardiomyopathy related to antimalarial therapy with illustrative case report. Cardiology 2006;107:73-80.
6. Plantone D, Koudriavtseva T. Current and future use of chloroquine and hydroxychloroquine in infectious, immune, neoplastic, and neurological diseases: A mini review. Clin Drug Investig 2018;38:653-71.
7. Flannery EL, Chatterjee AK, Winzeler EA. Antimalarial drug discovery approaches and progress towards new medicines. Nat Rev Microbiol 2013;11:849-62.
8. Ridley RG. Medical need, scientific opportunity and the drive for antimalarial drugs. Nature 2002;415:686-93.
9. Minie M. CANDO and the infinite drug discovery frontier. Drug Discov Today 2014;19:1353-63.
10. Paddon CJ. High level semi synthetic production of the potent antimalarial artemisinin. Nature 2013;496:528-32.
11. Hale V. Microbially derived artemisinin: A biotechnology solution to the global problem of access to affordable antimalarial drugs. Am J Trop Med Hyg 2007;77:198-202.
12. Mitchell W. Natural products from synthetic biology. Curr Opin Chem Biol 2011;15:505-15.
13. Conway DJ. Paths to a malaria vaccine illuminated by parasite genomics. Trends Genet 2015;31:97-107.
14. Karunamoorthi K. Malaria vaccine: A future hope to curtail the global malaria burden. Int J Prev Med 2014;5:529-38.
15. De Beer TA, Wells GA, Burger PB, Joubert F, Marechal E, Birkholtz L, *et al*. Antimalarial drug discovery: *In silico* structural biology and rational drug design. Infect Disord Drug Targets 2009;9:304-18.
16. Vedadi M, Lew J, Artz J, Amani M, Zhao Y, Dong A, *et al*. Genome scale protein expression and structural biology of Plasmodium falciparum and related Apicomplexan organisms. Mol Biochem Parasitol 2007;151:100-10.
17. Buckee CO, Wesolowski A, Eagle NN, Hansen E, Snow RW. Mobile phones and malaria: Modeling human and parasite travel. Travel Med Infect Dis 2013;11:15-22.
18. Hay SI, George DB, Moyes CL, Brownstein JS. Big data opportunities for global infectious disease surveillance. PLoS Med 2013;10:1-14.
19. Schrezenmeier E, Dörner T. Mechanisms of action of hydroxychloroquine and chloroquine: Implications for rheumatology. Nature 2020;16:155-66.
20. Akhavan PS, Su J, Lou W, Gladman DD, Urowitz MB, Fortin PR. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. J Rheumatol 2013;40:831-41.
21. Mok CC, Mak A, Ma KM. Bone mineral density in postmenopausal Chinese patients with systemic lupus erythematosus. Lupus 2005;14:106-12.
22. Petri M. Use of hydroxychloroquine to preventvthrombosis in systemic lupus erythematosus andvin antiphospholipid antibody positive patients. Curr Rheumatol Rep 2011;13:77-80.
23. Ballabio A, Bonifacino JS. Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat Rev Mol Cell Biol 2019;21:101-18.
24. Lotteau V, Teyton L, Peleraux A, Nilsson T, Karlsson L, Schmid SL, *et al*. Intracellular transport of class II MHC molecules directed by invariant chain. Nature 1990;348:600-5.
25. Popert AJ. Chloroquine: A review. Rheumatol Rehabilit 1976;15:235-9.
26. Andersag H, Breitner S, Jung H. Quinoline Compound and the Process of Making the Same, United States Patent No. 2, 233, 970; 1941.
27. Andersag H, Breitner S, Jung H. Germany. German Patent No. 683, 692; 1939.
28. Drake NL, Creech HJ, Garman JA, Haywood ST, Peck RM, Van Hook JO, *et al*. Synthetic antimalarials. the preparation and properties of 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN-7618)[1,2]. J Am Chem Soc 1946;68:1214-6.
29. Price CC, Roberts RM. The synthesis of 4-hydroxyquinolines.1 I. through ethoxymethylene malonic ester. J Am Chem Soc 1946;68:1204.
30. Ch FG, Rice LM. United States Patent No. 2, 947, 664; 1960.
31. Northey EH, Dreisbach PF. United States Patent No. 2, 478, 125; 1949.
32. Wang M, Cao R, Zhang I, Yang X, Liu J, Xu M, *et al*. Remdesivir and chloroquine effectively inhibit recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res 2020;30:269-71.
33. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of CoVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14:72-3.
34. Available from: http://www.lci.rivm..nl/covid-19/bijlage/behandeladvies. [Last accessed on 2020 Mar 06].
35. Available from: http://www.simit.org/medias/1555-covid-19-linee-guida-trattamento-01.mar.pdf. [Last accessed on 2020 Mar 06].