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Review Article

COVID19: State of the Art of Antiviral Management

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Abstract

The state of the art in terms of antiviral management of COVID19 is currently the most frequently addressed topic by researchers around the world, given the contingency of the pandemic. Despite more than half a year have passed since the first reported cases in China's Wuhan Province, there is no high-efficiency therapeutic scheme that could be considered as the world's leading arms. It is in this context that the preliminary benefit demonstrated in studies by most candidate drugs will be tested over the months. An important step in the progress towards understanding the disease was the establishment of 2 clinical phases: the first of viral replication and the second of systemic inflammation or "cytokine storm". This knowledge allowed the application of drugs with a specific target in decreasing viral replication and final viral load in the first week of the disease and using drugs aimed at decreasing the inflammatory reaction for the next weeks of disease. The use of "redirected" drugs pending definitive results in the area of vaccinology becomes the quick outlet available for public health systems in this pandemic struggle.

Keywords: *COVID-19; Antivirals; Corticosteroids; Treatment (COVID-19, Antiviral, Corticosteroids, Treatment)*

Introduction

Coronavirus disease (COVID19) spreads rapidly worldwide in July 2020, more than half a year after its appearance in Wuhan, China, however, there are still no definitively effective vaccines or proven treatments available to mitigate the pandemic. With more than 11,500,000 cases and half a million deaths, the numbers continue to scale globally, with epicentres in America at this time, but with re-outbreaks in countries in Europe and Asia. A July 2020 study [1] using artificial intelligence revealed that of 31 compounds with viral antiprotease activity, the best therapeutic alternatives were Remdesivir, Valrubicin, Aprepitant and Fulvestrant, given their preferential affinity for the viral enzyme. A compound called "nCorvEMBS", which has not yet indexed in any chemical database but had been demonstrated kinship to viral protease and is in preliminary stages of clinical application. Several drugs are now testing in an attempt to manage the disease, but there are no established guidelines with proven effectiveness. The results to date are variable: Remdesivir has decreased hospitalization and mortality rates, but it does not yet have the endorsement of large-scale studies [2], on the other hand, both Lopinavir/Ritonavir and Hydroxychloroquine were abandon due to apparent lack of efficacy in various scientific papers [3]. One of the most critical points that would allow overcome the current moment of the pandemic is to obtain a vaccine that guarantees a safe immunization and to reach new living standards before January 2020. The genetic variation suffered by SARS-CoV-2 does not allow for anticipation when a high-efficiency vaccine will be given [4]. In this article, we will mention potential candidates to establish themselves as first-line drugs in the following months.

Corticoid treatment

At the beginning of the pandemic, the use of anti-inflammatory was called into question. However, the last published evidence supports the use of corticoids with a high quality of evidence in the early stage of severe COVID [5,6] for example tocilizumab alongside dexamethasone to exert synergy and inhibit the cytokine storm produced by SARSCoV-2 [4]. Statistical significance was found with early administration of tocilizumab and corticosteroids to patients in terms of admission to intensive care and death units (6.25% in the "early" initiation group in the first 24 hours of hospitalization and with paO_2/FiO_2 above 250, 45.3% in the late treatment group) [5]. The transcendent role of corticosteroids as immunomodulators is established from 7 days of onset of the case and in patients with increasing hypoxemia, hospitalized and with severe disease. Dexamethasone is useful in patients weighing more than 40 kg and Tanner greater than 3, at doses of 6 mg/day for ten days or until hospital discharge, whichever was shorter. According to a randomized preliminary study, not yet published and conducted in the UK, oral or intravenous dexamethasone reduces mortality to 28 days in hospitalized patients compared to patients with standard care. More than 2000 patients in the subgroup mortality results were enrolled as shown below: Overall: 17% reduction (21.6 versus 24.6%, age-adjusted relative risk (RR) 0.83, 95% CI 0.74 to 0.92). Patients with invasive mechanical ventilation or ECMO: 35% reduction (29 versus 40.7%, RR 0.65, 95% CI 0.51 to 0.82). Patients with noninvasive oxygenation (including noninvasive ventilation): 20% reduction (25 versus 21.5%, RR 0.80, 95% CI 0.70 - 0.92). In this study the average age of patients was 59 years and unfortunately the same efficacy could not be demonstrated in the subgroup over 65 years of age. In patients without supplemental oxygenation or mechanical ventilation requirements, a higher mortality trend was seen (17 versus 13.2%, RR 1.22, 95% CI 0.93 - 1.61) when used in these mild to moderate cases.

IL-6 metabolic pathway inhibitors

Tocilizumab

The association to poor prognosis of biomarkers as dimer D, ferritin, IL-6, is established for COVID19 and is the basis of the "cytokine storm" phase of the disease. Tocilizumab is a monoclonal antibody targeting IL-6. Patients with severe COVID19 have a higher proportion of pathogenic T cells and inflammatory monocytes than patients who make mild to moderate forms of the disease, they may have a much more marked secretion of IL-6, the uncontrolled cytokine storm associated with increased mortality. The dosage of tocilizumab in clinical trials was 8 mg/kg (maximum dose of 800 mg/dose) in single-dose that may be administered at 12 hours in case of no improvement. In a study conducted in China, the efficacy of tocilizumab was evaluated in 15 patients with COVID19 and a moderate to a critical clinical condition, taking as parameters the decrease in levels of IL-6 and C-reactive protein. Patients who received more than one dose were more prone to clinical improvement, although the sample size is small [8]. In another study published in May 2020, the use of tocilizumab in patients with severe COVID19 led to an improvement in ferritin levels, C-reactive protein and D-dimer, with a progressive increase in the ratio of oxygen blood pressure related to the inspired fraction of the same (with means for paO_2/FiO_2 at hospital admission, day 7^{th} and day 14^{th} of treatment, at values of 152, 283 and 302, respectively, with $p < 0.001$) [9]. A retrospective case and control study conducted in France compared the evolution of patients treated with tocilizumab versus patients without this drug and analysed the proportion of deaths or admission to intensive care units. Patients with tocilizumab (n-20) had higher comorbidities, more severe clinical status (oxygen therapy at hospital admission (13 L/min vs 6 L/min, $p < 0.001$) and worse laboratory parameters (severe lymphopenia and higher levels of C-reactive protein, p-0.017) than patients with tocilizumab (n-25). However, death or admission to critical care units was higher in patients without tocilizumab (72% versus 25%, p-0.002) [10]. Lymphopenia has been considered a prognostic factor in COVID19 [11]. In the Xiaoling Xu study and collaborators [12], tocilizumab showed to improve lymphocyte count and C-reactive protein levels in 52.6% of patients at the 5^{th} days of treatment.

Vitamin D

Low vitamin D levels are associated with worse progression in patients with COVID19. In a study conducted in the UK, only 19% of patients admitted to the critical care unit had vitamin D levels above 50 nmol/L versus 39.1% of those not at intensive care (p-0.02) [13]. Vitamin D is involved in improving innate immunity at physical barrier points (maintenance of cell junctions, especially gap junctions), natural cellular immunity (Natural Killer cells) and adaptive immunity (cytokine storm decrease, inhibition of Th1 response). A recent review supports a vitamin D role in reducing the risk of illness or death from COVID19 [14-16]. Studies carried out in European populations in different countries following the respective peaks of the pandemic did not reach definitive conclusions on the direct link of low vitamin D levels and the severity of COVID19 cases. However, there is a tendency to link adequate serum levels of vitamin D as protectors against the negative evolution of the disease. The current medical literature shows as protective ingestion of 250 g/day for a month, effectively raising levels of 25 (OH) D to the optimal range of 75 - 125 nmol/L. The dose may be reduced to 100 g/day after one month to maintain circulating levels of 25 (O) D [17,18].

Convalescent plasma

Convalescent plasma is gathered from the blood of patients who suffered from the disease, and the theoretical basis is the use of antibodies as neutralizing agents on viral particles, avoiding binding to specific molecular receptors. Early administration of convalescent plasma before the onset of the acute exacerbation period of the disease (or cytokine storm phase) is the right time for greater usefulness given the proposed mechanism of action. Several cares should be taken into account in patients receiving convalescent plasma, for example avoiding volume overload considering that the lungs heavily inflamed by the infectious process already usually condition a certain degree of interstitial oedema [19,20]. Taking into account the updated information on its application to COVID19, there are no better prospects for becoming an appropriate therapeutic alternative. A systematic review of Cochrane [21] on a total of 5443 participants in 20 studies, of which 5211 received convalescent plasma, there is little certainty about any effect on mortality ((RR) 0.89, IC 95% 0.61 to 1.31; low evidence of effectiveness), on the delay of the occurrence of the event "death" ((HR) 0.74, 95% CI 0.30 to 1.82; low evidence of effectiveness) and the improvement of clinical symptoms ((RR) 1.20, IC 95% 0.80 to 1.81; low evidence of efficacy).

Reverse transcription inhibitors

Remdesivir

It is an adenosine nucleotide analogue previously used in the treatment of Ebola and MERS-CoV, in which potent activity against coronavirus *in vitro* had been shown. Its mechanism of action is to inhibit viral dependent RNA polymerase [22], competing with adenosine and causing the rising chain to terminate in 3 to 4 subsequent base pairs during viral RNA replication [23]. It is one of the potential candidate drugs to have a pillar role in the treatment of COVID19 [24,25]. It is authorized to be used by the FDA (USA) in patients with severe COVID-19 (determined by SaO_2 less than 94% breathing ambient air, need for supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) [26], to 200 mg IV on day 1 followed by 100 mg/day for ten days in patients with mechanical respiratory assistance or ECMO, and 5 days in total in other patients. The paediatric dosage is 5 mg/kg (loading dose) on day 1, then maintenance doses at 2.5 mg/kg [27]. Its main contraindications are hepatitis or glomerular filtering less than 30 mL/minute/1.73m^2. A randomized double-blind study developed in China [2] included 237 patients with severe covid19, with no significant differences between the compared groups (remdesivir versus placebo) the limitations of a single patient with mechanical respiratory assistance, the planned sample size had not been reached and the use of multiple additional drug schemes and that patients in the remdesivir group had a higher proportion of comorbidities. A multinational [28], randomized, placebo-controlled study included 1063 patients with COVID-19 and pneumonia, 89% of them with severe disease and 26% in invasive mechanical ventilation or ECMO to enrolment, demonstrating a benefit to achieving early medical discharge (median 11 versus 15 days with placebo, RR 1.32, CI 95% 1.12 - 1.55 $p < 0.001$)

and statistically non-significant trend to a decreased mortality at 14 days of treatment (7.1 versus 11.9% compared to placebo, HR 0.70, CI 95% 0.47 - 1.04). In the subgroup of patients with supplemental oxygen but without mechanical respiratory assistance, mortality was significantly reduced (2.5 versus 11%, HR 0.22, CI 95% 0.08 - 0.58). Beigel and collaborators [29], suggest initiating medication before the onset of hypoxia, a recommendation that follows the logic of inhibiting viral replication before day 7 (which is the turning point to move to the cytokine storm stage).

Favipiravir

It is a purine analogous triphosphate with intense inhibitory activity on viral-dependent RNA SARSCoV-2, used in Japan as an anti-influenza. Its spectrum of action encompasses RNA viruses in general. An open non-randomized study with 80 patients conducted in China identified a reduction in SARSCoV-2 elimination time when compared to historical controls treated with lopinavir/ritonavir ($p < 0.001$) [30]. However, some patients received interferon alfa-2b at the same time, which interferes with drug titration. Correctly designed studies are needed to confront the theory with the practice for this drug in the context of the SARSCOV-2 pandemic.

Intracellular protein flow inhibitor

Ivermectin

It is a drug well known since the 1970s for its use as an antiparasitic. Its mechanism of action at the level of the muscle tissue of the parasites is to cause the opening of chlorine cannelloni activated by gamma-aminobutyric acid (GABA), thus producing a hyperpolarization of the muscles of the helminth and achieving their death after the action of eosinophils. It has an immunomodulatory mechanism of action on viral infections, with proven *in vitro* effectiveness in inhibition of the flavivirus replication and to remove SARSCoV-2 from cell cultures at 48 hours [36]. Importin is chaperone proteins of the cytoplasm and cell nucleus, which carry viral proteins during the life cycle of SARSCoV-2. Specifically inhibits importin to alfa/beta1 decreasing viral load, and maybe prophylactic as therapeutic (in the latter case, it should be administered within the first seven days of disease). Considering that the levels reached *in vivo* with therapeutic doses are much lower than those achieved *in vitro*, it remains to be demonstrated to be effective in the clinical field. This drug has a wide safety margin, has no side effects such as the affectation on heart rate described with hydroxychloroquine or dyslipidemias caused by lopinavir/ritonavir and is six times cheaper than the average drugs under investigation. Even considering the gaps in its application in medical practice, it is useful to note that only ongoing clinical studies will finish defining their use in this pandemic.

Combined therapies

The administration of corticosteroids together with tocilizumab was able to decrease the severity of COVID19-associated pneumonia by taking as a parameter the increase in the paO_2/FiO_2 ratio measured sequentially, with diminished admission to intensive care units (RR 0.18, p 0.01 and HR 0.13, p 0.01) [31]. In the French experience, the association of azithromycin with hydroxychloroquine in observational studies did not demonstrate a benefit in addition to evidence of cardiac conduction disturbances due to QT prolongation. Therefore, no literature is in favour of the use of this association at present [32-35].

Empirical treatment of bacterial pneumonia over-aggregated to COVID 19 Coverage of bacterial pneumonia over-aggregated to COVID19 should be indicated according to the patient's severity criteria. It should be noted that severe forms of COVID19 have a similar clinical-radiological presentation as severe bacterial pneumonia. The onset of antimicrobial empirical coverage is based on increased tracheal secretions, worsened semiology, new pulmonary radiological imaging or increased mechanical ventilation parameters. Increase in leukocytes, with left-hand detour, or the presence of biomarkers such as serum procalcitonin, maybe a sustentation for the use of antibiotics. In case of empirical coverage with antibiotics, blood cultures, tracheobronchial aspirates and induced sputum intake with hypertonic serum nebulizations should be made, all these samples should be subjected to Gram staining, culture for common germs and fungi [11,36,37].

Extended-spectrum penicillins with or without macrolides (ampicillin/sulbactam plus azithromycin, for example) are proper treatment in pneumonia with less than 48 hours of hospitalization and non-severe. In severe cases a 3rd generation cephalosporin plus a macrolide or a fluoroquinolone alone are options. When S. aureus methicillin-resistant is suspected, clindamycin or vancomycin shall be added.

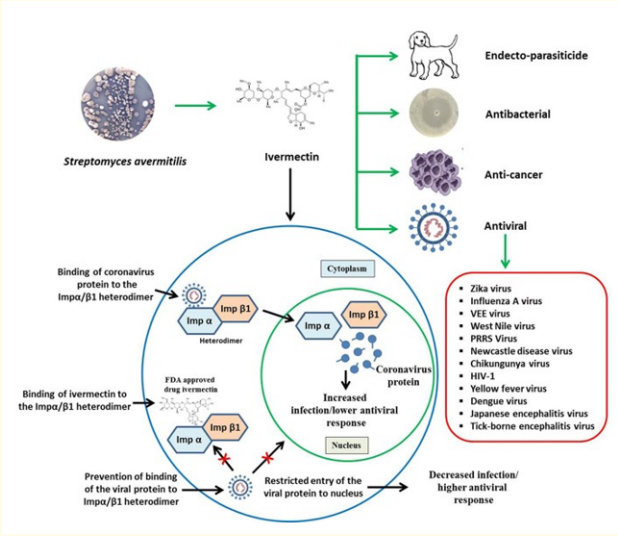

Figure 1: *Mechanism of action of ivermectin against SARSCoV-2. The binding of the drug competitively to alpha and beta imports ultimately decreases viral replication. Taken from Sharun, K., Dhama, K., Patel, S.K. et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob 19, 23 (2020).*

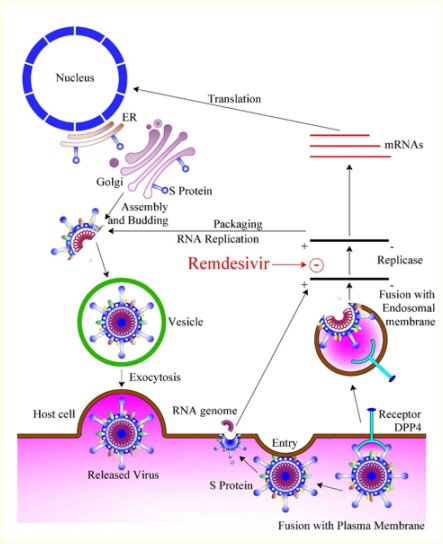

Figure 2: *Proposed mechanism of action of remdesivir. Inhibition of the action of RNA dependent. Taken from Hendaus, M.A. (2020). Remdesivir in the treatment of Coronavirus Disease 2019 (COVID-19): A simplified summary. Journal of Biomolecular Structure and Dynamics, 1-10.*

Conclusions and Final Summary

The global situation of the pandemic is going out of control. The lack of a drug scheme that is appropriate at controlling both viral replication and the "cytokine storm", sets up a sui generis situation in modern medicine because although human beings have found solutions to many epidemic situations, this is a challenge that after six months of global involvement has no vision of a solution.

Analyzing drugs with action against SARSCoV-2 involves the understanding of a dynamic framework, which showed us the chiaroscuros of medications from March to date.

The potentiality utility of hydroxychloroquine used isolated or in addition to azithromycin, had a period of great popularity during the peak of the pandemic in Europe, especially in France. There were even massive purchases of the drug by first-world governments to accumulate enough for a situation of need. However, as scientific evidence matured, the initial impetus was overshadowed by poor results in effectiveness and safety, with the World Health Organization's research efforts abandoned. In understanding, this temporal variability in terms of candidate drugs for the management of COVID19 allows us only to make forward projections based on pharmacodynamic knowledge of medications, in the current state of affairs we believe that the candidates with the most evidence are remdesivir, tocilizumab and ivermectin. These three medications have promising results regarding the inhibition of viral replication (remdesivir and ivermectin) and in terms of the control of the cytokine storm (tocilizumab). Even the combination of them is an option of future clinical essays.

We should also mention the use of corticosteroids as adjuvants, always using them at just times of the particular evolution of the disease in the sick. Monitoring of paO_2/FiO_2 and SaO_2 would be necessary to establish the start time of corticoid therapy as a cytokine storm modulator.

Vitamin D is mentioned as an easy-to-administer synthetic drug that could play a central role in conditioning the body's response to SARSCoV-2, both in innate immunity and specific immunity. It is important to note that many critical patients with covid19 will in mechanical ventilation for a long time, this being a condition for the development of pneumonia associated with mechanical ventilation, on the other hand, lung damage constitute a microenvironment favourable for bacterial invasion and superinfection. This aspect remains fundamental as it could be the ultimate trigger for death in patients with long periods at the hospital.

Much remains to be discovered in this historic time for medicine and why not to say it, for humanity. Let's hope that clinical studies will consolidate and allow the rapid implementation of these drugs with good evidence-based medicine.

Statement of Conflicts of Interest

None.

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Author.

Bibliography

1. Khandelwal R., *et al*. "Shape-based Machine Learning Models for the potential Novel COVID-19 protease inhibitors assisted by Molecular Dynamics Simulation". *Current Topics in Medicinal Chemistry* (2020).

2. Wang Y., *et al*. "Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial". *Lancet* 395.10236 (2020): 1569-1578.

3. Cao B., *et al*. "A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19". *The New England Journal of Medicine* 382.19 (2020): 1787-1799.

4. Khailany RA., *et al*. "Genomic characterization of a novel SARS-CoV-2". *Gene Rep* 19 (2020): 100682.

5. Channappanavar R and Perlman S. "Pathogenichumancoronavirusinfections:causes and consequences of cytokine storm and immunopathology". *Seminars in Immunopathology* 39.5 (2017): 529-539.

6. Capra R., *et al*. "Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia". *European Journal of Internal Medicine* (2020).

7. Recovery Collaborative Group. "Effect of Dexamethasone in Hospitalized Patients with COVID-19-Preliminary Report". medrxiv (2020).

8. Luo P., *et al*. "Tocilizumab treatment in COVID-19: A single center experience". *Journal of Medical Virology* 92.7 (2020): 814.

9. Sciascia S., *et al*. "Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19". *Clinical and Experimental Rheumatology* 38.3 (2020): 529.

10. Klopfenstein T., *et al*. "Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients". *Médecine et Maladies Infectieuses* (2020).

11. Wang D., *et al*. "Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus- infected pneumonia in Wuhan, China". *The Journal of the American Medical Association* (2020): e201585.

12. Xu X., *et al*. "Effective treatment of severe COVID-19 patients with tocilizumab". *Proceedings of the National Academy of Sciences of the United States of America* 117.20 (2020): 10970.

13. Panagiotou G., *et al*. "Low serum 25-hydroxyvitamin D (25[OH]D) levels in patients hospitalised with COVID-19 are associated with greater disease severity (2020).

14. Rondanelli M., *et al*. "Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and Echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds-practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds". *Evidence-Based Complementary and Alternative Medicine* (2018).

15. Grant WB., *et al*. "Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths". *Nutrients* 12 (2020): 988.

16. Cantorna MT., *et al*. "VitaminD and 1,25(OH)2 D regulation of T cells". *Nutrients* 7 (2015): 3011-3021.

17. Vieth R., *et al*. "Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients". *Nutrition Journal* 3 (2004): 8.

18. Bischoff-Ferrari HA., *et al*. "Benefit- risk assessment of vitamin D supplementation". *Osteoporosis International* 21 (2010): 1121-1132.

19. Chapman CE and Williamson LM. "National blood service TRALI reduction policies: implementation and effect". *Transfusion Medicine and Hemotherapy* 35.2 (2008): 93-96.

20. Moore JB and June CH. "Cytokine release syndrome in severe COVID-19". *Science* 368.6490 (2020): 473-474.

21. Piechotta V., *et al*. "Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review". *The Cochrane Database of Systematic Reviews* 7 (2020): CD013600.

22. Amirian ES and Levy JK. "Current knowledge about the antivirals remdesivir (GS-5734) and GS-441524 as therapeutic options for coronaviruses". *One Health* 9 (2020): 100128.

23. Gordon CJ., *et al*. "Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency". *Journal of Biological Chemistry* 295 (2020): 6785-6797.

24. Agostini ML., *et al*. "Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease". *mBio* 9 (2018): 221.

25. De Wit E., *et al*. "Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS- CoV infection". *Proceedings of the National Academy of Sciences of the United States of America* 117 (2020): 6771.

26. US FDA. Remdesivir letter of EUA (2020).

27. Sanford Guide 50th edition (2020).

28. Drugs and Sanitary Products Spanish Agency, Available Treatments for Management of SARS-CoV2 Respiratory infection (2020).

29. Beigel JH., *et al*. "Remdesivir for the Treatment of Covid-19 - Preliminary Report. ACTT-1 Study Group Members". *The New England Journal of Medicine* (2020).

30. Cai Q., *et al*. "Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study". *Engineering* (2020).

31. Urbistondo DM., *et al*. "Early Combination of Tocilizumab and Corticosteroids: An Upgrade in Anti- Inflammatory Therapy for Severe COVID". *Clinical Infectious Diseases* (2020).

32. Gautret P., *et al*. "Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial". *The International Journal of Antimicrobial Agents* (2020).

33. Rosenberg ES., *et al*. "Association of Treatment With Hydroxychloroquine or Azithromycin With In- Hospital Mortality in Patients With COVID-19 in New York State". *The Journal of the American Medical Association* (2020).

34. Molina JM., *et al*. "No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection". *Medecine et Maladies Infectieuses* (2020).

35. Million M., *et al*. "Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin: A retrospective analysis of 1061 cases in Marseille, France". *Travel Medicine and Infectious Disease* 35 (2020): 101738.

36. Caly L., *et al*. "The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *In vitro*". *Antiviral Research* 178 (2020): 104787.

37. Guan WJ., *et al*. "Clinical Characteristics of Coronavirus Disease 2019 in China. China Medical Treatment Expert Group for Covid-19". *The New England Journal of Medicine* 382.18 (2020): 1708.

38. Wu C., *et al.* "Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China". *JAMA Internal Medicine* (2020).

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