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Treatment of COVID-19: A review of emerging treatment

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Abstract

COVID-19 has caused a devastating pandemic, infecting 3,090,445 people and causing 217,769 deaths, as of 30 April, 2020. The current evidence base for selected drugs repositioned to treat COVID-19 are summarized here. Chloroquine (CQ) and hydroxychloroquine (HCQ) block the entry of the SARS-CoV-2 virus into cells and have immuno-modulatory effects. Early, poor quality studies pointed to benefit with CQ and HCQ treatment in COVID-19 infection, but no further evidence supporting their use is available to date, and the drugs cannot be recommended for treatment or prophylaxis. However, several countries use CQ or HCQ for compassionate treatment. Lopinavir-ritonavir, which is effective against HIV, was evaluated in one clinical trial which showed no benefit. Remdesivir, a drug developed for EBOLA, has been shown to have in-vitro efficacy against SARS-CoV-2, and the treatment has been used on compassionate grounds in severe cases. Limited studies have shown clinical improvement with remdesivir which is approved for emergency use in severe COVID-19. The RNA polymerase inhibitor favipiravir has been shown to improve clinical features, hasten viral clearance, and improve HRCT findings. Corticosteroids have shown no benefit. Trials are underway with the IL-6 receptor blocking monoclonal antibody tocilizumab, with retrospective data showing reduction in inflammatory markers and clinical improvement. Convalescent plasma has been shown to be of some benefit in severe cases of SARS, MERS and H1N1 influenza, and is recommended by the FDA for those with serious or immediately life-threatening infection with COVID-19. Several large randomized controlled trials are underway, evaluating these repositioned therapies as well as many other treatments. No effective specific treatments are available for COVID-19 infection as yet.

Key words: COVID-19, SARS-CoV-2, chloroquine, hydroxychloroquine, remdesivir, favipiravir, lopinavir-ritonavir

The virus SARS-CoV-2 emerged in December 2019 in Wuhan, China and spread rapidly worldwide. As of April 30, 2020, the virus has spread to 213 countries, infecting 3,090,445 and causing death in 217,769[1]. The SARS-CoV-2 is a single stranded RNA beta-corona virus, similar to SARS and MERS[2]. Therefore, drugs which were effective against SARS and MERS were repositioned for SARS-CoV-2. On behalf of the Ceylon College of Physicians' "Subcommittee for Guidance on Treatment and Prophylaxis against COVID-19", we herein summarize the current evidence as of May 2, 2020 for selected repositioned drugs which have been used in the current COVID-19 pandemic.

Antiviral agents

Chloroquine and hydroxychloroquine

Chloroquine (CQ) has been used effectively against malaria and hydroxychloroquine (HCQ) against systemic lupus erythematous and rheumatoid arthritis for a long time. They appear to block the entry of SARS-CoV-2 virus into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. They also appear to have immuno-modulatory effects through attenuation of cytokine production[3,4]. CQ was shown to be effective against SARS-CoV-2 in vitro with a low half maximal concentration (EC50)[5]. HCQ, a less toxic derivative of CQ, has an in vitro activity with a lower EC50 for SARS-CoV-2 compared with CQ[6] and by reducing the production of cytokines,

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is postulated to attenuate the cytokine storm associated with COVID-19[7].

No high-quality evidence exists for in-vivo efficacy of CQ/HCQ against COVID-19. A news conference in China held on February 15, 2020 reported the successful use of CQ in more than 100 COVID-19 cases who showed improved radiologic findings, enhanced viral clearance, and reduced disease progression[8,9]. The clinical trial designs and outcome data, however, have not been presented yet nor published for peer review.

Many of the clinical trials that appear to show an efficacy of HCQ against COVID-19 have been open-labelled non-randomized ones, performed without a control arm and underpowered to detect a significant clinical effect. While some show an early virologic clearance measured from nasopharyngeal swabs[10-12] and reduced body temperature recovery time and cough[12], others show no benefit with HCQ when compared with standard care[13,14]. The claim of increased clearance when HCQ was combined with azithromycin[10,11], was not shown in a randomized controlled trial conducted by Molina et al[13]. HCQ also showed no benefit when given to those with COVID-19 hypoxic pneumonia[14].

There is limited data regarding the optimal dose of CQ and HCQ to ensure the safety and efficacy when prescribed to those with COVD-19. The trials have used different regimens[10,12] which make comparisons difficult. While both these drugs are known to prolong QTc, in many trials this does not appear to be a problem. Higher doses of CQ in COVID-19 however, have been associated with prolongation of QTc[15]. It is therefore recommended to perform a baseline electrocardiogram (ECG) to evaluate prolonged QTc prior to and following initiation of these medications because of the potential for arrhythmias, especially in critically ill patients and those taking concomitant QT-interval prolonging medications such as azithromycin and fluoroquinolones. The occurrence of cardiac injury associated with COVID-19 and the greater risk of in-hospital mortality[16] may increase when CQ/HCQ is given.

Lopinavir-ritonavir

Lopinavir-ritonavir is a US Food and Drug Administration (FDA) approved oral combination agent for treating HIV. Lopinavir is a protease inhibitor, which blocks viral replication. Ritonavir inhibits the CYP3A mediated metabolism of lopinavir and thereby potentiates the serum level of lopinavir. Lopinavir has also been demonstrated to have in-vitro activity against SARS CoV[17] and MERS[18]. Despite the absence of evidence for in-vitro efficacy of lopinavir-ritonavir against SARS-CoV-2, a randomized, controlled, open-label trial, LOTUS China (Lopinavir Trial for Suppression of SARS-Cov-2 in China), was conducted in adult patients hospitalized with severe COVID-19. The trial showed no benefit with lopinavir-ritonavir treatment beyond standard care in hospitalized adult patients with severe COVID-19[19]. Significant drug-drug interactions and potential adverse drug reactions[19] are likely with lopinavir-ritonavir combination and careful review of concomitant medications and monitoring are required if they are used. Drug induced transaminitis may exacerbate liver injury that results from COVID-19.

Investigational antiviral agents

Remdesivir

Remdesivir (previously GS-57340), is an adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination[20]. It showed promise during the Ebola outbreak[21] and is currently under development for treatment of Ebola infection. Remdesivir was considered a potential therapeutic agent for COVID-19 as it has shown in-vitro efficacy against SARS-CoV-[5,22]. Some patients with severe disease have been given a 10-day course of remdesivir on compassionate grounds[23,24]. Analysis of data from these patients showed a significant improvement in oxygen-support class, reduction in the need for mechanical ventilation and a reduction in mortality in those given remdesivir. Interestingly, coexisting conditions and duration of symptoms before remdesivir treatment was initiated, were not significantly associated with clinical improvement[23,24]. Mild-to-moderate elevation of liver transaminases was seen in those given remdesivir and this needs to be carefully monitored in view of hepatic dysfunction seen in those with COVID-19. As viral load data was not collected, the antiviral effects of remdesivir and any association between baseline viral load and viral suppression, and clinical response could not be confirmed[24]. Preliminary results from the Adaptive COVID-19 Treatment Trial (ACTT) sponsored by the National Institute of Allergy and Infectious Diseases, National Institute of Health, USA showed that remdesivir accelerates recovery from advanced COVID-19[25]. However, a randomized, double-blind, placebo-controlled, multicenter trial conducted in adults with severe COVID-19 in Hubei, China, remdesivir was not associated with significant clinical benefit[26]. Based on current evidence, US FDA has

issued an emergency use authorization (EUA) of remdesivir for treatment of hospitalized severe COVID-19 patients[27].

Favipiravir

Favipiravir (FPV) is a new type of RNA-dependent RNA polymerase (RdRp) inhibitor. High concentration of favipiravir (EC50 = 61.88 μM, half-cytotoxic concentration (CC50), > 400 μM, selectivity index (SI)) > 6.46) has been shown to inhibit SARS-CoV-2 infection in Vero E6 cells[5]. An open-label nonrandomized controlled study of FPV vs lopinavir-ritonavir in COVID-19 patients with mild to moderate disease, has shown significantly shorter median time of viral clearance and better CT resolution in FPV group[28]. A prospective, multi-center, open-label, randomized superiority trial comparing umifenovir (Arbidol) and FPV showed a higher clinical recovery rate at 7 days and more effective reduction of fever and cough[29]. This study also showed a non-significant benefit with favipiravir in COVID-19 patients with multiple comorbidities. Currently favipiravir is approved in Japan for influenza[30] and is investigational for use in COVID-19.

Adjuvant therapies

In the absence of proven therapy for SARS-CoV-2, supportive care remains the cornerstone of management for patients with COVID-19. These range from symptom management, mainly as outpatients in many parts of the world to full intensive care support for those with critical disease. Of the many that have been tried, corticosteroids, immunomodulatory agents, and immunoglobulin therapy have shown some promise. In these too, the small numbers of patients who have received the therapies and the multiple treatment modalities tried, make data interpretation difficult.

Corticosteroids

The pathological similarity between COVID-19 pneumonia and those seen in SARS and MERS, with changes suggestive of acute respiratory distress syndrome (ARDS)[31] makes the use of methyl-prednisolone (MPP) an attractive therapeutic option. In these patients MPP is expected to attenuate lung inflammation, a result of the “cytokine storm” seen in those with severe COVID-19[32]. However, patients with MERS-CoV[33] or influenza[34] who were given corticosteroids were more likely to have prolonged viral replication, receive mechanical ventilation, and have higher mortality. A retrospective study on a cohort of patients with severe COVID-19 pneumonia with and without MPP showed that early, low-dose and short-term application of MPP was associated with shorter time for normalcy of body temperature, faster improvement of SpO2 with significantly shorter interval of using supplemental oxygen therapy and a significantly better absorption degree of the focus in chest CTs[35]. The authors recommend the early use of MPP is those with severe pneumonia as worsening occurs during 5th to 7th day of the illness. However, due to methodological limitations of the studies, delayed viral clearance and complication, corticosteroid treatment for COVID-19 lung injury remains controversial[36]. Guidelines issued by the World Health Organization, Royal College of Physicians (London) and Indian Council of Medical Research recommend against the routine use of steroids in those with severe COVID-19 pneumonia.

Immunomodulatory agents

The cytokine storm syndrome seen in those with severe COVID-19 pneumonia is the potential target for immunomodulatory therapies[37]. Tocilizumab (TCZ), a monoclonal antibody against IL-6 receptors, has been evaluated in few clinical trials of those with severe COVID-19. Retrospective analysis of data from patients treated with TCZ showed a gradual reduction of acute phase reactants and IL-6 with improved clinical stability[38,39]. Early, repeated dosing of TCZ appear to be beneficial in severe COVID-19[38,40]. Several RCTs of tocilizumab, alone or in combination, in patients with COVID-19 with severe pneumonia are being conducted and TCZ is included in the current edition of the Chinese national treatment guidelines for COVID-19[41].

Convalescent plasma or hyperimmune immunoglobulins

It has been postulated that antibodies from those recovered from the infection may help with immune clearance of the free virus and infected cells. Convalescent plasma (CP) has been used as salvage therapy in SARS[42], MERS[43] and H1N1 influenza [44]. In those with severe H1N1 influenza, treatment with CP was associated with a reduction of viral load and reduced mortality[45]. Use of convalescent plasma in those with severe respiratory infections was not associated with adverse events or complications after treatment[46]. In a limited number of patients with severe COVID-19 treated with CP in addition to antivirals and MPP, an increase in neutralizing antibodies, improvement in clinical symptoms and radiological evidence

for absorption of lung lesions without severe adverse events was observed[47,48]. Key factors associated with efficacy of CP therapy are neutralizing antibody titre and treatment time point[47]. The FDA has also approved the compassionate use of convalescent plasma to those with serious or immediately life threatening COVID-19 infections[49].

Dipyridamole

Experimental models of SARS-CoV infection, showed that Spike protein engagement decreases ACE2 expression and activates the renin-angiotensin system (RAS)[50]. RAS activation promotes platelet adhesion and aggregation and increases the risk for pulmonary embolism, hypertension and fibrosis[51]. Dipyridamole was shown to suppress HCoV-19 replication in-vitro and significantly increased platelet and lymphocyte counts and decreased D-dimer levels in comparison to controls when given as adjuvant therapy to patients with COVID-19[52].

Prophylactic therapy

Despite being used, no evidence exists for prophylactic use of either CQ or HCQ for COVI-19[53]. In Annals on Call, the COVID-19 Global Rheumatology Alliance reports that about 25% of those who were already on HCQ for rheumatological diseases had got COVID-19[54].

Problems with interpreting trial data

COVID-19 saw an unprecedented number of publications related to different aspect of the disease. In relation to treatment modalities a significant number were pre-publications which have not undergone peer review. Most studies are conducted in small numbers of patients and lack a control arm. Therefore, it is not possible to determine the true clinical effect of this intervention or whether patients might have recovered without these therapies. The baseline characteristics differ widely making comparisons between similar therapeutic modalities difficult. Those of adjuvant therapies are confounded by the concomitant use of different combinations of antivirals and adjuvant therapies. As such all these treatment options must be further investigated in randomized clinical studies. At present, 681 interventional clinical trials looking at the repositioned drugs for COVID-19 are registered with https://clinicaltrials.gov[55] and better evidence is likely to be available during the course of the year.

Conclusions

The COVID-19 pandemic remains the biggest global public health crisis to date. Despite rapidly conducted clinical trials and observational studies, no strong evidence exists for the efficacy of any of the repositioned drugs in the treatment of COVID-19. All studies conducted to date have methodological flaws which make claims of data questionable. The use of multiple medications, lack of uniformity among patients enrolled and diverse treatment regimens even with the same drug make comparison of results difficult. These issues highlight the need for good quality, randomized clinical trials even in the midst of a pandemic. For the moment management of COVID-19 rests with prevention of infection, case detection and monitoring and supportive care in those with severe illness. Any medicine or treatment modality for COVID-19 is only on compassionate/emergency use or in the setting of a clinical trial.

References

1. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200430-sitrep-101-covid-19.pdf?sfvrsn=2ba4e093_2 Accessed 1st May 2020
2. Zhou P, Yang X, Wang X, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273. https://doi.org/10.1038/s41586-020-2012-7
3. Devaux CA, Rolain JM, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *International Journal of Antimicroial Agents* (published online) March 12, 2020. doi:10.1016/j.ijantimicag.2020.105938
4. Liu J, Cao R, Xu M, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery. 2020:6:16. https://doi.org/10.1038/s41421-020-0156-0
5. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* 2020; **30**: 269-71. https://doi.org/10.1038/s41422-020-0282-0
6. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clinical Infectious Diseases* 2020.ciaa237, https://doi.org/10.1093/cid/ciaa237
7. Zhou D, Dai S, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *Journal of Antimicrobial Chemotherapy* 2020 dkaa114, https://doi.org/10.1093/jac/dkaa114

8. Gao J, Tian Z, Yang X. Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Bioscience Trends* 2020; **14**(1): 72-3. doi: https://doi.org/10.5582/bst.2020.01047

9. Multicentre collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. 2020 Feb 20; 43(0): E019. doi: 10.3760/cma.j.issn.1001-0939. 2020. 0019. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32075365/

10. 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 [published online ahead of print, 2020 Mar 20]. *International Journal of Antimicrob Agents.* 2020; 105949. doi: https://doi.org/10.1016/j.ijantimicag.2020.105949

11. Gautret P, Lagier JC, Parola P, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Medicine and Infeciost Disease* 2020; **34**: 101663. doi:10.1016/j.tmaid.2020.101663

12. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *Med Rxiv* 2020.03.22.20040758; doi: https://doi.org/10.1101/2020.03.22.20040758

13. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, de Castro N. No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection, M´edecine et Maladies Infectieuses.2020. doi: https://doi.org/10.1016/j.medmal.2020.03.006

14. Mahévas M, Tran Viet-Thi, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalised for COVID-19 infection and requiring oxygen: results of a study using routinely collected data to emulate a target trial. *medRxiv* 2020. https://doi.org/10.1101/2020.04.10.20060699

15. Mayla Gabriela Silva Borba, Fernando de Almeida Val, Vanderson Sousa Sampaio, et al. Chloroquine diphosphate in two different dosages as adjunctive therapy of hospitalized patients with severe respiratory syndrome in the context of coronavirus (SARS-CoV-2) infection: Preliminary safety results of a randomized, double-blinded, *medRxiv* 2020.04.07.20056424 doi: https://doi.org/10.1101/2020.04.07.20056424

16. Shi S, Qin M, Shen B, et al. Association of Cardiac Injury with Mortality in Hospitalized Patients with COVID-19 in Wuhan, China. *JAMA Cardiology* Published online March 25, 2020. doi: http://jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2020.0950

17. Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* 2004; **59**: 252-6. doi: http://dx.doi.org/10.1136/thorax.2003.012658

18. de Wilde AH, Jochmans D, Posthuma CC, et al. Screening of an FDA-approved compound library identifies four small-molecule inhibitors of Middle East respiratory syndrome coronavirus replication in cell culture. *Antimicrobial Agents Chemotherapy* 2014; **58**(8): 4875-84. doi: 10.1128/AAC.03011-14

19. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine* 2020; **382**: 1787-99 doi:10.1056/NEJMoa2001282

20. Warren, T, Jordan, R, Lo, M, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 2016; **531**: 381-5. Doi: https://doi.org/10.1038/nature17180

21. Siegel D, Hui HC, Doerffler E, et al. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. *Journal of Medicinal Chemistry* 2017; **60**(5): 1648-61. doi: https://doi.org/10.1021/acs.jmedchem.6b01594

22. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel Medicine and Infectious Disease.* Published online March 5, 2020; **34**:101615. doi: https://doi.org/10.1016/j.tmaid.2020.101615

23. Holshue ML, DeBolt C, Lindquist S, et al for Washington State 2019-nCoV Case Investigation Team. First case of 2019 novel coronavirus in the United States. *New England Journal of Medicine*. 2020; **382**(10): 929-36. doi: https://doi.org/10.1056/NEJMoa2001191

24. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine* 2020; doi: https://doi.org/10.1056/NEJMoa2007016

25. https://www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19 Accessed: April 30, 2020

26. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet* 2020; **395**: 1569-78. doi: https://doi.org/10.1016/S0140-6736(20)31022-9

27. https://www.fda.gov/media/137564/download Accessed May 2, 2020

28. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study, Engineering. Published online March 18, 2020. doi: https://doi.org/10.1016/j.eng.2020.03.007

29. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. *medRxiv* 2020.03.17.20037432; doi: https://doi.org/10.1101/2020.03.17.20037432

30. https://www.pmda.go.jp/files/000210319.pdf#page=3 Accessed: March 20, 2020

31. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID 19 associated with acute respiratory distress syndrome. *Lancet Respiratory Medicine* 2020; **8**: 420-22. doi: https://doi.org/10.1016/S2213-2600(20)30076-X

32. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020; **395**: 497-506. doi: https://doi.org/10.1016/S0140-6736(20)30183-5

33. Corman VM, Albarrak AM, Omrani AS, et al. Viral Shedding and Antibody Response in 37 Patients with Middle East Respiratory Syndrome Coronavirus Infection. *Clinical Infectious Diseases*: 2016; **62**(4): 477-83. doi: https://doi.org/10.1093/cid/civ951

34. Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam JS, Lim WS. Effect of corticosteroid therapy on influenza-related mortality: a systematic review and meta-analysis. *The Journal of infectious diseases* 2015; **212**(2): 183-94. doi: https://doi.org/10.1093/infdis/jiu645

35. Yin Wang, Weiwei Jiang, Qi He, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. *medRxiv* 2020.03.06.20032342; doi: https://doi.org/10.1101/2020.03.06.20032342

36. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet* **395**: 473-5 (2020). doi: https://doi.org/10.1016/S0140-6736(20)30317-2

37. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**(10229):1033-4. doi: https://doi.org/10.1016/S0140-6736(20)30628-0

38. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: a single centre experience. *Journal of Medical Virology* 2020. (online ahead of print). doi: https://doi.org/10.1002/jmv.25801
    Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences of the United States of America. 2020; **117**(20): 10970-5. doi:10.1073/pnas.2005615117

39. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? *Journal of Translational Medicine* 2020; **18**: 164. https://doi.org/10.1186/s12967-020-02339-3

40. National Health Commission and State Administration of Traditional Chinese Medicine. Diagnosis and treatment protocol for novel coronavirus pneumonia. https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf. Accessed March 20,2020

41. Soo YO, Cheng Y,Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clinical Microbiology and Infection* 2004; **10**(7): 676-8. doi: https://doi.org/10.1111/j.1469-0691.2004.00956.x

42. Arabi Y, Balkhy H, Hajeer AH, et al. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Springerplus* 2015; **4**: 709. doi: https://doi.org/10.1186/s40064-015-1490-9

43. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011; **52**: 447-56. doi: https://doi.org/10.1093/cid/ciq106

44. Hung IFN, To KKW, Lee CK, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013; **144**: 464-73. doi: https://doi.org/10.1378/chest.12-2907

45. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral aetiology: a systematic review and exploratory meta-analysis. *Journal of Infectious Diseases* 2015; **211**: 80-90. doi: https://doi.org/10.1093/infdis/jiu396

46. Duan Kai, Liu Bende, Li Cesheng, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences. 2020; 117(17) 202004168. doi: https://doi.org/10.1073/pnas.2004168117

47. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; **323**(16): 1582-9. doi: https://doi.org/10.1001/jama.2020.4783

48. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma (Accessed April 20, 2020)

49. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine* 2005; **11**(8): 875-9. doi: https://doi.org/10.1038/nm1267

50. Kalinowski L, Matys T, Chabielska E, Buczko W, Malinski T. Angiotensin II AT1 receptor antagonists inhibit platelet adhesion and aggregation by nitric oxide release. *Hypertension* 2002; **40**(4): 521-7. doi: https://doi.org/10.1161/01.HYP.0000034745.98129.EC

51. Xiaoyan Liu, Zhe Li, Shuai Liu, et al. Therapeutic effects of dipyridamole on COVID-19 patients with coagulation dysfunction. medRxiv 2020.02.27.20027557; doi: https://doi.org/10.1101/2020.02.27.20027557

52. Shah, S, Das, S, Jain, A, Misra, DP, Negi, VS. A systematic review of the prophylactic role of chloroquine and hydroxychloroquine in coronavirus disease-19 (COVID-19). *International Journal of Rheumatic Diseases* 2020; 00: 1-7. doi: https://doi.org/10.1111/1756-185X.13842

53. Centor RM, Kim AH, Sparks JA. Annals On Call - COVID-19: Is Chloroquine the Answer? Published at www.annals.org on 9 April 2020 dOI: https://doi.org/10.7326/A20-0003

54. https://clinicaltrials.gov/ct2/results?cond=COVID-19 Accessed April 30, 2020