COMMENTARY

Treatment options in people with COVID19: Selecting the best armamentarium against the novel virus

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Abstract

Novel coronavirus disease (COVID-19) infection is a global pandemic, of high infectivity, variable mortality, with currently no established treatment. This review summarizes different molecules which are being evaluated for COVID19 treatment. PubMed and Medline, search for articles published to March 2020 was done using terms "COVID19" OR "corona-virus 2019" OR "2019-nCoV" or "severe acute respiratory syndrome coronavirus" AND "treatment". As of today, we have >350 RCTs happening with different agents. COVID19 treatment agents can be broadly classified into immuno-modulators (prevent hyperimmune-activation and cytokine storm) and anti-viral therapies (prevent virus entry, replication or viricidal). Hydroxychloroquine/chloroquine, Interferon-λ, glucocorticoids, interleukin antagonists, Ulinastatin, intravenous immunoglobulins, plasmapheresis are main immunomodulators showing initial positive outcomes. Umifenovir. Lopinavir/Ritonavir, Ribavirin, remdesivir and Ravipiravir are some of the major antiviral agents showing initial encouraging results. It may be concluded that the most successful regimen is going to be multi-drug therapy, a combination of immunomodulatory agent with anti-viral agent.

Keywords: COVID19, Wuhan virus, hydroxychloroquine, remedesevir, antihelminth, anti-cytokine therapy, antiviral.

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Introduction

Novel coronavirus disease (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a dreaded pandemic sweeping across the globe, having a mortality of 2-6%.[1] What is concerning is the fact that most of the dead and critical patients on life-support did not have severe disease to start with, and had mild upper respiratory symptoms, fever and myalgias.[2] Death in COVID-19 is due to hyperactivation of the immune system, specifically macrophage activation syndrome (MAS), leading to a cytokine storm, acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS), which occurs suddenly and rapidly.[1,2] The enigma remains as to determine, which of the patients with mild symptoms will deteriorate rapidly. Elderly population, people living with comorbidities like diabetes, hypertension, cardiovascular disease have been noted to have higher mortality. High infectivity, ability to transmit exponential in populations, resulting in overwhelming of the medical infrastructure are some of the grave issues with COVID19. There has been a frantic search to develop definitive treatment options for the COVID19. This review summarizes the different molecules which are being evaluated and are in varying stages of approval for the treatment of COVID19.

Methods

PubMed and Medline, search for articles published to March 2020 was done using the terms "COVID19" [MeSH] OR "corona-virus 2019" [All fields] OR "2019-nCoV" [All Fields] or "severe acute respiratory syndrome coronavirus: [All Fields] AND "treatment" [All fields]. The reference lists of the articles thus identified were also searched. The search was not restricted to English-language literature.

Results

A total of 891 articles were found for a search done till 20th April 2020, of which 289 studies were clinical studies in human, which were further evaluated in detail.

It must be realized that till date we do not have any definitive therapy for COVID19. We have no validated data from randomized controlled trials (RCTs) for treatment as well as for prevention/prophylaxis for COVID19. A lot of treatment options are being evaluated across the globe. As of today, we have more than 350 RCTs happening with different agents. The key to develop treatment for COVID19 is to determine what are the

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Table-1: Pharmacotherapy under evaluation for managing COVID19.

Immuno-modulators	Anti-viral agents
Hydroxychloroquine/chloroquine*	
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Interferon-λ	Umifenovir
glucocorticoids	lopinavir/ritonavir
interleukin antagonists	Ribavirin
Ulinastatin	Remedesivir
intravenous immunoglobulins	Ravipiravir
Plasmapheresis/renal replacement therapy	Anti-helminthic agents

*Has both immunomodulatory and antiviral properties.

predictors of poor outcomes, and trying to address them may improve outcomes in COVID19 infection.

COVID19 and the immune response: making sense

High levels of pro-inflammatory cytokines (IL-1b, interferon (IFN)-α, IP-10, and monocyte chemoattractant protein 1 (MCP-1)) have been detected in people with COVID-19 infection, which in turn activates T-helper type 1 (Th1) cell response.[2] It must be noted that TNFa levels are not starkly elevated when compared to the IL1 and IL6 levels in patients with COVID19 infection.[2] Increased viral load also contributes to the increased cytokine response. This increase cytokine levels cause pulmonary and interstitial tissue damage leading to ARDS. Lung involvement severity, Multiple organ dysfunction syndrome (MODS) and mortality correlates well with the increased cytokine levels (cytokine storm) in COVID19 infection.[2] However, what is unique in COVID19 and not seen in SARS and MERS, is the increased levels of cytokines which inflammatory response (IL-4 and IL-10).[3] Why this occurs is not well understood yet, and may reflect body's attempt to tone down the hyper-immune response.

Hence potential treatment for COVID19 can be classified based on the mechanism they are likely to work on:

1) Immuno-modulators: They prevent hyperimmune activation and the related cytokine storm

2) Anti-viral therapies: They prevent either the virus entry into the cell or their replication, kills the virus and prevent the subsequent hyper-immune activation of the patient.

Immunomodulators under evaluation for COVID19

Hydroxychloroquine/Chloroquine

Hydroxychloroquine (HCQ) and chloroquine (CQ) have similar structure and mechanism of action. The hydroxyl group in hydroxychloroquine makes it less permeable to blood retina barrier, making it more retina safe compared to chloroquine. Multiple mechanism of action has been attributed to HCQ/CQ. HCQ/CQ inhibits the glycosylation of angiotensin-converting enzyme 2 (ACE2) receptor in intestine, heart, kidneys and lung, thus inhibiting the virus entry into the body and cells. HCQ/CQ increase endosomal pH and interferes with the glycosylation of cellular receptor of SARS-CoV.[4,5] Through alkalinisation of lysosome pH HCQ/CQ inhibits expression of cathepsin, thus inhibiting formation of autophagosome, which prevents cell death and spread of virus in the body.[4,5] Its attenuation of cytokine production (inhibits the production of IL6 and TNFα) and lymosomal inhibition may explain its immunomodulatory role, which explains its extensive use in rheumatologic disorders like lupus, rheumatoid arthritis among others.[6] Thus HCQ/CQ has both immunomodulatory as well as anti-viral properties.

Unpublished data from China involving more than 100 patients with COVID19 has suggested improvement in Chest X-ray findings, viral clearance and decreasing the rate of disease progression with CQ.[7] A highly publicized small open labelled RCT from France open-label nonrandomized French study involving 20 patients in the HCQ group (600mg/day) and 16 in the control group, documented increased virologic clearance (nasopharyngeal swab PCR) in the HCQ group (70%) as compared to the control group (12%; $P<0.01$).[8] The same group also reported that addition of azithromycin to HCQ in 6 patients with COVID19 infection resulted in an even better virologic clearance (100% va 57% in the dual therapy vs HCQ monotherapy).[8] However, it must be remembered that Azithromycin, a macrolide antibiotic is a cytochrome inhibitor, and increases the half-life of HCQ, which may increase the risks of side effects associated with HCQ, both cardiac and ocular. There are other reports which has seen no benefit with the use of HCQ/CQ.[9] Hence it is very important to determine which are the patients and at what stage of COVID19 infection would HCQ/CQ give the best results. Currently there are severe studies on with both HCQ/CQ evaluating their role in prophylaxis from COVID19 infection in health care workers as well as for treatment in patients.[9] As per the American Association of Ophthalmology in their 2016 statement, the daily dose of HCQ should be kept <4-5 mg/kg-weight/day to reduce the risk of retinal toxicity.[10] The corresponding safe dose of chloroquine would be less than 2-3mg/kg-weight/day.[10]

Interferon-λ

Interferon-λ activates the anti-viral genes in the alveolar epithelial cells (AECs) in the lung, the primary site of attack of the COVID19 virus. Hence it has some antiviral activity and prevents immune activation. Administration of Interferon-λ early in the course of COVID19 infection has been shown to decrease viral load and improve outcomes.[11,12] The challenge remains how to screen people with COVI19 infection when they are almost asymptomatic. Clinical response with Interferon-λ especially the pegylated versions in admitted sick patients have largely been disappointing.[13]

Glucocorticoids

Glucocorticoids are commonly used in autoimmune disorders cause of their broad anti-inflammatory and immunosuppressive properties. Glucocorticoids worked as effective anti-inflammatory agents during the 2003 SARS epidemic.[14,15] The key was to administer glucocorticoids early in the course of disease, which lead to improvement in oxygenation, X-ray chest features and earlier resolution of fever.[14,15] However, early treatment of COVID19 patients with glucocorticoids have shown to increase the viral load and disease aggravation in few reports.[16] The reason for this diametrically opposite response to infection by 2 different viruses of the same family is not known. As of date, use of glucocorticoids is recommended only in severely ill COVID19 patients with florid cytokine storm (methylprednisolone 1-2mg/kg/day or equivalent for 3-5 days) to prevent ARDS and MODS.[17] Glucocorticoids should be avoid in the initial stages of COVID19.

Interleukin-1 antagonists

Anakinra, an antagonist of IL-1β has been effectively used to treat the cytokine storm associated with infection related severe sepsis, improving the 28-day survival.[18] However, we currently do not have any data on the effectiveness of anakinra in COVID19 infection.

Interleukin-6 antagonists

Tocilizumab (IL6 antagonist) is used in rheumatology to manage rheumatoid arthritis, and cytokine storm secondary to vasculitis and other autoimmune disorders.[19] Tocilizumab (at 4-8mg/kg, 2 doses 12 hours apart, slow iv infusion) has been found to be effective in patients with severe COVID19 infection and raised IL6 levels, in reports from China.[2]

Ulinastatin

Ulinastatin, a natural anti-inflammatory substance in the body, used in the treatment of pancreatitis and acute circulatory failure, has the advantage of not having the immunosuppressive properties of glucocorticoids.[20] It may have great potential in managing the cytokine storm of COVID19 infection.

Intravenous immunoglobulin (IVIG)

IVIG has been tried in some of the severely ill patients with COVID19 infection at Wuhan, with mixed outcomes.[21] IVIG has dual role immune substitution and immunomodulation and is an area of active research for COVID19 treatment.

Blood purification/chelation therapies

Plasma exchange/filtration to filter away the excess cytokines has been shown to be an effective way of managing cytokine storm. They have been found to be useful in some of the patients with COVID19 infection.[22] Early renal replacement, artificial liver technology also works on the same principles.

Anti-viral therapies for COVID19

Umifenovir

Oseltamivir, approved for treatment of influenza has no impact against the SARSCoV-2 (the COVID19 virus). Umifenovir, a drug of the same family, which targets the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope, based on invitro studies is being evaluated in COVID19.[23] Umifenovir is approved in Russia and China for influenza treatment. The recommended dose is 200mg thrice daily for 9 days.[24] The current evidence is from small unblinded RCTs. There is an urgent need for larger better quality studies before it can be recommended for use in COVID19.

Lopinavir/Ritonavir (LoRi)

LoRi is approved for the treatment of HIV infection. LoRi has been found to be beneficial in inhibiting other coronaviruses by not the COVID19 virus.[25,26] A systematic review showed limited benefits of LoRi in SARS and MERS infection.[25,26] In SARS, LoRi works best when initiated during the early course of the disease (early peak viral replication phase; initial 7-10 days). No benefits were seen when started in more severe disease and sick patients.[25] A small open labelled RCT of LoRi in COVID19 infection involving 199 patients did not document any significant better outcomes in the treatment as compared to the control group.[27] Suggested dosing is 400mg of lopinavir with 100mg of ritonavir twice daily for 14 days.[9] Nausea, diarrhoea and hepatoxicity (2-10%) are the major side effects of this regimen. Transaminitis due to any cause

(including COVID19) is a contraindication for the use of LoRi.

Ribavirin

Ribavirin, an inhibitor of RNA dependent RNA polymerase, should ideally work in COVID19. However, it has previously been found to be effective in SARS infection (systematic review found the drug to be ineffective in 26 out of 30 studies; 4 studies reporting potential harm due to hepatotoxicity and hemolytic anemia).[28] There is as of now no conclusive data to recommend the same in COVID19.

Remdesivir

Remedesivir is a relatively new antiviral agent with limited clinical experience. It was first clinically used in the Ebola virus outbreak.[29] There are case reports of benefits of use of Remedesivir in COVID19. Currrently there are several ongoing RCTs to evaluate the efficacy and safety of Remdesivir in COVID19.[9,30] The molecule was recently hyped up by the president Trump of America in his press briefings.

Favipiravir

Favipiravir inhibits the RNA polymerase halting viral replication, and has previously been found to be effective against influenza and Ebola virus.[31] There are isolated case reports and data from an RCT suggesting the benefit of Favipiravir in COVID19 infection. There are several ongoing RCTs evaluating Favipiravir in COVID19.

Anti-helminthic agents

Nitrazoxanide, an anti-helminthic agent with good safety profile, has been shown to have anti-viral activities against SARS-CoV2 in invitro studies. RCTs are undergoing evaluating its safety in COVID19.[32] A lot of interest has been generated with regards to another anti-helminthic agent, ivermectin in COVID19.[33] Currently several trials are on evaluating the same.

Conclusion

Considering the exponential spread of COVID19 across the globe, establishing the perfect treatment regimen against the SARS-CoV2 is a race against time for the global medical community. As of now we have no concrete evidence to recommend a particular drug or regimen. Based on the above data, it is likely that the most successful regimen is going to be multi-drug therapy, being a combination of immunomodulatory agent with anti-viral agent. It is not only important to know which are the molecules which will work the best, but perhaps even more important is when in the disease course to start these drugs for the best clinical outcomes. The next few weeks to months shall give us some definitive answers in the war against COVID19.

References

1. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis. 2020;pii: S1201-9712(20)30136-3.
2. Qing Ye MD , Bili Wang MS , Jianhua Mao MD , Cytokine Storm in COVID- 19 and Treatment, Journal of Infection (2020), doi: https://doi.org/10.1016/j.jinf.2020.03.037
3. Chen L, Liu H-G, Liu W, Liu J, Liu K, Shang J, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. Chin J Tuberc Respir Dis. 2020;43.
4. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother. 2020;dkaa114. doi:10.1093/jac/dkaa114
5. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? Int J Antimicrob Agents. Published online March 11, 2020. doi:10.1016/j.ijantimicag.2020.105938
6. J G, Z T, X Y. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Bioscience trends. 2020;14(1):72-3.
7. 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(1):72-73.
8. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. Published online March 20, 2020. doi:10.1016/j.ijantimicag.2020.105949
9. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020 Apr 13. doi: 10.1001/jama.2020.6019
10. Sharma M, Kumar M, Dutta D. Hydroxychloroquine in diabetes and dyslipidaemia: primum non nocere. Diabet Med. 2019 Sep 26. doi: 10.1111/dme.14144.
11. Arabi YM, Shalhoub S, Mandourah Y, Al-Hameed F, Al-Omari A, Al Qasim E, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clinical Infectious Diseases. 2019.
12. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. The Lancet Infectious Diseases. 2014 2014/11/01/;14(11):1090-5.
13. Zumla A, Chan JFW, Azhar EI, Hui DSC, Yuen K-Y. Coronaviruses - drug discovery and therapeutic options. Nature Reviews Drug Discovery. 2016 2016/05/01;15(5):327-47.
14. Ho JC, Ooi GC, Mok TY, Chan JW, Hung I, Lam B, et al. High-dose pulse versus nonpulsecorticosteroid regimens in severe acute respiratory syndrome. American journal of respiratory and critical care medicine. 2003;168(12):1449-56.
15. Yam LY-C, Lau AC-W, Lai FY-L, Shung E, Chan J, Wong V, et al. Corticosteroid treatment of severe acute respiratory syndrome in Hong Kong. The Journal of infection. 2007;54(1):28-39.
16. Auyeung TW, Lee JSW, Lai WK, Choi CH, Lee HK, Lee JS, et al. The use of corticosteroid as treatment in SARS was associated with adverse outcomes: a retrospective cohort study. The Journal of infection. 2005;51(2):98-102.
17. Zhou Y-H, Qin Y-Y, Lu Y-Q, Sun F, Yang S, Harypursat V, et al.

Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomized controlled trial. Chin Med J. 2020 (00):E020-E. chi.
18. Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 Receptor Blockade Is Associated With Reduced Mortality in Sepsis Patients With Features of Macrophage Activation Syndrome: Reanalysis of a Prior Phase III Trial. Critical care medicine. 2016;44(2):275-81.
19. Tanaka T, Narazaki M, Kishimoto T. Immunotherapeutic implications of IL-6 blockade for cytokine storm. Immunotherapy. 2016;8(8):959-70.
20. H W, B L, Y T, P C, L Y, B H, et al. Improvement of Sepsis Prognosis by Ulinastatin: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Frontiers in pharmacology. 2019;10:1370
21. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020 2020/02/15/;395(10223):507-13.
22. K X, H C, Y S, Q N, Y C, S H, et al. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. Zhejiang da xue xue bao Yi xue ban. 2020;49(1):0. PubMed PMID: 32096367.
23. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc Natl Acad Sci U S A. 2017;114(2):206-214.
24. Wang Z, Yang B, Li Q,Wen L, Zhang R. Clinical Features of 69 cases with coronavirus disease 2019 In Wuhan, China. Clin Infect Dis. Published online March 16, 2020. doi:10.1093/cid/ciaa272
25. Yao TT, Qian JD, ZhuWY,Wang Y,Wang GQ. A systematic review of lopinavir therapy for SARSvcoronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. [published online February 27, 2020]. J Med Virol. 2020. doi:10.1002/jmv.25729
26. Chan KS, Lai ST, Chu CM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J. 2003;9 (6):399-406.
27. Cao B,Wang Y,Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. N Engl J Med. Published online March 18, 2020. doi:10.1056/NEJMoa2001282
28. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006;3(9):e343. doi:10.1371/journal.pmed.0030343
29. Jacobs M, Rodger A, Bell DJ, et al. Late Ebola virus relapse causing meningoencephalitis: a case report. Lancet. 2016;388(10043):498-503.
30. Kujawski SA,Wong K, Collins JP, et al. First 12 patients with coronavirus disease 2019 (COVID-19) in the United States. medRxiv. Preprint posted March 9, 2020. doi:10.1101/2020.03.09.20032896
31. Sissoko D, Laouenan C, Folkesson E, et al; JIKI Study Group. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea [published correction appears in PLoS Med. 2016;13(4): e1002009]. PLoS Med. 2016;13(3):e1001967. doi: 10.1371/journal.pmed.1001967
32. Rossignol JF. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. J Infect Public Health. 2016;9(3):227-230. doi:10.1016/j.jiph.2016.04.001
33. Patrì A, Fabbrocini G. Hydroxychloroquine and ivermectin: a synergistic combination for COVID-19 chemoprophylaxis and/or treatment? J Am Acad Dermatol. 2020 Apr 10. pii: S0190-9622(20)30557-0.